Summary of information provided in this briefing package:

Current Application:

NDA 22-425 MULTAQ (dronedarone hydrochloride) Tablets, 400 mg

Proposed Indication: MULTAQ is indicated in patients with either a recent history of, or current atrial fibrillation or flutter and with associated risk factors. MULTAQ has been shown to decrease the combined risk of cardiovascular hospitalization or death.

This application was submitted on July 31, 2008. The Agency has not yet taken an action on this application.

The following reviews associated with this application are included:

- Secondary medical review
- Combined medical-statistical review
- Clinical pharmacology review
- Pharmacology/Toxicology review

Previous Application:

NDA 21-913 MULTAQ (dronedarone hydrochloride) Tablets, 400 mg

Proposed Indication: MULTAQ is indicated for rhythm and rate control in patients with atrial fibrillation or atrial flutter, to maintain normal sinus rhythm or to decrease ventricular rate.

This application was submitted on June 10, 2005. A not-approvable letter was issued on August 29, 2006.

The following reviews associated with this application are included:

- Office Director's memo
- Division Director's memo
- Secondary medical review
- Combined medical-statistical review
- Clinical pharmacology review
- Pharmacology/Toxicology review

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 17, 2009

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader, Division of Cardiovascular and Renal Products, HFD-110.

TO: Cardiovascular and Renal Products Advisory Committee

SUBJECT: Dronedarone Hydrochloride (Multaq®, SR33589B); Sanofi –aventis, U.S., Inc. as sponsor; NDA 22-425.

This memo is a follow-up to my original memo dated April 26, 2006 (edited on February 18, 2009) for NDA 21,913 which recommending an approvable action for dronedarone, should the sponsor be able to demonstrate that a population can be defined which both benefited by treatment and which can be safely treated. The current NDA # 22-425 differs in the original NDA number for dronedarone because it requests additional claims compared to those of NDA 21,913. The pivotal information in this submission is the results of the ATHENA study. The results of the ATHENA appear to define a population which derives benefit from dronedarone use and in whom safety was demonstrated.

In addition to the ATHENA study, the new information summarized in this memo relates to the ANDROMEDA study. This study was previously reviewed. The sponsor halted the study for an adverse mortality outcome in the dronedarone treated subjects. In this memo, I have included an analysis of those subjects who died during this study who were withdrawn from angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs), or were not treated with these classes of drugs at baseline. It does not appear that the mortality excess, as observed in the ANDROMEDA study can be explained by a model in which subjects had asymptomatic creatinine increases which provoked discontinuation of ACE-I or ARB treatment and only then resulted in cardiac decompensation. All events which provoked discontinuation of the ACE-I/ARB treatment appear to be acute exacerbations of either renal or cardiac disease at the time these drugs were discontinued.

This review is largely based on the joint clinical-statistical review by Gail Moreschi M.D., MPH, FACP (clinical) and Valeria Freidlin, Ph.D., (statistics).

The ATHENA study randomized 4628 subjects, across 37 countries and 551 centers, who had one previous episode of atrial fibrillation or flutter and one normal ECG (not necessarily in that order), to receive either dronedarone at a dose of 400 mg BID with food or placebo in a 1:1 ratio. For those who were not in sinus rhythm at the

time of enrollment, the subject was to undergo an attempt at cardioversion. Subjects were to be elderly (over 70 years old). Initially, however, they could be any age but have additional risk factors for cardiovascular outcomes. A subsequent amendment modified the enrollment criteria to require subjects to be over 75 with the history of atrial fibrillation (AFib) or atrial flutter (AFL) as above, or over 70 with the same history but have one additional cardiovascular risk factor. Notable exceptions for enrollment included a history of chronic atrial fibrillation. Subjects were to be followed for one year after the last subject enrolled.

The primary endpoint of the study, time to first cardiovascular hospitalization or death, was highly significant favoring dronedarone. The primary secondary analysis, all-cause death was not significant but numerically favored of dronedarone (p=0.2). Several of these deaths that were captured occur at time points after to the proposed cut-off date. Most of those post-cut-off events occurred in the placebo group, making the lean on mortality slightly less convincing.

Since the primary secondary endpoint, all-cause death, was not significant, the other two secondary endpoints should be considered as exploratory.

With respect to cardiovascular deaths, the Steering Committee, which was composed of 5 independent cardiologist and three sponsor's representatives, assessed the nature of death. The broad outline of what constitutes a cardiovascular death appears somewhat arbitrary and in some cases irrelevant to events that would likely be preventable in this population. It is unclear if the new analysis of cause-specific mortality events adds clarity to the any benefit of dronedarone or the results merely allows for a second attempt at defining a mortal benefit.

Should only a small number of events be reclassified from cardiovascular to non-cardiovascular in the placebo-treated subjects, or from non-cardiovascular to cardiovascular in the dronedarone treated group, nominal significance would be lost, particularly when the analysis excludes those events, which occurred after the cut-off time. The results of the ATHENA study with respect to cardiovascular outcomes are so discrepant with the results from the ANDROMEDA study, that caution should be exercised in asserting dronedarone as having a mortal benefit.

With respect to cardiovascular hospitalizations, this result highly favors dronedarone. The significance is driven entirely by the AFib/AFl hospitalizations. The underlying reason that subjects were hospitalized for AFib/AFl is unclear.

I find the results of EURIDIS, ADONIS (previously reviewed) and ATHENA coupled with that of ANDROMEDA as consistent with the conclusion that dronedarone is a useful antiarrhythmic to delay recurrence of symptoms associated with the underlying arrhythmia and to prevent atrial fibrillation hospitalizations. The results are not convincing that, aside from hospitalization for atrial fibrillation, dronedarone prevents other morbid or mortal outcomes. I however, do not have adequate information at this time that efficacy applies both to the atrial fibrillation and atrial flutter populations, as

such, since the predominantly enrolled population is the AFib population, approval should be limited this group.

The sponsor has also shared with us the top-line results of the DIONYSIS study. This study has not yet been reviewed but based on the sponsor's assessment the effectiveness of dronedarone in preventing atrial fibrillation is substantially less than that of amiodarone.

In summary, based on the results of the ADONIS and EURIDIS studies previously reviewed and based on the prevention of hospitalization in the ATHENA study, dronedarone should be approved for the delay recurrence of symptomatic events and decrease hospitalization for atrial fibrillation, in a population likely to have recurrence of AFib. Because of the adverse mortality effect that was observed in the ANDROMEDA study, despite the favorable lean in the ATHENA study, no mortality claim should be granted.

Furthermore, based on the outcome of the ANDROMEDA study individuals with Class III or IV NYHA heart failure should be precluded from its use. The tricky issue is how to control those whose heart failure transitions into NYHA class III from less severe degrees of heart failure.

ANDROMEDA study:

This description of the ANDROMEDA study and the results that are included in this review were copied and pasted from the review for NDA 21-913. This review, however, contains a new analysis of those who died and were either on no ACE-I or ARB at baseline or who discontinued these medications.

The ANDROMEDA[1] study randomized 627 subjects (originally the study planned to enroll 1000 subjects) in a 1:1 ratio to either dronedarone 400 mg BID or placebo. The study was carried out in six Western European countries. It was prematurely discontinued seven months after the randomization of the first subject because of an adverse mortality outcome in the dronedarone-treated compared to placebo-treated subjects.

The ANDROMEDA study enrolled subjects with symptomatic CHF (NYHA class II-IV), a wall motion index (WMI)[2] of $\leq$ 1.2 and requiring recent hospitalization and treatment with diuretics. The abnormal wall motion index reflects left ventricular dysfunction. According to the sponsor, multiplying the WMI by 30 approximates the EF. Notable exclusion criteria included recent myocardial infarction, recent decompensated

[1] ANtiarrhythmic trial with DROnedarone in Moderate to severe CHF Evaluating morbidity DecreAse –EFC4966.

[2] The wall motion index was determined by a central echocardiography laboratory after reading the baseline 2D-echocardiogram. The assessment averaged the segmental wall motion score over 16 segments. The individual scoring was as follows: Pronounced paradoxical motion (-1.0); slight paradoxical motion (-0.5); akinesia (0); pronounced hypokinesia (0.5); moderate hypokinesia (1.0); slight hypokinesia (1.5); normokinesis (2.0), slight hyperkinesia (2.5); pronounced hyperkinesia (3.0).

heart failure (e.g., acute pulmonary edema, shock requiring pressors or acute MI), cardiomyopathy, or use of Vaughn-Williams Class I or III anti-arrhythmic agents.

There were 2402 patients screened, of which 650 were randomized and treated. The results from one center that enrolled 23 subjects, was excluded for poor quality control. Of the remaining 627 subjects 317 were randomized to placebo and 310 to dronedarone.

Selected baseline demographics are shown in Table 1.

Table 1: Demographics, cardiovascular history, cardiac status and selected concomitant medications in ANDORMEDA

Parameter	Placebo	Dronedarone
N=	317	310
Age, years (mean ± SD	69 ± 12	70 ± 12
Gender: Number male (%)	242 (76%)	230 (74%)
Race: # non-Caucasian (%)	1 (<1%)	2 (1%)
Weight: Mean ± SD, Kg	79 ± 19	78 ± 17
Cardiovascular history, selected, N= (%)		
Coronary heart disease	201 (63%)	266 (66%)
Valvular heart disease	175 (55%)	171 (55%)
Hypertension	107 (34%)	123 (40%)
Dilated cardiomyopathy	103 (33%)	79 (26%)
Diabetes mellitus	62 (20%)	73 (24%)
CABG	42 (13%)	57 (18%)
Severe ventricular arrhythmia	33 (10%)	33 (11%)
Stroke	31 (10%)	24 (8%)
Cardiac status		
Wall motion Index, mean ± SD	0.86 ± 0.23	0.90 ± 0.23
NYHA class (II/III/IV) (%/%/%)	118/186/13 (37%/59%/4%)	126/178/6 (41%/57%/3%)
Concomitant medications, selective, N (%)		
Diuretics	309 (98%)	297 (96%)
ACE-I/ARB	267 (84%)	274 (88%)
Chronic anti-platelet therapy	196 (62%)	203 (66%)
Oral anti-coagulants	102 (32%)	92 (28%)
Beta-blockers (except sotalol)	191 (60%)	192 (62%)
Statins	97 (31%)	113 (57%)
Cardiac glycosides	101 (32%)	96 (31%)
Verapamil/diltiazem	12 (4%)	9 (3%)

In general, the two groups appear well matched at baseline. Those enrolled were largely male and nearly all Caucasian, most were in NYHA class III failure. Given the underlying CHF, the fraction of subjects using of diuretics and ACE-I/ARB are appropriate.

Although the primary endpoint of the study was composite of time to death or hospitalization for CHF, the DSMB recommended the discontinuation of the study because of an increase in the number of deaths in the dronedarone-treated relative to the placebo-treated subjects. The relative risk for death and for the composite of death and hospitalization for adjudicated heart failure are shown below.

Figure 1 : Kaplan-Meier plots for death (left) and death or hospitalization for heart failure (right) in ANDROMEDA

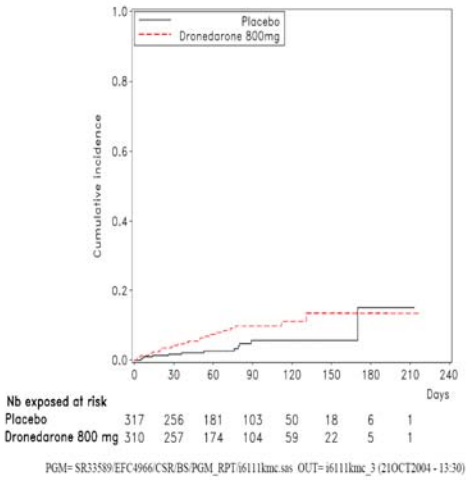

Figure (11.2.1) 1 - Kaplan-Meier cumulative incidence curves from randomization to death up to 16 January 2003- randomized and treated patients population excluding center 616004

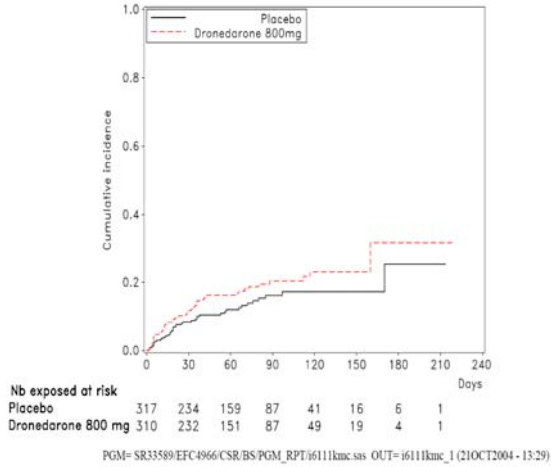

Figure (11.1.1) 1 - Kaplan-Meier cumulative incidence curves from randomization to death or hospitalization for worsening heart failure up to 16 January 2003- randomized and treated patients population excluding center 616004

Hazard ratios for several clinically meaningful measurements are shown in Table 2. All Hazard ratios favor placebo. The upper CI for death extends beyond a factor of 3. The adjudicated cause of death is shown in Table 3.

Table 2: Outcomes and statistical assessments for ANDROMEDA:

Parameter	Placebo N=317	Dronedarone N=310	Hazard ratio (95% CI	Log-rank p-value
Death	12	25	2.13 (1.1-4.2)	0.03
Died or hospitalized for worsening heart failure	40	53	1.38 (0.92-2.1)	0.12
Number hospitalized for worsening failure	31	39	Not calculated	0.27
Number hospitalized for cardiovascular reasons	50	71	Not calculated	0.02

Table 3: Adjudicated causes of death are shown below and (fraction of population) [fraction of deaths] ANDROMEDA:

	Placebo (N= 317)	Dronedarone (N=310)
Number of Events	12	25
Cardiovascular death:	9 (3%) [75%]:	24 (8%)[96%]:
MI	2 (1%) [17%]	0
Worsening CHF	2 (1%)[17%]	10 (3%) [40%]
Documented arrhythmia	2 (1%) [17%]	6 (2%) [24%]
Procedure related	0	1 (<1%) [4%]
Other CV reason	0	2 (1%) [8%]
Presumed CV reason	3 (1%) [25%]	5 (2%) [20%]
Non-cardiovascular	2 (1%)[17%]	1 (< 1%) [4%]
Cancer	1 (< 15) [8%]	1 (< 1%) [4%]
Other	1 (<1%) [8%]	0
Non-adjudicated death	1 (<1%)[8%]	0

The increase in mortality was predominantly attributed to worsening heart failure deaths, but arrhythmia deaths were also increased.

The sponsor postulated that the increase in deaths in the dronedarone group in the ANDROMEDA study is a consequence of dronedarone's ability to inhibit creatinine secretion into the urine, these subjects with elevated creatinine would be more likely to have their ACE-I /ARB medication discontinued, losing the benefit of these treatments and predisposing to a negative mortality and hospitalization outcome.

The above postulated mechanism would suggest the following sequence of events. First, the subject would have an asymptomatic creatinine elevation leading to the discontinuation of the ACE-I/ARB and only then would the patient be at risk for cardiac decompensation or death.

Although more dronedarone subjects discontinued the ACE-I/ARB treatment than did placebo subjects, among those who died, there were few subjects whose creatinine increases were unrelated to either a cardiac or renal insult. The percentage of subjects who were treated with dronedarone who died was substantially higher whether they were not treated with ACE-I/ARBs at baseline or discontinued from these medications. The relationship between ACE-I/ARB use status and mortal events is shown below.

Table 4: Outcome of ANDROMEDA based on ACE-I/ARB status

	Placebo	Dronedarone
Number enrolled		
Number not on ACE-I /ARB at baseline (A)	50	36
Number who died (% of A)	1 (2%)	6 (16%)
Number on ACE-I/ARB at baseline (B)	267	274
Number on B who died (% B)	10 (4%)	10 (4%)
Number who discontinued from ACE-I/ARB (C)	12	19
Number who died (% C)	1 (8%)	9 (47%)

There were 12 placebo subjects and 25 dronedarone-treated subjects who died. Of these deaths, nine of the placebo subjects and 24 of the dronedarone subjects died of cardiovascular events. Among the subjects in the placebo group who died, one death occurred in a subject who never received ACE-I or ARB. In the dronedarone group there were six subjects who died in this category. Among the subjects who were treated and remained on ACE-I/ARB, deaths were the same in both groups.

The capsular summaries for these subjects who were treated with dronedarone and were discontinued from the ACE-I or ARB are provided below. None of these events can be interpreted as an asymptomatic creatininemia, provoking the discontinuation of ACE-I /ARB treatments.

Dronedarone subjects:
Subject # 208 103009 was an 81 year-old female with a history of myocardial infarction and chronic atrial fibrillation. Her NYHA was Class III. She was hospitalized for increased blood creatinine but received a glucose infusion (was it really glucose + insulin

for hyperkalemia?) and transfusions. The subject died 11 days after admission from worsened heart failure. The hospitalization death was attributed to worsened CHF.

Subject 208116008 was a 66 year-old female with a history of myocardial infarction and dilated cardiomyopathy. She was hospitalized on (b) (4) (6 days after randomization) for interstitial nephropathy. She stopped her ACE-I (trandolapril) one day after admission. She required hemodialysis beginning two days after admission. She died one week after admission. At admission she had elevated serum K+ (5.9 mEq/L) and increased weight gain.

Subject 208126010 was a 70 year-old male with a cardiac history of hypertrophic cardiomyopathy. The subject was admitted after approximately 4 weeks of treatment with dronedarone for unstable angina for a CABG procedure. Cozaar was stopped during this hospitalization. The subject had an MI two days after the discontinuation of the Cozaar and he died about a week later. The MI preceded ventricular tachycardia and the need for a mechanical heart.

Subject 208137001 was an 87 year-old male with a history of coronary artery disease and NYHA class III. The subject was admitted two weeks after enrollment for increase in creatinine and worsening heart failure. Ramipril was discontinued two days later. The subject died two months later from worsening heart failure. There was one intervening hospitalization for worsening failure and palpitations.

Subject 578304006 was a 77 year-old female with a history of coronary artery disease, myocardial infarction, mitral regurgitation and diabetes mellitus. She discontinued Cozaar on (b) (4) and died on (b) (4) from metastatic disease.

Subject 616002003 was a 56 year-old male with idiopathic dilated cardiomyopathy and chronic atrial fibrillation. The subject was admitted and had among other conditions, worsening renal function, and heart failure, which required assisted ventilation. The subject died during that hospitalization (2 1/2 weeks after admission). Quinapril was discontinued at the time of the hospitalization.

Subject 752211001 was an 82 year-old male with a history of coronary artery disease, myocardial infarction, mitral regurgitation and atrial fibrillation. The subject was admitted approximately one week after enrollment for among other reasons worsening heart failure and pneumonia. The subject discontinued ramipril after the subject was admitted. The subject died approximately 5 weeks later from worsening heart failure.

Subject 752215002 was admitted for worsening heart failure after about 3 days of dronedarone treatment and had ramipril discontinued at that time. The subject was admitted approximately two weeks later for worsening heart failure and died during that hospitalization.

Subject 752220004 was a 79 year-old female with a history of myocardial infarction. She was in sinus rhythm and NYHA class III at randomization. She was hospitalized

approximately 3 weeks later for worsening heart failure and her ramipril was stopped during that hospitalization. She died 1 ¾ months later from worsening heart failure.

Aside from the one subject who died from a metastatic process, all subjects who discontinued their ACE-I or ARB treatments were symptomatic either with renal or cardiac decompensation at the time of discontinuation.

The ATHENA[3] study:

This study was a double-blind, placebo-controlled study comparing dronedarone to placebo in subjects who had both an ECG demonstrating atrial fibrillation and one demonstrating normal sinus rhythm within 6 months (in either order) of enrollment. The original enrollment criteria required subjects, in addition, to be over 70 years old or to have one of the following risk factors: (hypertension, diabetes, prior CVA, left atrial diameter greater than 50 mm by M-mode echocardiography or left ventricular ejection fraction less than 0.40 by 2D echocardiography). The protocol was amended to alter the enrollment criteria to those who had the above document ECG rhythms and who were over 75 years old or those who were over 70 and also had one of the above noted risk factors. Ostensibly, the reason for this change was to more closely align the age range of this study with that of the AFFIRM[4] study and the SPORTIF studies[5].

Notable exclusions from the study included subjects in permanent atrial fibrillation, subjects with unstable cardiovascular status including those who have pulmonary edema (within 12 hours), require pressors (within 4 weeks), or subjects with GFR < 10 ml/min. Concomitant precluded medications included include Vaughan-Williams class I and III antiarrhythmic drugs. Subjects were stratified based on center and the presence or absence of atrial fibrillation/atrial flutter at the time of randomization.

The pre-specified endpoint of the study was time to first cardiovascular hospitalizations or death. Subjects were to be followed for the duration of the study which was to be 12 months after the enrollment of the last subject. For those who completed the study the data were to be right censored at that time.

The primary method of analysis is a 2-sided Log-rank asymptotic test at a level of 0.05. The cumulative incidence function in each treatment group was to be calculated using a non-parametric Kaplan-Meier estimate with a Cox proportional Hazard model to estimate the Hazard ratio.

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[3] A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patENts with Atrial fibrillation/atrial flutter (AF/AFL).

[4] Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control I patients with atrial fibrillation. N Eng J Med 2002; 347: 1825-33.

[5] Ford GA, Choy AM, Deedwania P, Karalis DG, Lindholm CJ, Pluta W, Frison, L, Olsson SB, and on behalf of the SPORTIF III,V Investigators. Direct Thrombin Inhibition and Stroke Prevention in Elderly Patients With Atrial Fibrillation: Experience From SPORTIF III and V Trials. Stroke 2007 38: 2965-2971.

The primary secondary endpoint is all cause mortality. If the difference in death was statistically significant, other secondary endpoints, cardiovascular deaths and first hospitalization for cardiovascular reasons would be analyzed. The cardiovascular nature of either a hospitalization or death was left to the investigator who filled out a check-box form. There was no pre-specified adjudication committee nor was a complete description of the event available to this reviewer to assess the validity of the cause-specific events. An amendment to the protocol transferred the responsibility for categorizing mortal events to the Steering Committee (after 85 deaths had already occurred). The Steering Committee consisted of 5 independent cardiologists and 3 members of the sponsor. Subjects were followed throughout the study even after the first cardiovascular hospitalization or discontinuation of therapy. An interim look for efficacy/futility was included after 485 subjects achieved the end point.

The study planned to originally enroll 3700 subjects in order to achieve 970 total events. An amendment was submitted August, 2006 (this was early in the study) to increase the sample size to 4300 subjects in order to have a better chance to demonstrate a benefit on mortality. The sponsor notes that the decision to change the size of the study was based on a blinded assessment of mortal events.

The study randomized 2327 subjects to placebo and 2301 to dronedarone 400 mg BID. There were 551 study centers from 37 countries (Eastern and Western Europe, South America, North America, Middle East and Asia).

The disposition of subjects within the study and the demographics of those enrolled are shown below.

Figure 2: Disposition of subjects in the ATHENA study

Placebo	Dronedarone
Total Randomized N=4628	
Randomized N= 2327	Randomized N=2310
Completed study N=2325 Lost to follow-up N=2	Completed study N= 2301 Lost to follow-up N= 0
Completed on drug N= 1611 Discontinued drug but followed N=716 Reason for discontinuation: Adverse event N= 191 Poor compliance N= 14 Subject's request N=175 Other N =336	Completed on drug N= 1605 Discontinued drug but followed N=696 Reason for discontinuation: Adverse event N= 293 Poor compliance N= 14 Subject's request N=173 Other N=216

The demographics of those enrolled per sponsor are shown below:

Table 5: Demographics of those enrolled in the ATHENA study

Parameter	Placebo (n=2327)	Dronedarone (n=2301)
Age, years mean ± SD	72 ± 9.0	72 ± 8.9
Gender [male/female] (% female)	[1289/1038[(45%)	[1170/1131] (49%)
Race [Caucasian/black/Asian/Other] (%Caucasian)	[2072/31/154/70] (89%)	2065/19/150/70 (89%)
Cardiovascular history N (%)		
Hypertension	1996 (86%)	1999 (87%)
Structural heart disease	1402 (61%)	1330 (58%)
Tachycardia	797 (34%)	752 (33%)
Coronary heart disease	728 (31%)	661 (29%)
Non-rheumatic valvular heart disease	354 (15%)	331 (14%)
Pacemaker	243 (10%)	214 (9%)
Lone atrial fibrillation	139 (6%)	140 (6%)
Ischemic dilated cardiomyopathy	118 (5%)	92 (4%)
Ablation for AFib/AFl	106 (5%)	90 (4%)
Supraventricular tachycardia not AFib/AFl	98 (4%)	97 (4%)
Previous cardiac valve surgery	95 (4%)	80 (4%)
Non-ischemic dilated cardiomyopathy	84 (4%)	80 (4%)
Hypertrophic cardiomyopathy	50 (2%)	45 (2%)
Other history N (%)		
Hypercholestrolemia	1002 (43%)	1034 (45%)
Dyslipidemia	778 (33%)	756 (33%)
NIDDM	398 (17%)	423 (18%)
Chronic pulmonary disease	314 (14%)	297(13%)
Hypothyroidism	227 (10%)	263 (11%)
Malignant neoplasm	192 (8%)	165 (7%)
Embolic or thrombotic disease	159 (7%)	175 (8%)
Syncope	140 (6%)	154 (7%)
Hyperthyroidsm	100 (4%)	154 (7%)
Chronic renal failure	83 (4%)	85 (4%)
Other parameters N (%)		
Number of subjects in atrial fibrillation/flutter at randomization per stratification factor (%)	586 (25%)	569 (25%)
Left atrial diameter (2D –echocardiogram)	44 ± 7.0	44 ± 6.8
Left ventricular ejection fraction (%) 2-D echocardiogram	57 ± 11	57 ± 11
NYHA class III	109 (5%)	91 (4%)

There were some differences in the baseline demographic characteristics of the two groups. In particular, there were more females, less structural heart disease (coronary heart disease and/or dilated cardiomyopathy and/or non-ischemic dilated cardiomyopathy), less coronary heart disease, more hypercholestolemia, in the dronedarone treated group. The mean ejection fraction in this study was at 57%, there were few subjects who were NYHA class III and the overlap between this population and that of the ANDROMEDA study is likely minimal. Some concomitant therapies are shown below.

Table 6; Baseline medication for those enrolled in the ATHENA study N (%)

Beta blockers	1860 (80%)	1785 (78%)
ACE inhibitors/angiotensin II receptor antagonists	1800 (77%)	1771 (77%)
Oral anticoagulants	1643 (71%)	1601 (70%)
Spironolactone	136 (6%)	148 (6%)
Diuretics	1522 (65%)	1492 (65%)
Digitalis	574 (25%)	468 (20%)
Calcium antagonists (non-dihydropyridine)	490 (21%)	459 (20%)
Statins	1131 (49%)	1044 (45%)

Baseline medication seems reasonably well balanced between treatments. There were more subjects in the placebo group treated with beta blockers at baseline.

Before describing the outcome of the study, it is perhaps appropriate to describe how the information was captured. The following data were the entirety of the information collected as part of the CRF. The information that was collected was skeletal and forced a categorization that may not have been totally accurate.

Figure 3 : Case report form for hospitalization- ATHENA study

SR33589B
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Country No. | Centre No. | Subject No. | NO 801 Page | Hosp.number 04

VISIT 99 V 99 Subject initials

Please report only hospitalizations (i.e. admission with an overnight stay in hospital covering at least 2 consecutives dates) which, occur after randomization and that were not scheduled prior to randomization.

HOSPITALIZATION REPORT C.CLINHOSP_1

HOSPITALIZATION STATUS:

- Initial Hospitalization ☐
- Prolonged hospitalization due to a new event ☐
- Date of admission or date of decision to prolong hospitalization: ☐☐☐☐/☐☐/☐☐ (year / month / day)
- Number of nights in ICU/CCU: ☐☐
- In step down unit of medium care: ☐☐
- on ward or on floor: ☐☐
- **HOSPITALIZATION FOR CARDIOVASCULAR REASON?** ..... Yes ☐ No ☐

If YES, specify:

- Main cause for cardiovascular hospitalization (*please refer to the opposite page to report the appropriate code*): ☐☐
- Does the patient have left CHF? ..... Yes ☐ No ☐

If yes, specify NYHA class: I ☐ II ☐ III ☐ IV ☐

(*please refer to the opposite page of page 8 for NYHA classification*)

If NO, please complete an AE form and a SAE form (with the reason for non cardiovascular hospitalization as description) and forward the 3 forms at the same time.

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HOSPITALIZATION REPORT C.CLINCHSP_1

01. Atherosclerosis related (if not otherwise specified)
02. Myocardial infarction or unstable angina
03. Stable angina pectoris or atypical chest pain
04. Syncope
05. TIA or Stroke (except intracranial hemorrhage)
06. Atrial Fibrillation and other supraventricular rhythm disorders
07. Non-fatal cardiac arrest
08. Ventricular Arrhythmia
09. Cardiovascular surgery except cardiac transplantation
10. Cardiac Transplantation
11. Implantation of a pacemaker, ICD or any other cardiac device
12. Transcutaneous coronary, cerebrovascular or peripheral procedure
13. Blood pressure related (hypotension, hypertension; except syncope)
14. Cardiovascular infection
15. Major Bleeding (requiring two or more units of blood or any intracranial hemorrhage)
16. Pulmonary Embolism or deep vein thrombosis
17. Worsening CHF, including pulmonary edema or dyspnea of cardiac origin

Figure 4: Case report form for death- ATHENA Study

SR33589B
EFC5555

Country No. | Centre No. | Subject No. | NO 811 Page

VISIT 99 V 9 9 | Subject Initials

DEATH REPORT C.DEATH_1

- Date of death: ☐☐☐☐/☐☐/☐☐ (year / month / day)
- Was the patient still on treatment with investigational product at time of death? Yes ☐ No ☐
- DEATH FOR CARDIOVASCULAR REASON? ..... Yes ☐ No ☐

If Yes, specify:

- Main cause for cardiovascular death
  (please refer to the opposite page to report the appropriate code): ☐☐

If No, please complete an AE form and a SAE form (with the reason for non cardiovascular death as description) and forward the 3 forms at the same time.

Please complete the Final Follow-Up Visit

SR33589B
EFC5555

VISIT 99

DEATH REPORT C.DEATH_1

01. Aortic dissection / aneurysm
02. Cardiac tamponade
03. Cardiogenic shock
04. CHF
05. Death during a cardiovascular transcutaneous interventional procedure or cardiovascular surgical intervention
06. Hemorrhage (except cardiac tamponade)
07. Myocardial infarction or unstable angina (including complications of MI, except arrhythmias)
08. Pulmonary or peripheral embolism
09. Stroke
10. Sudden Cardiac Death (e.g. unwittnessed death or documented asystole)
11. Ventricular arrhythmia
12. Unknown cause

Figure 5: Case report form for worsening heart failure-ATHENA study

SR33589B
EFC5555

Country No. | Centre No. | Subject No. | XT | 805 Page

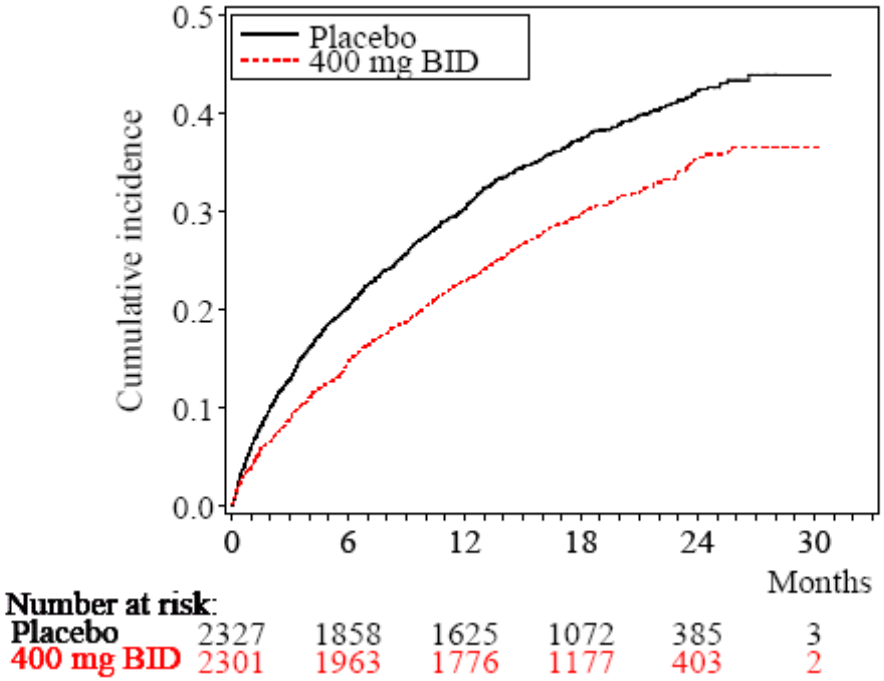
VISIT 99 V 99 Subject initials

WORSENING CHF COMPLEMENTARY HOSPITALIZATION REPORT HSCCHF_1

- Date of hospital admission or date of hospitalization prolongation: ____/__/__ (year / month / day)
- Onset Date: ____/__/__ (year / month / day)
- Were the characteristic symptoms or signs of CHF listed below present at hospital admission?
  - Shortness of Breath ..... Yes ☐ No ☐
    - If Yes, specify: - at rest ☐ - on exertion ☐
  - Orthopnea ..... Yes ☐ No ☐
  - Paroxysmal nocturnal dyspnea ..... Yes ☐ No ☐
  - Peripheral edema ..... Yes ☐ No ☐
  - Evidence of JVD (jugular vein distension) ..... Yes ☐ No ☐
  - Rales ..... Yes ☐ No ☐
- Radiologic evidence of pulmonary edema or congestion: Yes ☐ No ☐
- Echocardiography:
  - Date performed: ____/__/__ (year / month / day) - Left ventricular ejection fraction (LVEF) : __ %
- Did the patient have any of the following accompanying this event ? (Did this precede the Heart failure event?)
  - Pneumonia/Respiratory infection Yes ☐ No ☐ ➲ Yes ☐ No ☐
  - Other infections Yes ☐ No ☐ ➲ Yes ☐ No ☐
    - Specify : _____
  - Acute ischemic event Yes ☐ No ☐ ➲ Yes ☐ No ☐
  - Anemia Yes ☐ No ☐ ➲ Yes ☐ No ☐
  - Other precipitating cause Yes ☐ No ☐ ➲ Yes ☐ No ☐
    - Specify : _____
- Acute treatment given during hospitalization :
  - IV Diuretics Yes ☐ No ☐ - IV Nitrates Yes ☐ No ☐
  - IV Inotropes Yes ☐ No ☐ - Mechanical ventilation Yes ☐ No ☐

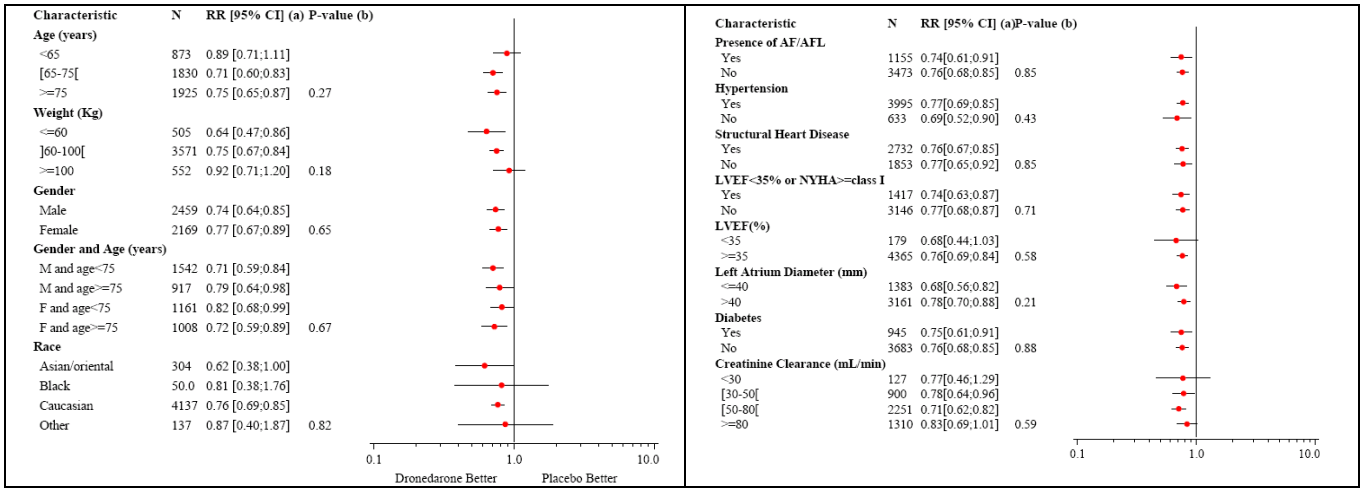
The primary metric of efficacy in the study was first episode of either cardiovascular hospitalization or death. The Kaplan-Meier curves for this metric are as per sponsor and are shown below. The difference between the two groups is highly significant (P<<0.0001). The relative risk comparing dronedarone to placebo was 0.76.

Figure 6: Kaplan-Meier cumulative incidence curves from randomization to first cardiovascular hospitalization or death from any cause-all randomized subjects

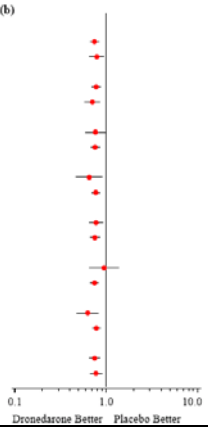


Forest plots for subgroup do not indicate any heterogeneity base on the following baseline demographic characteristics.

Figure 7: Forest plot based on baseline characteristics-ATHENA study



Characteristic	N	RR [95% CI] (a)	P-value (b)
ACE or AII receptor antagonists			
Yes	3216	0.74[0.66;0.83]	
No	1412	0.79[0.66;0.95]	0.59
Beta blocking agents			
Yes	3269	0.78[0.69;0.87]	
No	1359	0.71[0.58;0.86]	0.41
Digitalis			
Yes	629	0.76[0.59;0.98]	
No	3999	0.76[0.68;0.84]	0.96
Moderate/potent inhibitors of CYP3A4			
Yes	440	0.65[0.47;0.91]	
No	4188	0.77[0.69;0.85]	0.37
Statins metabolized by CYP3A4			
Yes	1492	0.77[0.66;0.91]	
No	3136	0.75[0.67;0.85]	0.77
Statins not metabolized by CYP3A4			
Yes	313	0.95[0.66;1.36]	
No	4315	0.75[0.67;0.82]	0.20
Calcium antagonists (c)			
Yes	638	0.63[0.48;0.82]	
No	3990	0.78[0.70;0.87]	0.15
Diuretics			
Yes	2492	0.75[0.66;0.85]	
No	2136	0.77[0.67;0.90]	0.76



(a) Determined from Cox regression model
(b) P-value of interaction between baseline characteristics and treatment based on Cox regression model

The Hazard ratio for the US sites was similar to the overall study effect Hazard ratio 0.81 [95% CI, 0.68, 0.96].

Secondary endpoints:
All cause mortality:

The primary secondary endpoint is all cause death. The sponsor notes that there were 139 deaths in the placebo group and 116 deaths in the dronedarone group. The sponsor's analysis indicates that this result was not statistically significant. The sponsor's analysis captures six deaths that occurred after the 12-month follow-up period. The last subject was enrolled on December 30, 2006. In essence all events occurring after December 29, 2007 should not have been included in this analysis. Of the additional six events which were captured after this cut-off date 5 were placebo-treated subjects and one a dronedarone-treated subject. Excluding these subjects there were 134 events in the placebo group and 115 in the dronedarone group. The Log-rank test p-value was 0.23.

Cause-specific mortality:

Since all-cause mortality was not significant and was the first secondary endpoint, all subsequent endpoints should be considered only as exploratory.

Before detailing the results for cause-specific mortality, it is appropriate to look at the CRF forms for cause-specific events. The concerns that are described here could be similarly applied the primary endpoint of cardiovascular hospitalizations plus all cause deaths. The results for the primary endpoint are so overwhelmingly positive, that it is unlikely that attributing a cardiovascular cause to the events would alter the conclusion.

For all cause mortality, however, since overall mortality was not significant, cause-specific mortality creates some problems. Let me first list the events that were so classified.

Table 7: Classification of cardiovascular or non-cardiovascular deaths in the ATHENA study

Classified as cardiovascular	Classified as non-cardiovascular.
Aortic dissection	Sepsis
Cardiogenic shock	Neoplasms
CHF	Asthenia
Death	Chronic obstructive pulmonary disease
Death during intervention	Hepatitis (cytolytic, toxic)
Hemorrhage	Influenza
MI unstable angina	Interstitial lung disease
Pulmonary peripheral embolism	Multi-organ failure
Stroke	Edema
Sudden death	Pneumonia
Unknown cause	Pulmonary fibrosis
Ventricular fibrillation.	Dementia
	Trauma (drowning , electrocution, crime, brain contusion)
	Renal failure
	Failure to thrive

I've highlighted those events that I think fit poorly in the category in which they are classified.

I have looked at several of the case report forms as well as narratives in an unblinded manner. The complete information available for writing the narratives was not available to this reviewer. The timing of the writing of the narratives relative to the time of unblinding of the study is not stated. I have only commented on a few cases, for which I think inconsistency was demonstrated. Since only a few reclassifications would alter the nominal significance of cardiovascular events these descriptions are of importance. Although it is possible that there would be equal and opposite questionable classifications in the opposite direction, which strengthen the contention that cardiovascular events are mitigated by the use of dronedarone, my intent was to show that the causal assessment has substantial problems.

Among those classified as cardiovascular were 12 individuals whose death was classified as unknown; 6 in each treatment. There was one subject whose death was classified as "death" also treated as cardiovascular (dronedarone). Some of these deaths, based on the death certificates (not submitted with the CRFs) are likely to be sudden cardiac deaths; others are possibly, some are truly unknown.

One subject #840106008 entered hospice care for Parkinson's disease, she was found dead. The death was attributed to a cardiovascular cause.

Hemorrhagic deaths were classified as cardiovascular deaths. This classification appears unreasonable. There were 11 such hemorrhagic deaths, 6 in the dronedarone- and 5 in the placebo-treated group. Some of these events may be hemorrhagic strokes, other are major bleeds unrelated to the cardiovascular system.

A subdural hematoma as a consequence of trauma was sometimes classified as a cardiac event other time a non-cardiovascular event. There was one subject among the dronedarone-treated subjects with an event termed "brain contusion" and not considered

a cardiovascular death. Below is the capsular summary of the two cases. I find the categorization of the event inconsistent. The information below was copied form the subject's narratives as written by the sponsor.

Subject number 246008008 (Treated with dronedarone –**classified as a brain contusion and not considered cardiovascular event**). This patient treated with low dose of aspirin and oral anticoagulant (international normalized ratio at 1.1), fell from his bicycle and became unconscious with profuse bleeding from nasopharynx, on Day 362. Skull fracture and large right subdural hematoma, massive edema of the brain with transtentorial and subfalcine herniation were observed on computed tomography scan. Furthermore he suffered from 3 rib fractures without pneumothorax. Despite poor prognosis, an emergency evacuation of subdural hematoma was performed. During this procedure the patient experienced an uncontrollable intracranial pressure increase leading to cerebral edema and the patient died the same day. No autopsy was performed.
Patient 528003011 treated with placebo (**treated as a cardiovascular event**). This patient, who was taking oral anticoagulants, was admitted to a Turkish hospital on Day 158 after falling and hitting his head during a visit to Turkey. The patient went into a coma due to subarachnoid and intracerebral bleeding, which was treated by a surgical decompensation. The investigational product was discontinued. On Day 169 the patient was transported back to the Netherland with a Glasgow coma scale of 6. Due to the poor (infaust) neurological prognosis, it was decided that neither resuscitation nor readmittance to the intensive care unit should be done in the future. The patient died in the hospital as a consequence of the initial event on Day 201.

One subject (in the dronedarone group) with a death defined as "edema" was classified as a non-cardiovascular death. The case report form however classified the subject as cardiovascular non-arrhythmic event. This subject should be classified as a cardiovascular death.

Patient 32012003 treated with dronedarone not counted as a cardiac death. This patient complained of vomiting, asthenia and anorexia leading to hospitalization and investigational product discontinuation on Day 156 (last intake). On admission, the patient presented with severe edema including ascites, hepatomegaly and pleural effusion. Despite a corrective treatment with furosemide and albumin the patient's status worsened and required assisted ventilation. On Day 190, the patient experienced bradycardia with cardiac arrest leading to death. The etiology of the ascites-edema syndrome was never established. No autopsy was performed.

There were 8 subjects who died due to pneumonia. In a cardiovascular at-risk population, the underlying cardiovascular disease is often the disease responsible. In at least several cases, the capsular summary sites the chest X-ray report as indicating pulmonary consolidation cannot rule-out failure. These subjects were classified as non-cardiac.

Respiratory failure was sometimes classified as non-cardiac. For example, subject 840135009, a dronedarone-treated patient, was admitted on (b) (4) for an aortic aneurism repair. The patient, while still ventilator dependent apparently had an exacerbation of COPD. The patient died. The cause of death was not attributed to a cardiovascular event (aneurism repair) but to respiratory failure.

There were 6 patients whose deaths were attributable to renal disease (either acute or chronic). Renal-related deaths may often be attributable to the underlying cardiovascular disease.

Dr. Freidlin calculated that if four placebo-treated patients had their CV deaths reclassified as non-cardiac (based on changing the cause nature of some of those assessed as unknown cause), the p-value would not be significant. As I noted above, there were 6 deaths that occurred after the nominal cut-off date, three in the placebo group were classified as cardiovascular; the one death in the dronedarone group was classified as non-cardiovascular.

The ostensible reason for categorizing the underlying cause of the deaths is to remove the noise that is engendered in capturing all causes of death. In this manner deaths that are non-preventable by antiarrhythmic therapy would not taint the prevention signal. What I am finding is that the inconsistency in the characterization of mortal events. The characterization of deaths adds a different form of noise. Given the small wiggle room, I don't see an analysis of cardiovascular mortality as convincing.

With respect to the steering committee's characterization of cardiovascular death, the table below shows their assessment.

Table 8: Characterization of cardiovascular death by the Steering Committee-ATHENA study

Type of death	Placebo	Dronedarone
Cardiovascular deaths	94	65
Aortic dissection aneurism	0	1
Congestive heart failure	10	13
Cardiogenic shock	2	5
Death during cardiac interventional procedure or cardiovascular surgical procedures	2	0
Hemorrhage (except cardiac tamponade)	5	6
Myocardial infarction or unstable angina	7	5
Pulmonary or peripheral embolism	6	2
Stroke	18	11
Sudden cardiac death	35	14
Unknown cause	6	6
Ventricular fibrillation	2	2
Ventricular tachycardia	1	0

Of note, there were substantially more neoplasms-related deaths in the dronedarone relative to the placebo group (25 versus 14).

Hospitalization for cardiovascular reasons:

The third and subordinate secondary endpoint was time to first cardiovascular hospitalization. The results are shown below. There was clearly a decrease in the rate of first cardiovascular hospitalization in the dronedarone group (N=675) compared to the placebo group (N=859). The nominal Hazard ratio and confidence intervals are 0.75 (0.68, 0.82). The specific reasons for hospitalization are shown below.

Table 9: Reason for first hospitalization in the ATHENA study

	Placebo (N=2327)	Dronedarone (N=2301)	HR (95%CI)[+]
Any Hospitalization	859 (37%)	675 (29%)	0.75 (0.67, 0.82)
Atrial fibrillation and other supraventricular rhythm disorders	457 (20%)	296 (13%)	0.62 (0.53,0.71)
Worsening heart failure, including pulmonary edema or dyspnea of cardiac origin	92 (4%)	78 (3%)	0.80 (0.6, 1.09)
Myocardial infarction or unstable angina	61 (3%)	48 (2%)	0.74 (0.51, 1.08)
Stable angina pectoris or atypical chest pain	41 (2%)	45 (2%)	1.04 (0.69, 1.6)
TIA or stroke (except intracranial hemorrhage)	35 (2%)	28 (1%)	0.75 (0.5, 1.5)
Transcutaneous coronary, cerebrovascular or peripheral procedure	31 (1%)	27 (1%)	0.82 (0.5, 1.4)
Implantation of a pacemaker, ICD or any other device	29 (1%)	32 (1%)	1.04 (0.6, 1.7)
Major bleeding (requiring two or more units of blood) or intracranial hemorrhage	24 (1%)	21 (1%)	0.82 (0.45, 1.5)
Syncope	24 (1%)	21 (1%)	0.83 (0.5, 1.5)
Cardiovascular surgery except cardiac transplantation	23 (1%)	21 (1%)	0.85 (0.5, 1.54)
Blood pressure related (hypotension-except syncope), hypertension	21 (1%)	21 (1%)	0.95 (0.5, 1.74)
Atherosclerosis-related (if not otherwise specified)	8 (< 1%)	11 (< 1%)	1.3 (0.5, 3.2)
Ventricular tachycardia (non-sustained and sustained)	6 (< 1%)	6 (< 1%)	0.95 (0.31, 2.96)
Pulmonary embolism or deep vein thrombosis	3 (< 1%)	10 (<1%)	3.2 (0.9,11.5)
Non fatal cardiac arrest	2 (<1%)	3 (<1%)	1.4 (0.2, 8.7)
Ventricular extrasystoles	1 (< 1%)	1 (<1%)	0.97 (0.06,15.6)
Ventricular fibrillation	1 (< 1%)	1 (<1%)	0.94 (0.06-15.1)
Cardiovascular infection	0	4 (0.2%)	????
Other ventricular arrhythmias	0	1 (< 1%)	????

[+] Nominal values

Nearly all the benefit in hospitalization is attributable to the decrease in atrial fibrillation hospitalizations. There was no specific case report form for atrial fibrillation hospitalization to further assess the underlying provocative symptoms.

With respect to heart failure hospitalizations, there were numerically more individuals who were hospitalized in the placebo group compared to the dronedarone group. Although the number of subjects hospitalized for CHF was numerically greater in the placebo group, the nature of the interventions required were more aggressive in the dronedarone group. Fewer subjects in the placebo group required any treatment including diuretics. Numerically more dronedarone groups were treated with IV nitroglycerin or inotropes. The number of subjects with class IV at any time was somewhat higher in the placebo group.

Table 10: Characterization of heart failure events- ATHENA study

Parameter	Placebo (N=2327)	Dronedarone (N=2301)
Number of subjects	130	112
Number of events	188	166
Interventions:		
None	40	26
Required diuretics	138	135
IV nitroglycerin	22	26
Inotropes	18	25
Mechanical ventilation	7	7
NYHA class IV at any time	52	41

Safety:

Duration of exposure:

The duration of exposure is shown below:

Table 11: Duration of safety exposure- ATHENA study

	Placebo(N=2327)	Dronedarone (N=2301)
Mean duration of exposure ± SD, days	485 ± 249	483 ± 254
Total patient-years	3071	3031

Deaths:

Deaths were captured above.

Discontinuations:

The reason for the temporary or permanent discontinuation of therapies (> 10 subjects in either group) is shown below and derived form sponsor's Table 37.

Table 12: Reason for drug discontinuation-ATHENA study (≥ 10 events in either treatment)

	Placebo (N=2313)	Dronedarone (N=2291)
Any	187 (8%)	290 (13%)
Gastrointestinal disorders	44 (2%)	90(4%)
Diarrhea	11 (< 1%)	37 (2%)
Nausea	6 (< 1%)	26 (1%)
Investigations	22 (1%)	58 (3%)
QT prolonged (electrocardiogram)	12 (1%)	33 (1%)
Blood creatinine increased	2 (<1%)	16 (1%)
General disorders and administration site conditions	26 (1%)	27 (1%)
Fatigue	5 (< 1%)	11(<1%)
Skin and subcutaneous disorders	13 (1%)	27 (1%)
Nervous system disorders	18 (1%)	25 (1%)
Dizziness	7 (< 1%)	11 (< 15)
Cardiac disorders	13 (1%)	23 (1%)
Bradycardia	1 (<1%)	10 (< 1%)
Musculoskeletal and connective tissue disorders	13 (1%)	16 (1%)
Respiratory and mediastinal disorders	16 (1%)	15 (1%)
Dyspnea	(<1%)	8 (< 1%)
Neoplasms benign and unspecified	8 (< 1%)	13 (1%)
Psychiatric disorders	10 (< 1%)	6 (< 1%)

There were more drug discontinuations in the dronedarone group largely manifest as by gastrointestinal events; in particular more subjects diarrhea. Cardiac events which led to discontinuation included QT prolongation and bradycardia.

Overall adverse events are shown below:

Table 13; Adverse events in the ATHENA study (≥2% events in any treatment)

	Placebo	Dronedarone
Any event	**1603 (69%)**	**1649 (72%)**
Gastrointestinal disorders	**508 (22%)**	**600 (26%)**
Diarrhea	**144 (6%)**	**223 (10%)**
Nausea	**72 (3%)**	**122 (5%)**
Vomiting	**27 (1 %)**	**49 (2 %)**
Infections and infestations	582 (25%)	542 (24%)
Urinary tract infections	64 (3%)	74 (3%)
Upper respiratory tract infections	83 (4%)	70 (3%)
Nasopharyngitis	75 (3%)	69 (3%)
Bronchitis	72 (3%)	67 (3%)
Pneumonia	71 (3%)	50 (2%)
General disorders and administrative site conditions	**356 (15%)**	**403 (18%)**
Edema peripheral	**119 (5%)**	**147 (6%)**
Fatigue	**90 (4%)**	**115 (5%)**
Asthenia	**47 (2%)**	**68 (3%)**
Chest pain	55(2%)	52(2%)
Musculoskeletal and connective tissue disorders	396 (17%)	381 (17%)
Back pain	80 (4%)	73 (3%)
Arthralgia	62 (3%)	64 (3%)
Pain in extremity	44 (2%)	50 (2%)
Nervous system disorder	381 (17%)	373 (16%)
Dizziness	146 (6%)	161 (7%)
Headache	84 (4%)	70 (3%)
Respiratory, thoracic and mediastinal disorders	337 (15%)	332 (15%)
Dyspnea	**97 (4%)**	**120 (5%)**
Cough	83 (4%)	83 (4%)
Investigations	206 (9%)	309 (13%)
Blood creatinine increased	31 (1%)	108 (5%)
INR increased	47 (2%)	48 (2%)
Cardiac disorders	**221 (10%)**	**260 (11%)**
Bradycardia	**28 (1%)**	**81 (4%)**
Skin and subcutaneous tissue disorders	**176 (7%)**	**237 (10%)**
Rash	**37 (2%)**	**60 (3%)**
Injury poisoning and procedural complications	227 (10%)	219 (10%)
Fall	70 (3%)	69 (3%)
Metabolism and nutrition disorders	203 (9%)	186 (8%)
Hypokalemia	62 (3%)	40 (2%)
Vascular disorders	193 (8%)	182 (8%)
Hypertension	89 (4%)	82 (3%)
Renal and urinary disorders	118 (5%)	116 (5%)
Eye disorders	106 (5%)	115 (5%)
Psychiatric disorders	131 (6%)	111 (5%)
Neoplasms benign and unspecified	118 (5%)	105 (5%)
Reproductive system and breast disorders	57 (3%)	61 (3%)
Ear and Labyrinth	70 (3%)	56 (3%)
Blood and lymphatic systems	65 (3%)	47 (2%)

The main differences suggesting an increase in adverse events in the dronedarone group are bolded. Gastrointestinal disorders were increased in the dronedarone treated subjects. Of note, is that among the events that are more prevalent in the dronedarone group are symptoms often associated with worsening heart failure including peripheral edema, dyspnea, fatigue and asthenia. Bradycardia was much more frequent in the dronedarone treated subjects. Among investigations there was an increase in the incidence of QT prolongation and bradycardia.

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/s/

Abraham Karkowsky
2/19/2009 08:43:45 AM
MEDICAL OFFICER

CLINICAL and STATISTICAL REVIEW

Application Type	NDA
Submission Number	22-425
Submission Code	N 000
Letter Date	June 27, 2008
Stamp Date	
PDUFA Goal Date	April 30, 2009
Reviewers Names	Gail Moreschi, MD, MPH, FACP Valeria Freidlin, Ph.D.
Review Completion Date	February 18, 2009
Established Name	Dronedarone hydrochloride
(Proposed) Trade Name	Multaq
Therapeutic Class	Antiarrhythmic drug
Applicant	Sanofi-Aventis, U.S.
Priority Designation	P
Formulation	Tablets
Dosing Regimen	400 mg twice a day
Indication	Prevention of CV Hospitalization & Death
Intended Population	Patients with AF/AFL

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1 EXECUTIVE SUMMARY

The ATHENA Study in this NDA 22-425 is a large multinational study in patients with atrial fibrillation/atrial flutter (AF/AFL) intended to provide a reassurance of dronedarone safety in contrast to the prior ANDROMEDA study (NDA 21-913) which showed statistically significantly (25 vs. 12, p=0.027) increased death rate in patients on dronedarone. In ATHENA, the primary composite endpoint of death from any cause or CV hospitalization was highly statistically significant. However, the dronedarone efficacy in the prevention of death from any cause was not established (p=0.176). The composite endpoint was driven mostly by the other component, CV hospitalizations. Note that the need to hospitalize these patients varies from physician to physician and country to country. Most importantly, the study investigates a population which is different from the ANDROMEDA Study, the patients in this ATHENA trial were not as sick as those in the ANDROMEDA Study.

Relative to a claim for preventing CV death in ATHENA study, there are some important issues.

1. According to the pre-specified hierarchical procedure to control global type 1 error at the 5% level, the secondary efficacy endpoint of CV death can be tested only if the first secondary endpoint, death from any cause, is statistically significant at the 5% level. As death from any cause was not statistically significant (p=0.176), the secondary endpoint of CV death should not be tested at all. The analysis for CV death is shown in this review only as exploratory for the completeness of clinical evaluation.

2. There are some issues with the reliability of classifications of CV deaths and the robustness of p=0.03 for the CV death.

For example, in ATHENA, 12 patients with unknown cause of death were classified as having CV death. If 6 placebo patients with unknown cause of death are reclassified as having non-CV death, then the analysis of CV death in ATHENA becomes non-significant: p=0.07 (log-rank test) or p=0.09 (Wilcoxon test). Even if only 4 placebo patients with unknown cause of death are reclassified as non-CV death, then the analysis for CV death in ATHENA already becomes non-significant: p=0.05 (log-rank test) or p=0.065 (Wilcoxon test).

In the ATHENA Study, with a nominal p-value of only p=0.03 for CV mortality and many other issues mentioned above, the statistical significance based on this p-value is inconclusive and may be due to data dredging. Therefore, an additional study is needed to determine whether this finding is real.

Given the risk of death discrepancy between ANDROMEDA and ATHENA studies, these reviewers are concerned regarding the safety of dronedarone. There is a continuum in patients with AF/AFL, they go in and out of congestive heart failure. We feel that the safety of dronedarone presents a problem that the label alone may not be able to cover. The prior studies in NDA 21-913 for rhythm and rate control did establish that patients stay in normal sinus rhythm a little longer than placebo, but their heart rate on dronedarone when exercising is not within the ACC Guidelines.

1.1 Recommendation on Regulatory Action

To be decided after Advisory Committee Meeting March 18, 2009.

1.2 Recommendation on Postmarketing Actions

To be decided after Advisory Committee Meeting March 18, 2009.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This was a prospective, multinational, multicenter, double-blind, randomized, placebo-controlled, parallel-group Phase 3 study to evaluate the effects of dronedarone 400 mg BID versus placebo (ratio 1:1) over a minimum treatment and follow-up duration of 12 months in AF/AFL patients. A total of 4300 patients were to be randomized; ultimately, however, 4628 patients were randomized. All patients were to have documentation of at least 1 risk factor together with documentation of having been in both AF/AFL and sinus rhythm within the last 6 months preceding inclusion.

1.3.2 Efficacy

The primary endpoint in NDA 22-425, the composite of death from any cause or CV hospitalization, was highly statistically significant. However, the efficacy of the prevention of death from any cause was not established (p=0.176). The composite endpoint was driven mostly by the other component, CV hospitalizations. Note that the need to hospitalize these patients varies from physician to physician and country to country. Most importantly, the study investigates a population which is different from the prior ANDROMEDA Study, NDA 21-913, which had a statistically significantly (25 vs. 12, p=0.027) higher rate of death from any cause in the patients on dronedarone. Also, the patients in this ATHENA trial were not as sick as those in the prior ANDROMEDA Study.

1.3.3 Safety

Hospitalizations and death were evaluated as part of efficacy. The same side effects were seen as in NDA 21-913: gastrointestinal disorders, EKG QT prolongation, and increased blood serum creatinine. The population evaluated in this NDA was very different from the earlier, sicker population in the ANDROMEDA Study. Of great concern, is that patients in AF/AFL will go into heart failure; they may not do well if on dronedarone as shown in the ANDROMEDA Study.

This drug, if approved, will be utilized chronically. We do not know if ultimately patients will develop the side effects as seen with amiodarone or if they will develop the endocrine, teratogenicity, and carcinogenicity problems as seen in the animal models described in Dr. Hausner's review.

1.3.4 Dosing Regimen and Administration

The sponsor has proposed that the dronedarone dosage is 400 mg twice daily and is to be given with the morning and evening meal. The Agency recommended to the Sponsor early in the development program that various doses be available.

According to Dr. Kumi's original review for NDA 21-913, healthy elderly males have exposures that are about 40 % higher relative to healthy young males; elderly females have exposures that are approximately 30 % higher relative to elderly males; and healthy Asian (Japanese) males have exposures that are about 100 % higher relative to healthy male Caucasians. Also, Dr. Kumi stated in his earlier review that a clear dose-response relationship was shown for QT prolongation in healthy subjects.

1.3.5 Drug-Drug Interactions

The following table is from Dr. Kumi's original review for NDA 21-913.

Table 1: PK/PD drug-drug interaction information

Drug	Classification	Effect of co-administration		
		PD (either or both drugs)	Dronedarone	Other Drug
	Miscellaneous			
digoxin	PGP substrate	NA	NA	↑ 2.5 fold
pantoprazole	decrease gastric pH	NA	↔	NA
theophylline	CYP1A2 substrate	NA	↔	↓ 20 %
	CYP3A function			
rifampicin	inducer	None	↓ 80 %	NA
dilitiazem	weak inhibitor	↑ repolarization time	↑ 60 %	NA
nifedipine	weak inhibitor	Lowered blood pressure	↑ 20 %	NA
grapefruit juice	moderate inhibitor	NA	↑ 3-fold	NA
ketoconazole	strong inhibitor	↑ PR, no effect on QT	↑ ≥ 9-fold	NA
verapamil	Substrate, inhibitor	↑ repolarization time	↑ 40 %	↑ 40 %
nisoldipine	substrate	↔	↔	↑ 100 %
simvastatin	substrate	↔	↔	↑ 4-fold
ethinylestradiol	substrate	NA	NA	↑ 25 %
levonorgestrel	substrate	NA	NA	↑ 18 %
	CYP2C9 function			
losartan	substrate	↑ heart rate	↔	↔
S-warfarin/R-warfarin	substrate	↑ INR by 7 %	↔	↑ AUC 11 %
	CYP2D6 function			
metoprolol	Substrate	↓ cardiac contractility	NA	↑ 60 -150 %
propranolol	substrate	↓ HR, DBP, SBP	↔	↑ 16 to 33 %

1.3.6 Special Populations

Dronedarone has not been studied in the pediatric population. It is contraindicated with Class 4 and probably Class 3 patients in congestive heart failure (CHF). Also, patients with severe liver failure probably should not take dronedarone.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Dronedarone hydrochloride was previously submitted to the FDA as NDA 21-913 in June 2005 for rhythm and/or rate control in patients with atrial fibrillation/flutter. In this earlier submission the Sponsor included five studies for efficacy: DAFNE, ERATO, ADONIS, ERUIDIS and ANDROMEDA. The DAFNE study was dose ranging in which doses greater than 400 mg twice a day did not provide additional efficacy. However, the Agency as early as 1999 advised the Sponsor to provide a dose range rather than a fixed dose; the Sponsor has chosen not to. In the ERATO study, for rate control, the patients with symptomatic permanent atrial fibrillation on dronedarone showed no improvement over placebo in an exercise test.

In the two pivotal studies of NDA 21-913, ADONIS and ERUIDIS, the primary endpoint was rhythm control with the symptoms documented with ECGs relayed via a transtelephonic device. These studies demonstrated that patients taking dronedarone remain longer in normal sinus rhythm compared to placebo; however, their ventricular rate was not lowered to a clinically acceptable range when they reverted to AF/AFL. The studied population was young and in relatively good health. (A substudy, which has not been reviewed, in the current ATHENA trial, revealed no difference in symptoms in patients on dronedarone or placebo).

The ANDROMEDA study in NDA 21-913 investigated patients with a previous episode of "severe" congestive heart failure (CHF). Death and hospitalizations were the clinical endpoints and dronedarone statistically significantly ($p = 0.027$) increased the risk of death from any cause (more than doubled this risk by 113%) and also dronedarone increased ($p = 0.024$) the risk of hospitalizations for acute cardiovascular reasons as compared to placebo. The ANDROMEDA study was terminated early because of this increase in mortality. The Sponsor received a Not Approvable letter on August 26, 2006, which stated "Conceivably, a study of substantial size in the target population could provide reassurance."

This current NDA 22-425 presents the ATHENA Study that was conducted as an outcome study to answer the high mortality rate seen in the ANDROMEDA study. However, the population studied is quite different which will be discussed in our review.

2.2 Currently Available Treatment for Indications

Currently there are no available pharmacological treatments approved for the prevention of hospitalizations and death in patients with atrial fibrillation and atrial flutter. However, there are medications and procedures for AF/AFL that have not been compared to dronedarone in large prospective trials for the prevention of hospitalizations and death in this population.

2.3 Availability of Proposed Active Ingredient in the United States

Dronedarone is a new molecular entity and is not currently available in the United States and is not marketed in any other country.

2.4 Important Issues With Pharmacologically Related Products

The parent compound, amiodarone, originally marketed as an antianginal agent because of its coronary vasodilator properties, was observed to have potent antiarrhythmic effects. It was approved in 1985 for ventricular arrhythmias. Although amiodarone is not FDA approved for AF/AFL, it is clinically utilized for this indication and appears safe for patients with congestive heart failure (CHF). However, the use of amiodarone may have significant adverse reactions which include pulmonary toxicity, thyroid dysfunction, corneal deposits, and phototoxicity.

2.5 Presubmission Regulatory Activity

Please refer to the original NDA 21-913.

2.6 Other Relevant Background Information

NA

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

This review is not available at this time.

3.2 Animal Pharmacology/Toxicology

Dr. Elizabeth Hausner in her review cites the possible endocrine and carcinogen effects of dronedarone. Regarding the endocrine effects: “There were changes in circulating hormone levels, sometimes statistically significant, in both rats and dogs.” Also, Dr. Hausner states that the Sponsor agrees with her that the dronedarone is teratogenic and that it has an effect on female cyclicity. These issues the Sponsor states are addressed in the clinical section of this NDA. However, as the Medical Reviewer, I am unable to locate the information the Sponsor refers to. Additionally, there are

histiocytic sarcoma in male mice, mammary adenocarcinomas in female mice and hemangiomas in male rats which are drug related.

The above findings present a clinical concern as this drug, if approved, will be utilized on a chronic basis.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The only clinical trial, the ATHENA Study, was submitted electronically, reviewed and presented here.

4.2 Tables of Clinical Studies

There was only one new clinical trial, the ATHENA study, submitted for review in this NDA

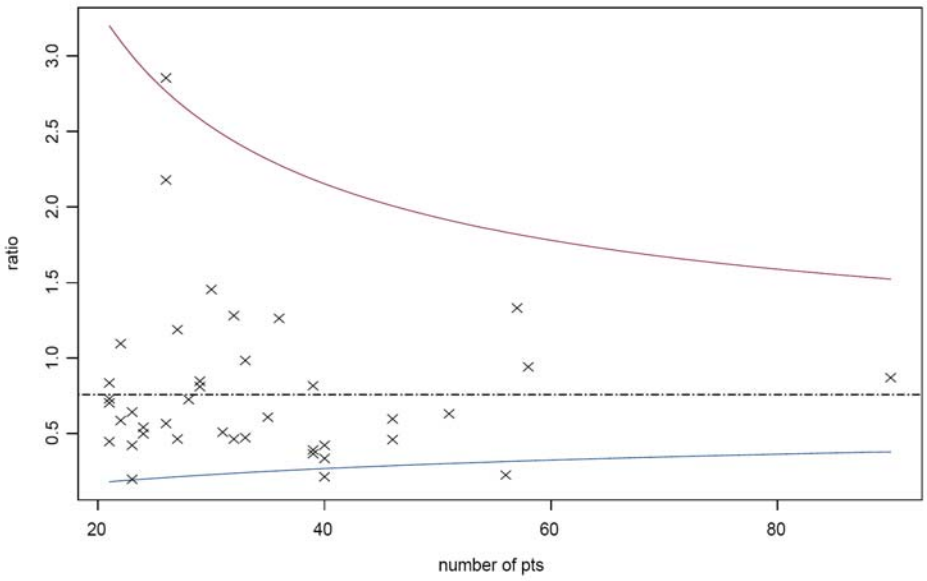
4.3 Review Strategy

This was a joint review done by Dr. Freidlin and Dr. Moreschi together.

4.4 Data Quality and Integrity

Dr. Freidlin did a funnel plot for relative risk for the primary endpoint by center which is shown below.

Figure 1: FDA Analysis of ATHENA Primary Efficacy Results by Large Centers with 95% CI



A large majority of the centers in the trial were outside the United States. The three centers that were recommended for Division of Scientific Investigations' inspection were outliers having outstanding results. The three sites which were inspected were:
1. Site # 203002; Dr. Vratislav Dedek, Czech Republic (N=56, RR=0.22, P=0.03)
2. Site # 643010; Dr. Yuri Shubik, St-Petersburg, Russia (N=23, RR=0.20, p=0.1)
3. Site # 643036; Dr. Vladimir Barbarich, Novosibirsk, Russia (N=40, RR=0.21, p=0.004)

In general, all three sites adhered to the applicable FDA regulations and Good Clinical Practice Guidelines. The study at these sites appears to have been conducted adequately, and the data generated by these sites could be used in support of the indication.

4.5 Compliance with Good Clinical Practices

There is no reason known to these reviewers to doubt that the ATHENA trial was performed under acceptable ethical standards and with Good Clinical Practice.

4.6 Financial Disclosures

The following Clinical Investigators had disclosable financial interests:
1. Dr. Kurt Huber, a Principal Investigator participating in the ATHENA Study, has received payments for speaking fees totaling $ (b) (4).

2. Dr. Hans-Jürgen Rupprecht, a Principal Investigator participating in the ATHENA Study, has received payments for training fees, consulting fees, and speaking fees totaling $ (b) (4).

3. Dr. George Massing, a Subinvestigator participating in the ATHENA Study, has stock holdings totaling more than (b) (4)

4. Dr. George Eyrich, a Subinvestigator participating in the ATHENA Study, has stock holdings totaling more than (b) (4).

5. Dr. Gerald Naccarelli, a Principal Investigator participating in the ATHENA Study, has received payments for Honoraria and consulting engagements totaling $ (b) (4).

6. Dr. Albert Waldo, a Subinvestigator participating in the ATHENA Study, has received payments for Honoraria and consulting engagements totaling (b) (4).

7. Dr. Eric Prystowsky, a Principal Investigator participating in the ATHENA Study, has received payments for Honoraria and consulting engagements totaling (b) (4).

8. Dr. Marc Cohen, a Subinvestigator participating in the ATHENA Study, has received payments for Honoraria and consulting engagements totaling (b) (4).

There are five Investigators whose financial disclosure information is missing or incomplete.

5 CLINICAL PHARMACOLOGY

According to Dr. Kumi's review, the new information in this NDA included studies in liver and renal impaired patients. Dr. Kumi recommended that patients with moderately impaired hepatic function should be monitored closely for adverse events and that dronedarone should be contraindicated in patients with severe hepatic impairment unless there is clinical experience. In the study in renal impaired patients, dronedarone plasma concentrations were similar in all patients. Also, creatinine plasma concentrations increased over the first three days, peaking on Day 5. Creatinine plasma concentrations decreased to baseline level three days after treatment was discontinued. The magnitude of creatinine changes was independent of the renal function.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

In the original NDA 21-913, the primary indication was the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of AF/AFL. The secondary objectives included the efficacy on AF/AFL related symptoms and ventricular rate control in case of AF/ AFL recurrence. In this NDA 22-425, the indication is preventing cardiovascular hospitalizations or death from any cause in a population of high risk patients with AF/AFL.

6.1.1 Methods

One study, the ATHENA trial, was submitted in this NDA.

6.1.2 General Discussion of Endpoints

In the prior ANDROMEDA Study, the reduction of death from any cause or hospitalizations for worsening heart failure was investigated, but in patients with recent severe congestive heart failure (CHF). The ANDROMEDA study was terminated early because of an increase in mortality. This present study, the ATHENA Study, was the prevention of cardiovascular hospitalization or death from any cause in patients with AF/AFL. Therefore, the endpoints in these two important trials are different.

6.1.3 Study Design

Study Title: A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter (AF/AFL) (ATHENA Study). (Study EFC5555)

Study centers: 551 active centers in 37 countries: Argentina, Australia, Austria, Belgium, Canada, Chile, China, Czech Republic, Finland, Germany, Greece, Hong Kong, Hungary, India, Israel, Italy, Malaysia, Mexico, Morocco, Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Republic of Korea, Russia, Singapore, South Africa, Spain, Sweden, Taiwan, Thailand, Tunisia, Turkey, United Kingdom, United States of America

Principal Investigator: Stefan Hohnloser, MD, J. W. Goethe University, Department of Cardiology, Frankfurt, Germany

Study dates: June 29, 2005 to March 5, 2008

Objectives:
Primary: To assess the efficacy of dronedarone in preventing cardiovascular hospitalizations or death from any cause in a population of high risk patients with AF/AFL.
Secondary: To assess that dronedarone is well-tolerated in this population.

Committees:
1. **The Steering Committee** consisted of 5 cardiologists who:
• provided advice on the scientific and clinical aspects of the study protocol
• had responsibility for the execution and scientific reporting of the study
• had responsibility for the conduct of the study according to good clinical practice
• reassessed the benefit/risk ratio of the Data Monitoring Committee recommendations
• resolved policy issues
• classified all deaths to 4 groups: cardiac/arrhythmic, cardiac/nonarrhythmic, vascular/noncardiac, nonvascular (Protocol Amendment 3)

The **Protocol Amendment 3** dated January 5, 2007 included:
a. Assessment of symptoms using the Bubien and Kay symptom checklist as a substudy.
b. The Steering Committee was recommended to classify all deaths for descriptive purpose as:
• Cardiac, arrhythmic
• Cardiac, nonarrhythmic
• Vascular, noncardiac
• Nonvascular

Reviewer's comment:
It is not clear from this amendment which was dated late into the commencement of the study whether the deaths which had proceeded were described or not. To describe deaths into 1 of 4 categories is different from the adjudication of deaths by a committee as was done in the ANDROMEDA Study.

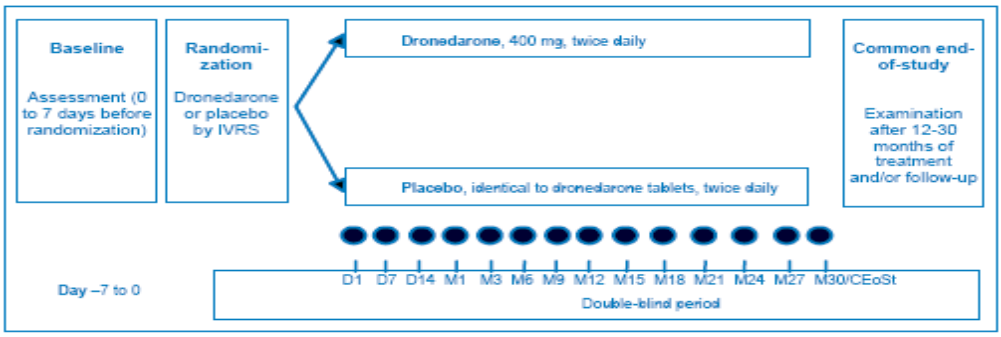
2. **Data Monitoring Committee** consisted of 2 cardiologists and a biostatistician. They performed the ongoing monitoring to provide:
• The safety of patients in the clinical trial
• The ethical conduct of the trial
• Ensure the highest integrity of the trial
• Oversee the interim analysis
• Carry out a review of efficacy and safety data at regular intervals
• Request additional data and/or review meetings as necessary
• Make recommendations to the Steering Committee concerning the conduct of the study

The S-Clinica Randomization Center, Brussels, Belgium, provided randomization of the patients and management of the study drugs.

Study Description: This was a prospective, multinational, multicenter, double-blind, randomized, placebo-controlled, parallel-group Phase 3 study to evaluate the effects of dronedarone 400 mg BID versus placebo (ratio 1:1) over a minimum treatment and follow-up duration of 12 months in AF/AFL patients. A total of 4300 patients were to be randomized. All patients were to have documentation of at least 1 risk factor together with documentation of having been in both AF/AFL and sinus rhythm within the last 6 months preceding inclusion.

Patients could be randomized in the study while in sinus rhythm if conversion had occurred either spontaneously or following a procedure. Patients could also be randomized while in AF/AFL, and then they could undergo cardioversion after appropriate anticoagulation. Patients first entered a screening period for a maximum of 7 days. After randomization they were to be followed until the common study end date, which was to be 1 year after the last patient was randomized and therefore the minimum follow-up time was to be 12 months.

Fig. 2: Study design



Patients were allocated to dronedarone 400 mg BID or placebo according to a central randomization. A placebo was selected by the Sponsor because of the absence of a recognized first-line therapy for the prevention of cardiovascular hospitalization or death in AF/AFL patients.

Medical Reviewer's comment:
Although there are no "first-line therapies" approved explicitly for the prevention of hospitalization or death in AF/AFL patients, there are approved medications and procedures which may prevent hospitalizations and death in these patients. This relatively large study may have been a missed opportunity for a comparative-research study which is in demand today.

Inclusion criteria:
Patients could be either in sinus rhythm, or in AF/AFL to be eligible. Originally, the following criteria had to be fulfilled:
1. One or more of the following risk factors must be present at baseline:
Age equal to or greater than 70 years

Hypertension (taking 2 different classes of drugs)
Diabetes
Prior cerebrovascular accident or systemic embolism
Left atrium diameter greater than or equal to 50 mm by M-mode echocardiography
Left ventricular ejection fraction less than 0.40 by 2D-echocardiography
2. Availability of 1 ECG within the last 6 months showing that the patient was or is in AF/AFL
3. Availability of 1 ECG within the last 6 months showing that the patient was or is in sinus rhythm

Reviewer's comment:
The patients' EKGs were not provided with the case report forms in this NDA.

The Steering Committee recommended an increase in the minimum age for recruitment, and an increase in the threshold for age as an additional risk factor, in order to prevent a lowering of the event rate and to better match the baseline characteristics of the ATHENA patients with those of studies of the AFFIRM study. Accordingly, in Amendment 1 approved on March 8, 2006 (when 1993 patients had been randomized) and was to be implemented on March 25, 2006, the inclusion criteria were changed to:
1. Patients aged 75 years or older are eligible with or without additional risk factors
Or
A minimum age of 70 years with one or more of the following risk factors must be present at baseline:
Hypertension (taking antihypertensive drugs of at least 2 different classes)
Diabetes
Prior cerebrovascular accident (stroke or transient ischemic attack) or systemic embolism
Left atrium diameter greater than or equal to 50 mm by M-mode echocardiography
Left ventricular ejection fraction less than 0.40 by 2D-echocardiography
2. Availability of one 12-lead ECG within the last 6 months, showing that the patient was or is in AF/AFL
3. Availability of one 12-lead ECG within the last 6 months showing that the patient was or is in sinus rhythm

Reviewer's comment:
The Sponsor states that with the change in age they were trying to "better match the baseline characteristics of the ATHENA patients with those of studies of the AFFIRM study". However, there are significant differences in the design of ATHENA study and the AFFIRM trial which include the AFFIRM trial was exclusively in North America, the primary end point was all cause mortality, an inclusion criteria was the ability to be anticoagulated, there were fewer women than men, and 23% had a history of CHF.

Exclusion criteria:
1. Unable to provide informed consent.
2. Any serious non-cardiovascular illness which would limit survival including cancer with metastasis and organ transplantation requiring immune suppression.
3. Pregnant and breastfeeding women.
4. Previous (2 preceding months) or current participation in another clinical trial.

6. Previous participation in this trial

Exclusion Criteria related to a cardiac condition:
"7. Patients in permanent atrial fibrillation
8. Patients in unstable hemodynamic condition such as acute pulmonary edema within 12 hours prior to start of study medication; cardiogenic shock; treatment with intravenous pressor agents; patients on respirator; congestive heart failure of stage New York Heart Association (NYHA) IV within the last 4 weeks; uncorrected, hemodynamically significant primary obstructive valvular disease; hemodynamically significant obstructive cardiomyopathy; a cardiac operation or revascularization procedure within 4 weeks preceding randomization
9. Planned major noncardiac or cardiac surgery or procedures including surgery for valvular heart disease, coronary artery bypass graft, percutaneous coronary intervention, or on urgent cardiac transplantation list
10. Acute myocarditis or constrictive pericarditis
11. Bradycardia <50 beats per minute (bpm) and/or PR-interval ≥0.28 sec on the last 12-lead ECG
12. Significant sinus node disease (documented pause of 3 seconds or more) or second or third degree atrioventricular (AV) block unless treated with a pacemaker"

Reviewer's comment:
These above cardiac exclusions make this study population quite different from the prior Andromeda patients. This study excluded very sick patients.

Exclusion Criteria related to concomitant medications:
"13. Need of a concomitant medication that is prohibited in this trial, including the requirement for Vaughan-Williams Class I and III antiarrhythmic drugs, that would preclude the use of study drug during the planned study period"

Exclusion Criteria related to laboratory abnormalities:
"14. Plasma potassium <3.5 mmol/L (as antiarrhythmic drugs can be arrhythmogenic in patients with hypokalemia, this must be corrected prior to randomization).
15. A calculated glomerular filtration rate (GFR) at baseline <10 mL/min using the Cockroft Gault formula (Protocol Amendment 1)"

Reviewer's comments:
Within the Exclusion Criteria several items are noteworthy. They have excluded patients with cancer however, many died from cancer. Therefore, of clinical concern is what general work-up was carried out by each of the study practitioners prior to enrolling their patients. Also, because they excluded the patients in permanent atrial fibrillation, they have excluded a large percent of AF patients from this study.

Study drug administration: The first study drug intake was to take place as soon as possible after randomization. Both dronedarone and placebo were to be administered as 1 tablet in the morning during or shortly after breakfast and 1 tablet in the evening during or shortly after dinner.

Reviewer's comment:
It is very interesting to note that no comment is made regarding the fact that the level of the drug is higher in women than men and is also higher after a fatty meal. The outcome based on the differences of the sexes and diets in various countries could be affected. Also, no attention is paid to a history of liver disease which also may affect drug blood levels. This study did not provide any pharmacokinetic data.

Instructions related to dronedarone and creatinine: The following information was provided to Investigators in their brochure: "It has been documented that within 1 to 2 weeks following the start of treatment with dronedarone a moderate (10% to 15%) increase in creatininemia may be seen. This increase is rapidly reversible during the week following dronedarone discontinuation. This increase is not due to a decrease in glomerular filtration rate, but to inhibition of creatinine secretion at the tubular level."

Therefore, if a moderate asymptomatic increase in creatininemia was observed after beginning of treatment the Investigator was advised to use clinical judgment, taking into account that this may be expected with dronedarone. Furthermore, it was recommended, depending on patient condition and symptoms, that an increase in creatininemia concentration should not necessarily lead to specific actions such as discontinuation of treatment with ACE inhibitors or AII receptor antagonists. In case of doubt it was recommended that the Investigator consider temporary interruption of study medication administration, with reintroduction of study medication as soon as possible once any concern was resolved."

Prior and concomitant therapy: Patients included in the study could receive the usual standard therapy for their cardiac condition according to published guidelines.

Not permitted concomitant therapy: Vaughan-Williams Class I and III antiarrhythmic drugs were not to be administered simultaneously with the investigational product. Amiodarone administration was to be permanently stopped for at least 4 weeks prior to randomization. All concomitant drugs that could cause torsades de pointes were contraindicated; including some phenothiazines, cisapride, bepridil, tricyclic antidepressants, and certain oral macrolides.

Given the involvement of the CYP450 3A4 cytochrome in the metabolism of dronedarone, the concomitant use of grapefruit juice and all potent inhibitors of CYP450 3A4, such as ketoconazole, itraconazole, nefazodone, ritonavir, cyclosporin, and troleandomycin, were prohibited. Other drugs, which are CYP450 3A4 substrates and have a narrow therapeutic margin, were to be avoided.

Permitted concomitant therapy:
• Calcium antagonists with depressant effects on the sinus and AV node (e.g., diltiazem and verapamil) could be used with caution.
• Some calcium antagonists such as diltiazem and verapamil are moderate CYP3A4 inhibitors, but their coadministration with dronedarone resulted in a limited interaction on dronedarone only (1.7-fold and 1.4-fold increase in dronedarone exposure, respectively). Nisoldipine, which is a weak

CYP3A4 inhibitor, increased dronedarone exposure only slightly (1.2-fold). If necessary, calcium antagonists could be started concomitantly with the investigational product. In such a case low doses of the calcium antagonist were to be given first and increased after ECG verification of good tolerability.
• Beta-blockers could be used with caution (except sotalol, which was contraindicated). As potentiation of the depressant effects was possible, beta-blockers could be started concomitantly with the investigational product, but with a low dose that would only be increased after ECG verification of tolerability.
• Digoxin could be coadministered, if necessary, with caution and the plasma levels were to be monitored locally. An interaction study had shown that dronedarone increased plasma levels of digoxin. Therefore it was expected that patients would require and tolerate lower than usual doses of digoxin.

Oral anticoagulation was recommended as per current guidelines. The international normalized ratio was to be monitored locally.

Cardioversion: Electrical cardioversion could be performed while on study drug in case of AF/AFL recurrence without prompt spontaneous conversion. Cardioversion was to be considered unsuccessful if sinus rhythm was not restored for at least 10 consecutive minutes after 2 shocks at the highest energy of the device. The standard anticoagulation guidelines were to be followed before cardioversion was performed. If the patient was on digoxin, it was to be withheld and the digoxin plasma level assessed.

Treatment compliance: Compliance was to be assessed based on counts of tablets taken and from packs of the investigational product returned by the patient at routine clinical follow-up visits.

Study Assessments: The following table defines the clinical studies completed at various time frames.

Table 2: Study flow chart – treatment and follow-up

	Treatment / Follow-up phase														
Evaluation Day	Baseline D-7 to D1	D7 ± 2D	D14 ± 5D	M1 ± 7D	M3 ± 14D	M6 ± 14D	M9 ± 14D	M12 ± 14D	M15 ± 14D	M18 ± 14D	M21 ± 14D	M24 ± 14D	M27 ± 14D	M30 ± 14D	Final follow-up visit (common study end date up to +14D)
Design															
Inclusion/exclusion criteria	X*														
Cardiovascular history	X*														
Medical history	X*														
Informed consent/demography	X*														
Prior medication history	X*														
Clinical examination with NYHA for CHF	X*	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**
2D echocardiography***	X*														
IVRS calls	X*					X		X		X		X		X	X
Randomization	X														
Treatment															
IP dispensing	X		X	X	X	X	X	X	X	X	X	X	x	X	
Study drug administration	----------														X
Compliance		X	X	X	X	X	X	X	X	X	X	X	X	x	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	x	X
Vital signs															
Weight and height	X*														
Supine blood pressure	X*	X	X	X	X	X	X	X	X	X	X	X	X	x	X
Efficacy															
Endpoints		X	X	X	X	X	X	X	X	X	X	X	X	x	X

	Treatment / Follow-up phase														
Evaluation Day	Baseline D-7 to D1	D7 ± 2D	D14 ± 5D	M1 ± 7D	M3 ± 14D	M6 ± 14D	M9 ± 14D	M12 ± 14D	M15 ± 14D	M18 ± 14D	M21 ± 14D	M24 ± 14D	M27 ± 14D	M30 ± 14D	Final follow-up visit (common study end date up to +14D)
Safety															
12-lead ECG	X*	X	X	X	X	X		X		X		X		x	X
AE/SAE	X*	X	X	X	X	X	X	X	X	X	X	X	X	x	X
Local laboratory tests	Biochem*, β-HCG*	Biochem	Biochem	Biochem	Biochem	Biochem		Biochem		Biochem		Biochem		Biochem	Biochem

* Prior to randomization
** Only in case of hospitalization
*** 2D- and M mode echocardiography in the month preceding randomization (data obtained from echocardiography taken prior to informed consent to the ATHENA study can be used if that investigation was performed for other reasons than baseline evaluation for the study)
****A questionnaire about symptoms of AF/AFL was to be completed either at Month 12 or Month 18 visit (whichever visit was first after implementation of the substudy).
Biochem: Potassium, Creatinine, Urea, Digoxin, INR

Baseline assessments:
Cardiovascular history: Past cardiovascular history was recorded. Prespecified categories for cardiovascular history terms were defined as follows:
• Coronary artery disease: documented history of acute myocardial infarction and/or significant (≥70%) coronary artery stenosis and/or history of a revascularization procedure (percutaneous transluminal coronary angioplasty, stent implantation in a coronary artery, coronary artery bypass graft, etc) and/or a positive exercise test and/or positive nuclear scan of cardiac perfusion
• Ischemic dilated cardiomyopathy: clinically significant left ventricular dilatation secondary to coronary artery disease
• Non-ischemic dilated cardiomyopathy: clinically significant left ventricular dilatation not secondary to coronary artery disease
• Hypertrophic cardiomyopathy: ventricular hypertrophy not secondary to hypertension
• Rheumatic valvular heart disease: typical rheumatic valvular lesions present at baseline echocardiography and/or past surgery for rheumatic valvular heart disease

• Non-rheumatic valvular heart disease: screening echocardiography confirmed clinically relevant non-rheumatic valvular abnormalities including true mitral valve prolapse
• Congenital heart disease
• Tachycardias: ventricular rate above 100 beats per minute
• Supraventricular tachycardia: rapid rhythm of the heart in which the origin of the electrical signal was either the atria or the AV node
• Sustained ventricular tachycardia: ventricular tachycardia that lasted more than 30 seconds
• Ventricular fibrillation
• Hypertension: current treatment with an antihypertensive agent for elevated blood pressure and/or supine diastolic blood pressure >90 mmHg and/or supine systolic blood pressure >140 mmHg

Disease characteristics: the following 3 categories were defined in the statistical analysis plan:
• Structural heart disease: coronary heart disease and/or ischemic dilated cardiomyopathy and/or non-ischemic dilated cardiomyopathy and/or rheumatic valvular heart disease and/or ventricular ejection fraction <45% and/or history of congestive heart failure
• Lone atrial fibrillation: patients without hypertension and without structural heart disease
• Heart failure criteria: considered present if the patient had left ventricular ejection fraction <35% or NYHA class I or above

Cardiovascular examination: Cardiovascular examination performed at screening and then in case of hospitalization, and was to include the NYHA class assessment for congestive heart failure. These data were to be reported in the case report form.

2D-echocardiography: Echocardiography was to be performed at screening, or within the month preceding randomization, and included left atrial diameter (M-mode) and left ventricular ejection fraction (2D-echocardiography) as well as the presence/absence of clinically significant valvular abnormalities.

Efficacy assessments: The efficacy endpoints were to be assessed by the individual Investigators (usually the treating physician) who classified all hospitalizations or deaths as cardiovascular or noncardiovascular on the case report forms. Death from any cause and cardiovascular hospitalization (both primary endpoints) were classified according to prespecified categories. The primary efficacy variable was the time from randomization to the first cardiovascular hospitalization or death from any cause as assessed by the individual Investigator.

Reviewer's comment:
This study differs from the Andromeda Study where both hospitalizations and death were adjudicated by the Critical Events Committee.

Cardiovascular hospitalization: This was defined as any unplanned hospitalization, an admission with an overnight stay in a hospital covering at least 2 consecutive dates. This admission was categorized by the Investigator who was generally also the providing physician and was based on the cause, either cardiovascular or noncardiovascular. The prespecified main causes for cardiovascular hospitalization were:

• Atherosclerosis related (if not otherwise specified)
• Myocardial infarction or unstable angina
• Stable angina pectoris or atypical chest pain
• Syncope
• Transient ischemic attack (TIA) or stroke (except intracranial hemorrhage)
• Atrial fibrillation and other supraventricular rhythm disorders
• Nonfatal cardiac arrest
• Ventricular arrhythmia, subclassified as torsades de pointes, ventricular extrasystole, ventricular fibrillation, ventricular tachycardia (non-sustained and sustained ventricular tachycardia), or other ventricular arrhythmia
• Cardiovascular surgery except cardiac transplantation
• Cardiac transplantation
• Implantation of a pacemaker, implantable cardioverter defibrillator, or any other cardiac device
• Transcutaneous coronary, cerebrovascular, or peripheral procedure
• Blood pressure related (hypotension; hypertension, except syncope)
• Cardiovascular infection
• Major bleeding (requiring 2 or more units of blood or any intracranial hemorrhage)
• Pulmonary embolism or deep vein thrombosis
• Worsening congestive heart failure (CHF), including pulmonary edema or dyspnea of cardiac origin (worsening of CHF was to be understood as including the new onset of CHF as well as reoccurrence of CHF)

Hospitalizations starting prior to randomization, or scheduled prior to randomization (such as an electrical cardioversion) were to be considered planned and were not reported unless the hospitalization was prolonged.

Reviewer's comment:
The definition of what constitutes a hospitalization as defined above certainly would vary from physician to physician, hospital to hospital, and country to country. It is unclear if a patient remained in an ER or a cardiac unit but not on a hospital floor if this is an admission. Many of the above listed hospitalizations, such as syncope or pacemaker implantation, would vary as to whether the patient remained in the hospital for 2 nights from physician to physician and might even be dependent on the patient's insurance.

Death: Death was defined as any death during the study period. For descriptive purpose, deaths were categorized by the Investigator (treating physician) as cardiovascular or noncardiovascular. The prespecified main causes for cardiovascular death were:
• Aortic dissection/aneurysm
• Cardiac tamponade
• Cardiogenic shock
• CHF
• Death during a cardiovascular transcutaneous interventional procedure or cardiovascular surgical intervention
• Hemorrhage (except cardiac tamponade)
• Myocardial infarction or unstable angina (including complications of myocardial infarction,

except arrhythmias)
• Pulmonary or peripheral embolism
• Stroke
• Sudden cardiac death (e.g., unwitnessed death or documented asystole)
• Ventricular arrhythmia, subclassified as torsades de pointes, ventricular extrasystole, ventricular fibrillation, ventricular tachycardia (non-sustained and sustained ventricular tachycardia), or other ventricular arrhythmia
• Unknown cause

Reviewer's comment:
Under the above definition, patients who bled to death from their cancer were classified as vascular and therefore cardiac death.

Additionally, for descriptive purposes only, the Steering Committee classified deaths into 1 of the following 4 categories (This occurred approximately 2 years after the study began, with Protocol Amendment 3):
• Cardiac/arrhythmic
• Cardiac/nonarrhythmic
• Vascular/noncardiac
• Nonvascular

Reviewer's comment:
Again, there appears to be a significant difference between adjudication of hospitalizations and death which was done in the ADROMEDA Study and pre-defined descriptive classification by individual treating Investigators as was done in this ATHENA study.

Secondary efficacy variables:
• Death from any cause
• First cardiovascular hospitalization
• Cardiovascular death

Adverse events: According to the protocol, cardiovascular hospitalizations and death from cardiovascular causes were waived from expedited reporting. For deaths from non-cardiovascular causes, as part of the primary efficacy endpoint, the randomization code was not to be broken by the Sponsor when expedited reporting to Health Authorities was required. Recurrences of AF/AFL and AF/AFL-related symptoms were not to be reported either as adverse events or as serious adverse events.

Reviewer's comment:
It is interesting that symptoms were not reported and yet a substudy on these symptoms was conducted in some of the ATHENA patients and revealed that there was no difference between patients on placebo and those treated with dronedarone.

Vital signs:
Systolic blood pressure and diastolic blood pressure were measured after the patient rested for

3 minutes in the supine position. Height and weight were measured at baseline only.

Reviewer's comment:
Taking the blood pressure after 3 minutes in the supine position is not considered the standard procedure.

Pharmacokinetic assessments were not done in this study.

End of Study and Removal of Patients from Therapy:
The study planned to enroll 4300 patients (4628 patients were randomized). Study common end was to be one year after the last patient was randomized (i.e., on December 30, 2007).

Patients could withdraw from the treatment phase if they decided to do so. Even if treatment with the study drug was stopped, every attempt was to be made to ensure that the patient was following each of the planned study visits until the common study end date.

If a patient was potentially lost to follow-up before he/she had completed the treatment and/or follow-up period, Investigators were asked to make every effort to re-contact the patient; if unsuccessful, Investigators were asked to make every effort to provide the patient's vital status and if he/she had been hospitalized for cardiovascular or non-cardiovascular reasons until the common study end date.

Patients who did not remain in the study until the common study end and who did not die were considered as lost to follow up based on the "End of Study" or "last contact" form; they were summarized by treatment group.

In case of a transient interruption of treatment, treatment could be started again if restarting treatment was considered safe for the patient (interruption was not due to a possibly drug-related adverse event).

Statistical Methods:
All statistical tests were performed at the 5% (2-sided) significance level.
Efficacy analyses were based on all randomized patient population that consisted of those patients who were randomized regardless of the actual study drug intake or the patient's study protocol compliance.

The efficacy analysis considered all assessments from randomization to the end of study date, which was defined as the final follow-up visit/last contact date or the date of death, whatever came first.

The primary analysis was the comparison of the time from randomization to the primary endpoint between the 2 treatment groups using a 2-sided log-rank asymptotic test.

Reviewer's Comment:
As many deaths occurred at the end of the study, this review also looked at the results of the Wilcoxon test which places more weight on the larger survival times.

Cumulative incidence functions in each treatment group were calculated and plotted using nonparametric Kaplan-Meier estimate. The corresponding 95% CI was computed at each scheduled time-point of the protocol using Greenwood's variance estimation.

The hazard ratio with 95% CI was estimated using a Cox model with treatment group as the only factor. Acceptability of proportional hazards assumption was checked graphically, plotting the natural logarithm of the cumulative hazard Kaplan-Meier estimate versus the natural logarithm of time for each treatment group.

Secondary efficacy endpoints:
In order to protect the global type I error of 5%, a hierarchical procedure was to be applied to testing of secondary efficacy endpoints. "All deaths whatever the cause" was to be tested first. If "all deaths" endpoint is not statistically significant at the 5% significance level, then no further testing of the secondary endpoints can be performed. If "all deaths" endpoint is statistically significant at the 5% significance level, then testing of "cardiovascular hospitalization" was to be performed, and then "cardiovascular death" was to be tested lastly. The same analysis approach as for the primary endpoint was used for all secondary endpoints.

Determination of sample size:
Based on the pooled results of EFC4788 (ADONIS) and EFC3153 (EURIDIS) studies, around 1850 patients per group (3700 in total) were originally considered necessary to evaluate the protocol-specified primary objective.

During the course of the study, following blinded review of the overall death event rate, the incidence of death was less than expected. An increase in sample size to 4300 patients (2150 per group) was implemented by Protocol Amendment 2. Based on the historical inclusion rate and the ability to identify the 600 additional patients, the inclusion period was extended to the end of December 2006.

Reviewer's comments:

1. *The ATHENA study did not stop on December 30, 2007, as was to be done according to the Protocol Amendment 2, one year after the last patient was randomized. Instead the study was stopped on March 5, 2008. Five deaths on placebo and one death on dronedarone were recorded after December 30, 2007.*
2. *The ATHENA study randomized 4628 patients instead of randomizing 4300 patients (as was specified in the Protocol Amendment 2).*

Interim analysis:
A formal interim analysis on the primary efficacy endpoint was to be performed when the half (485) of the estimated primary endpoints have occurred. Early termination for favorable results or futility was to be considered. The analysis of efficacy was to be done using a Haybittle-Peto type boundary for alpha spending function to maintain the global alpha at 5% level (alpha=0.0001 for interim analysis and 0.05 for the final analysis).

Amendments to the Study Protocol:
There were 3 amendments to the protocol, which are summarized in the following table.

Table 3: Summary of protocol amendments

Amendment number	Date of sponsor approval	Summary of amendment
1	08 Mar 2006	Inclusion criterion 1 was modified at the recommendation of the Steering Committee to increase the minimum age for recruitment and to increase the threshold for age as an additional risk factor. An interim analysis was planned to prematurely stop the study in case of overwhelming efficacy or futility. The assessment of kidney function was harmonized to the assessment of urea and a conversion for blood urea nitrogen was provided. The Cockcroft-Gault formula for glomerular filtration rate was corrected.
2	25 Aug 2006	The sample size was increased to 4300 patients, and the global inclusion period was consequently increased to 1.5 years and the estimated duration of the study was increased to 2.5 years.
3	05 Jan 2007	A substudy for the assessment of symptoms according to the Bubien and Kay scale was added. Classification of all deaths by the Steering Committee for descriptive purposes was also added.

Amendment 1, which modified the minimum age and risk factor criteria for patient inclusion, was approved on March 8, 2006 when 1993 patients had already been randomized. It was to be implemented on March 25, 2006.

Changes to the analyses, made after the blind was broken:
The median study duration was calculated. In order to further investigate the effect of dronedarone on the number of cardiovascular death during the on-study period, the time from randomization to sudden death as well as the time from randomization to death due to stroke were analyzed with the same analysis used in the primary analysis of the primary endpoint.

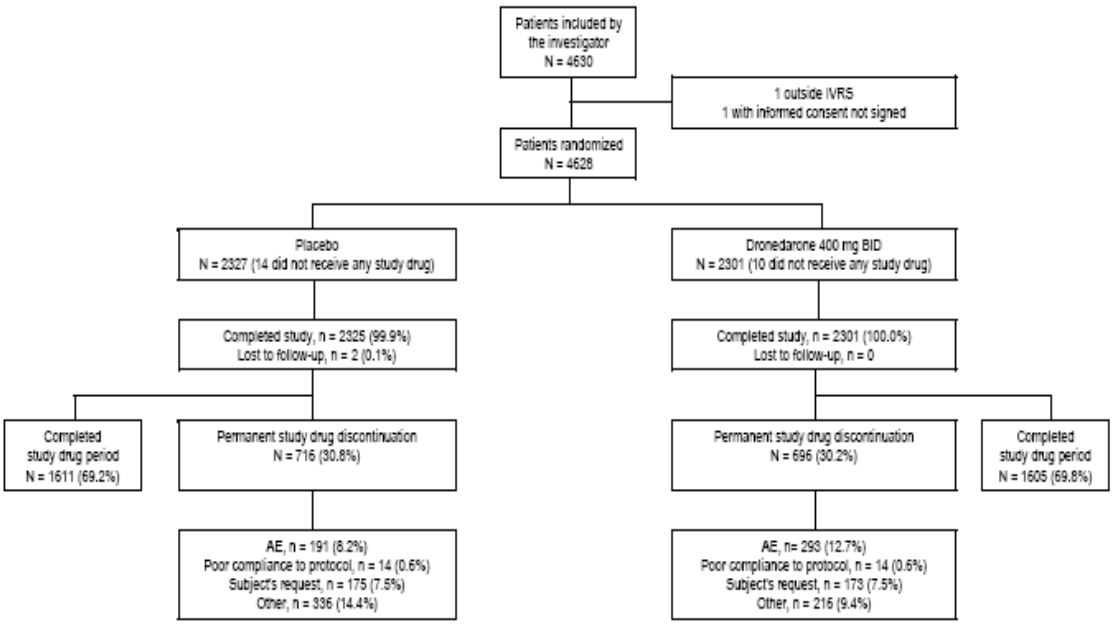
In order to further investigate the homogeneity of the effect of pre-defined endpoints (time to cardiovascular hospitalization or death from any cause, all deaths, cardiovascular hospitalization, cardiovascular death) in consideration of baseline characteristics and medications, hazard ratios (labeled in tables as "relative risk") with 95% CI were calculated for each level of the following baseline parameters, and the interaction between the treatment and each baseline covariate was calculated by comparing the model without interaction with the one containing the interaction using the likelihood ratio test:
• Age (<65, [65-75[, ≥75)
• Weight (<60, [60; 100[≥100]
• Gender [male (M), female (F)]
• Factor combining age and gender (F+age≥75, F+age<75, M+age≥75, M+age<75)
• Presence of AF/AFL as per stratification factor (Yes, No)
• Hypertension (Yes, No)
• Structural heart disease (Yes, No)
• Left ventricular ejection fraction (LVEF) <35% or Class I or above (Yes, No)
• LVEF (<35%, ≥35%)
• Left atrium diameter (≤40mm, >40mm)
• Diabetes (Yes, No)
• Creatinine clearance (<30 mL/min, [30-50[mL/min, [50-80[mL/min, ≥80 mL/min)

• ACE or AII receptor antagonists (Yes, No)
• Beta blocking agents (Yes, No)
• Digitalis (Yes, No)

Reviewer's comment:
Whether a patient was adequately anticoagulated is an important baseline parameter that was not calculated into interaction using the above likelihood ratio test.

Study Patients: A total of 4630 patients were randomized by the investigators, 2327 patients were randomized to placebo and 2301 to dronedarone. Two patients were excluded; twenty-four never received study drug: 14 patients in the placebo group and 10 in the dronedarone group. The following figure describes the disposition of the patients.

Figure 3: Disposition of patients



The following table shows the percentage of patients in each category of the inclusion criteria.

Table 4: Number (%) of patients by category of inclusion criteria

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
Age >= 75 years with or without any additional risk factors or a minimum age of 70 years with one or more additional risk factors	1610 (69.2%)	1594 (69.3%)	3204 (69.2%)
Hypertension (taking antihypertensive drugs at least two different classes).	1192 (51.2%)	1212 (52.7%)	2404 (51.9%)
Diabetes.	324 (13.9%)	333 (14.5%)	657 (14.2%)
Prior cerebrovascular accident (stroke or transient ischemic attack) or systemic embolism.	236 (10.1%)	233 (10.1%)	469 (10.1%)
Left atrium diameter greater than or equal to 50 mm by M-mode echocardiography.	343 (14.7%)	329 (14.3%)	672 (14.5%)
Left ventricular ejection fraction less than 0.40 by 2D-echocardiography.	139 (6.0%)	102 (4.4%)	241 (5.2%)
Age in [70-75[years without additional risk factor	51 (2.2%)	43 (1.9%)	94 (2.0%)
Age less than 70 years with additional risk factor	660 (28.4%)	662 (28.8%)	1322 (28.6%)
Hypertension (taking antihypertensive drugs at least two different classes).	574 (24.7%)	546 (23.7%)	1120 (24.2%)
Diabetes.	141 (6.1%)	142 (6.2%)	283 (6.1%)
Prior cerebrovascular accident (stroke or transient ischemic attack) or systemic embolism.	64 (2.8%)	83 (3.6%)	147 (3.2%)
Left atrium diameter greater than or equal to 50 mm by M-mode echocardiography.	135 (5.8%)	148 (6.4%)	283 (6.1%)
Left ventricular ejection fraction less than 0.40 by 2D-echocardiography.	47 (2.0%)	53 (2.3%)	100 (2.2%)
No inclusion criteria ticked	6 (0.3%)	2 (<0.1%)	8 (0.2%)

Patients aged 70 to 75 years without additional risk factors and those aged < 70 years with additional risk factors were allowed to be randomized before the implementation of Protocol Amendment 1

Premature permanent treatment discontinuation: The following table shows the proportion of patients who discontinued treatment prematurely, placebo (716 of 2327, 30.8%) and dronedarone (696 of 2301, 30.2%), and was similar for both groups. More patients in the dronedarone group compared with the placebo group discontinued treatment due to adverse events which were mainly gastrointestinal. Patients in the placebo group discontinued for "other reason," which was related to AF/AFL recurrence or the need for an alternative antiarrhythmic medication.

Table 5: Number (%) of patients who prematurely discontinued treatment

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
Patients who prematurely discontinued the study drug	716 (30.8%)	696 (30.2%)
Main reason for premature discontinuation		
Adverse event	191 (8.2%)	293 (12.7%)
Poor compliance to protocol	14 (0.6%)	14 (0.6%)
Subject's request	175 (7.5%)	173 (7.5%)
Other reason	336 (14.4%)	216 (9.4%)

Temporary treatment discontinuation: The number of patients who temporarily discontinued their study drug was greater in the placebo group (185 of 2327, 8.0%) than in the dronedarone group (133 of 2301, 5.8%) due to a condition that required other treatment. More patients in the dronedarone group compared to the placebo group temporarily discontinued their study drug due to an adverse event or an increase in creatinine. This is shown in the following table:

Table 6: Number (%) of patients who temporarily discontinued study drug

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
Number of patients who temporarily discontinued study drug	921 (39.6%)	928 (40.3%)
Reason for stopping temporarily study drug		
Patient forgot treatment	187 (8.0%)	194 (8.4%)
Condition requiring other treatment	185 (8.0%)	133 (5.8%)
Adverse event	301 (12.9%)	382 (16.6%)
Creatinine increase	11 (0.5%)	39 (1.7%)
Other reason	468 (20.1%)	457 (19.9%)

Note : a patient can be counted more than once in several reasons

The following table shows that only a few patients in either treatment groups stopped their ACE inhibitors or AII receptor antagonists, therefore following the protocol recommendations on the management of creatininemia.

Table 7: Summary of temporary discontinuation of study drug due to creatinine increase

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
Number (%) of patients with at least one discontinuation due to creatinine increase	11 (0.5%)	39 (1.7%)
Level of creatinine (umol/L) just before the 1st stop for creatinine increase		
n	11	39
Mean (SD)	195.0 (52.3)	166.1 (65.2)
Median	186	149
Min - Max	134 - 274	74 - 354
Change from baseline of creatinine level(umol/L)		
n	11	37
Mean (SD)	48.5 (41.8)	47.2 (48.3)
Median	44	40
Min - Max	-27 - 122	-29 - 212
Number(%) of patients who stopped ACE inhibitors or AII receptor antagonists after temporary discontinuation due to creatinine increase	1 (<0.1%)	2 (<0.1%)

Reviewer's comment:
More patients on dronedarone temporarily discontinued their study drug due to an increase in creatinine than those on placebo.

Baseline Characteristics:
Demography: In the following table the demographic characteristics are shown. In both treatment groups, more than 40% of the patients were ≥75 years old. In the placebo group there is slightly more men than in the dronedarone group.

Table 8: Summary of demographic characteristics - all randomized patients

Parameter		Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
Age (years)	n	2327	2301	4628
	Median	73	73	73
	Mean	71.7	71.6	71.6
	SD	9.0	8.9	9.0
	Min - Max	33 - 95	23 - 97	23 - 97
Age (years) [n(%)]	<65	442 (19.0%)	431 (18.7%)	873 (18.9%)
	[65-75[	907 (39.0%)	923 (40.1%)	1830 (39.5%)
	>=75	978 (42.0%)	947 (41.2%)	1925 (41.6%)
Height (cm)	n	2327	2301	4628
	Median	168	168	168
	Mean	168.1	167.5	167.8
	SD	10.5	10.1	10.3
	Min - Max	126 - 211	139 - 203	126 - 211
Weight (kg)	n	2327	2301	4628
	Median	79.2	79.5	79.4
	Mean	80.54	80.35	80.45
	SD	17.78	17.18	17.48
	Min - Max	31.0 - 208.2	33.0 - 168.2	31.0 - 208.2
BMI (Kg/m²) [n(%)]	<30	1594 (68.5%)	1544 (67.1%)	3138 (67.8%)
	>=30	733 (31.5%)	757 (32.9%)	1490 (32.2%)
Gender [n(%)]	Male	1289 (55.4%)	1170 (50.8%)	2459 (53.1%)
	Female	1038 (44.6%)	1131 (49.2%)	2169 (46.9%)
Race [n(%)]	Caucasian	2072 (89.0%)	2065 (89.7%)	4137 (89.4%)
	Black	31 (1.3%)	19 (0.8%)	50 (1.1%)
	Asian/Oriental	154 (6.6%)	150 (6.5%)	304 (6.6%)
	Other	70 (3.0%)	67 (2.9%)	137 (3.0%)
	- Hispanic	56 (80.0%)	48 (71.6%)	104 (75.9%)
	- Latin	12 (17.1%)	13 (19.4%)	25 (18.2%)
	- Other	2 (2.9%)	6 (9.0%)	8 (5.8%)

Medical History: The medical history is in the following table. Approximately 60% in each group have structural heart disease. In the placebo group there is a higher incidence of coronary heart disease and cardiac valve surgery.

Table 9: Number (%) of patients with cardiovascular history - all randomized patients

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
Hypertension	1996/ 2327 (85.8%)	1999/ 2301 (86.9%)	3995/ 4628 (86.3%)
Structural heart disease	1402/ 2304 (60.9%)	1330/ 2281 (58.3%)	2732/ 4585 (59.6%)
Tachycardia	797/ 2327 (34.3%)	752/ 2301 (32.7%)	1549/ 4628 (33.5%)
Coronary heart disease	728/ 2327 (31.3%)	661/ 2301 (28.7%)	1389/ 4628 (30.0%)
Non-rheumatic valvular heart disease	354/ 2327 (15.2%)	331/ 2301 (14.4%)	685/ 4628 (14.8%)
Pacemaker	243/ 2327 (10.4%)	214/ 2301 (9.3%)	457/ 4628 (9.9%)
Lone atrial fibrillation	139/ 2318 (6.0%)	140/ 2297 (6.1%)	279/ 4615 (6.0%)
Ischemic dilated cardiomyopathy	118/ 2327 (5.1%)	92/ 2301 (4.0%)	210/ 4628 (4.5%)
Ablation for AF/AFL	106/ 2327 (4.6%)	90/ 2301 (3.9%)	196/ 4628 (4.2%)
Supra-ventricular tachycardia other than AF/AFL	98/ 2327 (4.2%)	97/ 2301 (4.2%)	195/ 4628 (4.2%)
Cardiac valve surgery	95/ 2327 (4.1%)	80/ 2301 (3.5%)	175/ 4628 (3.8%)
Non-ischemic dilated cardiomyopathy	84/ 2327 (3.6%)	82/ 2301 (3.6%)	166/ 4628 (3.6%)
Hypertrophic cardiomyopathy	50/ 2327 (2.1%)	45/ 2301 (2.0%)	95/ 4628 (2.1%)
Implanted cardioverter defibrillator	43/ 2327 (1.8%)	42/ 2301 (1.8%)	85/ 4628 (1.8%)
Rheumatic valvular heart disease	29/ 2327 (1.2%)	51/ 2301 (2.2%)	80/ 4628 (1.7%)
Sustained ventricular tachycardia	19/ 2327 (0.8%)	21/ 2301 (0.9%)	40/ 4628 (0.9%)
Congenital heart disease	16/ 2327 (0.7%)	21/ 2301 (0.9%)	37/ 4628 (0.8%)
Ablation for other reason than AF/AFL	17/ 2327 (0.7%)	12/ 2301 (0.5%)	29/ 4628 (0.6%)
Ventricular fibrillation	12/ 2327 (0.5%)	12/ 2301 (0.5%)	24/ 4628 (0.5%)

Structural heart disease: Coronary heart disease and/or Ischemic dilated cardiomyopathy and/or Non-ischemic dilated cardiomyopathy and/or Rheumatic valvular heart disease and/or Non-rheumatic valvular heart disease and/or Hypertrophic cardiomyopathy and/or LVEF < 45 % and/or History of congestive heart failure (CHF)
Lone atrial fibrillation: patients without hypertension and without structural heart disease

Reviewer's comment:
The fact that structural heart disease, coronary heart disease, and non-rheumatic valvular heart disease are higher in the placebo group may be of some significance.

The medical history at baseline is in the following table. There is slightly more chronic obstructive pulmonary disease, insomnia, cardiac value surgery, and ablation for AF/AFL in the placebo group.

Table 10: Number of patients with medical history

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
Hypercholesterolemia	1002/ 2327 (43.1%)	1034/ 2301 (44.9%)	2036/ 4628 (44.0%)
Dyslipidaemia	778/ 2327 (33.4%)	756/ 2301 (32.9%)	1534/ 4628 (33.1%)
Non insuline-dependent diabetes mellitus	398/ 2327 (17.1%)	423/ 2301 (18.4%)	821/ 4628 (17.7%)
Chronic pulmonary disease	314/ 2327 (13.5%)	297/ 2301 (12.9%)	611/ 4628 (13.2%)
Hypothyroidism	227/ 2327 (9.8%)	263/ 2301 (11.4%)	490/ 4628 (10.6%)
Insomnia	190/ 2327 (8.2%)	175/ 2301 (7.6%)	365/ 4628 (7.9%)
Malignant neoplasm	192/ 2327 (8.3%)	165/ 2301 (7.2%)	357/ 4628 (7.7%)
Depression	178/ 2327 (7.6%)	162/ 2301 (7.0%)	340/ 4628 (7.3%)
Embolism and thrombosis (including phlebothrombosis and arterial embolism)	159/ 2327 (6.8%)	172/ 2301 (7.5%)	331/ 4628 (7.2%)
Syncope	140/ 2327 (6.0%)	154/ 2301 (6.7%)	294/ 4628 (6.4%)
Hyperthyroidism	100/ 2327 (4.3%)	77/ 2301 (3.3%)	177/ 4628 (3.8%)
Chronic renal failure	83/ 2327 (3.6%)	85/ 2301 (3.7%)	168/ 4628 (3.6%)
Insuline-dependent diabetes mellitus	68/ 2327 (2.9%)	60/ 2301 (2.6%)	128/ 4628 (2.8%)
Chronic liver disease	25/ 2327 (1.1%)	27/ 2301 (1.2%)	52/ 4628 (1.1%)
Haemorrhagic stroke	23/ 2327 (1.0%)	21/ 2301 (0.9%)	44/ 4628 (1.0%)
Parkinson's disease	24/ 2327 (1.0%)	15/ 2301 (0.7%)	39/ 4628 (0.8%)
Seizures	19/ 2327 (0.8%)	15/ 2301 (0.7%)	34/ 4628 (0.7%)

At baseline three-quarters of the patients were in sinus rhythm and simply had a history of AF/AFL; only one quarter were in AF/AFL at randomization.

Table 11: Number of patients according to the stratification factor atrial fibrillation/atrial flutter

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
Number of patients in AF/AFL at randomization stage, as per stratification factor	586 (25.2%)	569 (24.7%)	1155 (25.0%)

Reviewer's comment:
The fact that only 25% were in AF/AFL at randomization in the ATHENA Study is in sharp contrast to the ANDROMEDA study patients where almost 30% were in permanent atrial fibrillation.

The baseline cardiovascular examination is shown in the following table. Approximately 30% of patients in both treatment groups had congestive heart failure, i. e., either a LVEF <35% or NYHA Class I or greater. Only about 4% of patients were NYHA Class III.

Table 12: Baseline cardiovascular examination

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
2D-Echocardiogram - Left atrium diameter (mm)			
n	2279	2265	4544
Median	44.0	44.0	44.0
Mean	44.03	44.08	44.06
SD	7.04	6.79	6.92
Min - Max	20.0 - 75.0	22.3 - 72.0	20.0 - 75.0
LA<=40 mm	698 / 2279 (30.6%)	685 / 2265 (30.2%)	1383 / 4544 (30.4%)
LA>40 mm	1581 / 2279 (69.4%)	1580 / 2265 (69.8%)	3161 / 4544 (69.6%)
2D-Echocardiogram - Left ventricular ejection fraction (%)			
n	2281	2263	4544
Median	60.0	60.0	60.0
Mean	57.31	57.36	57.34
SD	11.25	10.95	11.10
Min - Max	9.4 - 93.0	10.0 - 86.0	9.4 - 93.0
LVEF<35%	87 / 2281 (3.8%)	92 / 2263 (4.1%)	179 / 4544 (3.9%)
LVEF>=35%	2194 / 2281 (96.2%)	2171 / 2263 (95.9%)	4365 / 4544 (96.1%)
Cardiovascular clinical examination			
Patients with left CHF	693 (29.8%)	672 (29.2%)	1365 (29.5%)
NYHA classification [n(%)]			
Class I	178 (7.6%)	208 (9.0%)	386 (8.3%)
Class II	406 (17.4%)	373 (16.2%)	779 (16.8%)
Class III	109 (4.7%)	91 (4.0%)	200 (4.3%)
LVEF < 35% or NYHA class I or above			
Yes	723 (31.1%)	694 (30.2%)	1417 (30.6%)
No	1568 (67.4%)	1578 (68.6%)	3146 (68.0%)

Reviewer's comment:
The small percent of patients who were in heart failure, especially Class II or higher in this ATHENA Study is significantly smaller and is in sharp contrast to the ANDROMEDA study where the percentage in heart failure was 100%.

Table 13: Summary of creatinine clearance at baseline

Parameter		Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
Creatinine clearance (mL/min)	n	2306	2282	4588
	Median	65	65	65
	Mean	70.7	70.6	70.6
	SD	29.9	28.8	29.4
	Min - Max	14 - 292	13 - 397	13 - 397
Creatinine clearance (mL/min) [n (%)]	<30	68 (2.9%)	59 (2.6%)	127 (2.8%)
	[30-50[	478 (20.7%)	422 (18.5%)	900 (19.6%)
	[50-80[	1082 (46.9%)	1169 (51.2%)	2251 (49.1%)
	>=80	678 (29.4%)	632 (27.7%)	1310 (28.6%)
	Missing	21	19	40

Reviewer's comment:
The placebo group in the above table had more patients with compromised kidney function at baseline compared to the dronedarone group.

Prior and/or concomitant medication: The baseline medication used reflected the standard of care. The 2 treatment groups appear to be well balanced for baseline medication use. At baseline, approximately 32% of patients in both treatment groups reported use of statins metabolized by CYP3A4.

Table 14: Number baseline selected medications

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
Beta blocking agents (except sotalol)	1641 (70.5%)	1628 (70.8%)	3269 (70.6%)
ACE inhibitors or A II receptor antagonists	1602 (68.8%)	1614 (70.1%)	3216 (69.5%)
Oral anticoagulant	1384 (59.5%)	1403 (61.0%)	2787 (60.2%)
Diuretics	1265 (54.4%)	1227 (53.3%)	2492 (53.8%)
Diuretics other than spironolactone	1224 (52.6%)	1187 (51.6%)	2411 (52.1%)
Spironolactone	136 (5.8%)	148 (6.4%)	284 (6.1%)
Low dose of aspirin (<= 365 mg)	1019 (43.8%)	1018 (44.2%)	2037 (44.0%)
Statins	914 (39.3%)	878 (38.2%)	1792 (38.7%)
Statins metabolized by CYP3A4	755 (32.4%)	737 (32.0%)	1492 (32.2%)
Statins not metabolized by CYP3A4	166 (7.1%)	147 (6.4%)	313 (6.8%)
Calcium antagonists with heart rate lowering effects	307 (13.2%)	331 (14.4%)	638 (13.8%)
Digitalis	308 (13.2%)	321 (14.0%)	629 (13.6%)
Drugs interacting with the creatinine tubular secretion	237 (10.2%)	229 (10.0%)	466 (10.1%)
Moderate inhibitors of CYP3A4	226 (9.7%)	214 (9.3%)	440 (9.5%)
Other chronic antiplatelet therapy	166 (7.1%)	126 (5.5%)	292 (6.3%)
NSAID	123 (5.3%)	114 (5.0%)	237 (5.1%)

Reviewer's comment:
It appears from the above table that fewer patients in the placebo group were anticoagulated which may be important.

As expected in AF/AFL patients, the medications most frequently prescribed between the date of first study drug intake and the date of last study drug intake were beta-blocking agents, ACE inhibitors/angiotensin II receptor antagonists, and oral anticoagulants, with rates similar to baseline, reflecting continuation of background therapy as shown in the following table.

Table 15: Number of patients who received concomitant medications

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
Beta blocking agents (except Sotalol)	1860 (79.9%)	1785 (77.6%)
ACE inhibitors / A II receptor antagonists	1800 (77.4%)	1771 (77.0%)
Oral anticoagulant	1643 (70.6%)	1601 (69.6%)
Diuretics	1559 (67.0%)	1524 (66.2%)
Diuretics other than Spironolactone	1522 (65.4%)	1492 (64.8%)
Spironolactone	262 (11.3%)	257 (11.2%)
Low dose of aspirin (<= 365 mg)	1231 (52.9%)	1225 (53.2%)
Statins	1131 (48.6%)	1044 (45.4%)
Metabolized by CYP3A4	973 (41.8%)	909 (39.5%)
Not metabolized by CYP3A4	305 (13.1%)	264 (11.5%)
Digitalis	574 (24.7%)	468 (20.3%)
Calcium antagonists with heart rate lowering effects	490 (21.1%)	459 (19.9%)
Drugs interacting with the creatinine tubular secretion	434 (18.7%)	382 (16.6%)
Moderate inhibitors of CYP3A4	369 (15.9%)	323 (14.0%)
NSAID	359 (15.4%)	308 (13.4%)
Other chronic antiplatelet therapy	260 (11.2%)	182 (7.9%)

Reviewer's comment:
It is of interest that more patients in the placebo group were on statins and digitalis.

More patients in the placebo group received drugs that can cause torsades de pointes, Vaughan-Williams Class I or III antiarrhythmic drugs, amiodarone, sotalol, and potent inhibitors of CYP3A4 (10.7%, 8.4%, 8.5%, 2.8%, and 0.7%, respectively) compared with the dronedarone group (8.4%, 5.8%, 5.5%, 1.5%, and 0.4%, respectively) as shown in the following table.

Table 16: Number of patients who received forbidden concomitant medications during study

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
Drugs which can cause Torsades de Pointes	250 (10.7%)	194 (8.4%)
Vaughan-Williams class I or III antiarrhythmic drugs (without Amiodarone)	196 (8.4%)	134 (5.8%)
Amiodarone	197 (8.5%)	126 (5.5%)
Sotalol	66 (2.8%)	35 (1.5%)
Substrates of CYP3A4 with a narrow therapeutic margin	15 (0.6%)	17 (0.7%)
Potent inhibitors of CYP3A4	16 (0.7%)	10 (0.4%)

Reviewer's comment:
As may be expected, more patients in the placebo group were on forbidden concomitant medications.

6.1.4 Efficacy Findings

The following table shows that dronedarone decreases by 24.2% the incidence of cardiovascular hospitalization or death from any cause compared with placebo ($p = 2 \times 10^{-8}$).

Table 17: Time from randomization to first cardiovascular hospitalization or death from any cause

	Placebo (N= 2327)	Dronedarone 400mg BID (N= 2301)
Number of events, n	917	734
Median survival [95% CI](day)	NA	NA
Cumulative incidence of events at 6 months [95% CI] Cumulative incidence of events at 1 year [95% CI] Cumulative incidence of events at 2 years [95% CI]	0.202 [0.185 ; 0.218] 0.302 [0.283 ; 0.320] 0.422 [0.400 ; 0.444]	0.147 [0.132 ; 0.161] 0.228 [0.211 ; 0.245] 0.354 [0.332 ; 0.377]
Endpoint's composition: Cardiovascular hospitalization Death from any cause - Cardiovascular death - Non cardiovascular death	 859 58 33 25	 675 59 26 33
Log-rank test p-value Relative risk [95% CI]*	2E-8 0.758 [0.688; 0.835]	

* Determined from cause-specific Cox regression model

Death from any cause: The following table shows that fewer deaths from any cause occurred in the dronedarone group (n = 116) compared with the placebo group (n = 139), however, this difference was not statistically significant (p=0.176). Also, there is a reduction in the number of cardiovascular deaths (dronedarone: 65; placebo: 94).

Table 18: Time from randomization to death from any cause

	Placebo (N= 2327)	Dronedarone 400mg BID (N= 2301)
Number of events, n	139	116
Median survival [95% CI](day)	NA	NA
Cumulative incidence of events at 6 months [95% CI] Cumulative incidence of events at 1 year [95% CI] Cumulative incidence of events at 2 years [95% CI]	0.016 [0.011 ; 0.021] 0.033 [0.026 ; 0.040] 0.063 [0.052 ; 0.074]	0.012 [0.007 ; 0.016] 0.027 [0.020 ; 0.033] 0.061 [0.049 ; 0.072]
Endpoint's composition: - Cardiovascular death - Non cardiovascular death	 94 45	 65 51
Log-rank test p-value Relative risk [95% CI]*	0.1758 0.844 [0.660; 1.080]	

* Determined from cause-specific Cox regression model

Deaths over time show a reduction in all deaths and cardiovascular deaths in the following table.

Table 19: Deaths over time

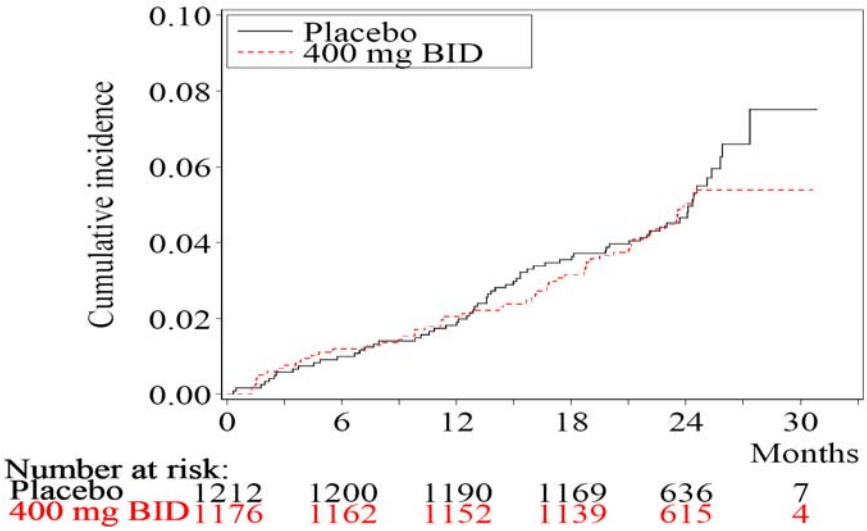
	Placebo (N=2327)		Dronedarone 400 mg BID (N=2301)	
All deaths				
On Study	139	(6.0%)	116	(5.0%)
On Treatment	65	(2.8%)	54	(2.3%)
Beyond study period (a)	1	(<0.1%)	0	(0%)
CV deaths				
On Study	94	(4.0%)	65	(2.8%)
On Treatment	50	(2.1%)	37	(1.6%)
Beyond study period (a)	1	(<0.1%)	0	(0%)
Non CV deaths				
On Study	45	(1.9%)	51	(2.2%)
On Treatment	15	(0.6%)	17	(0.7%)

(a) Data no longer collected systematically

Respiratory events were the most frequent reason for noncardiovascular deaths in both treatment groups. Seven patients in each group had a main reason of death associated with respiratory and mediastinal neoplasm; 4 patients in each group had pneumonia; 1 patient in the placebo group and 6 in the dronedarone died of respiratory disorders (respiratory failure, chronic respiratory disease), while 6 patients in the placebo group and 1 in the dronedarone group died from chronic obstructive pulmonary disease.

In our correspondence with the Sponsor, they provided on November 11, 2008, primary and secondary analyses of those patients who were enrolled prior to the protocol change on March 2006 and those enrolled after the protocol change. The following figure shows the cumulative curves of deaths for any cause for those who were enrolled prior to the protocol change.

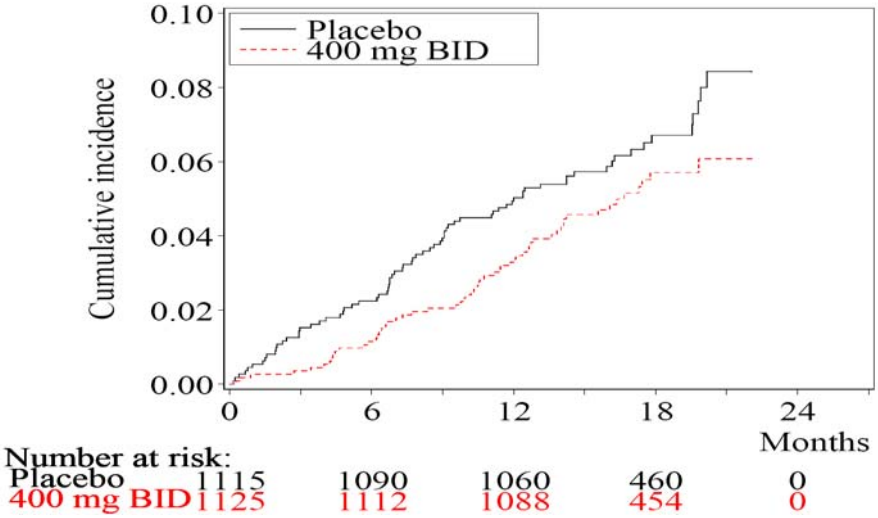
Figure 4: Kaplan-Meier cumulative incidence curves from randomization to death from any cause during the on-study period - All patients randomized before 2006-03-25 (EFC5555/ATHENA)



Reviewers comment:
There was no difference between the treatment groups before month 24.

Below are the respective cumulative curves in Fig. 4 for those enrolled after the protocol change.

Fig. 5: Kaplan-Meier cumulative incidence curves from randomization to death from any cause during the study after Amendment 1



Reviewers comment:
There is a big difference between the cumulative curves before and after the protocol amendment on March 25, 2006.

The Steering Committee classified the reduction of cardiac/arrhythmic deaths in the dronedarone group compared with placebo which is shown in the following table.

Table 20: Summary of death classification as per Steering Committee

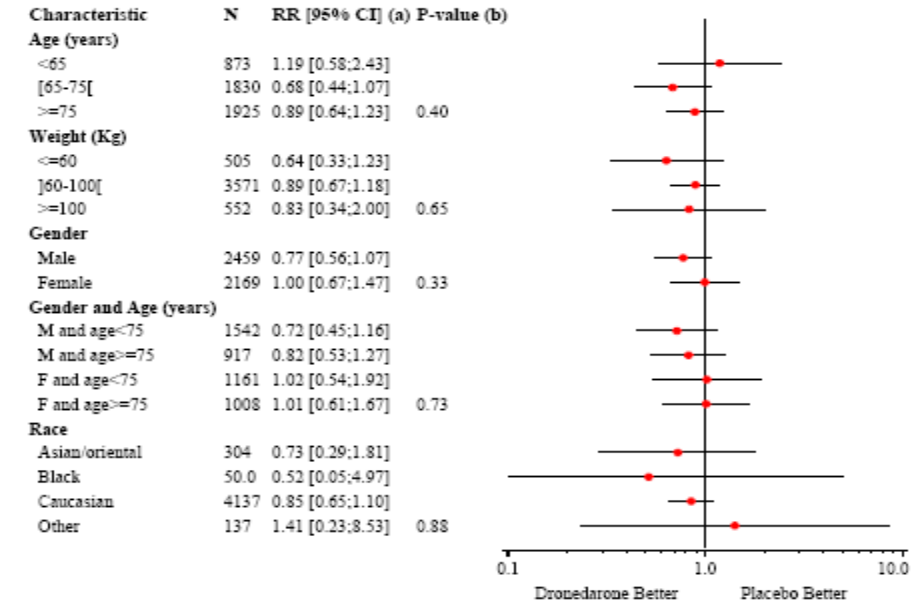
	Placebo (N=2327)		Dronedarone 400 mg BID (N=2301)	
Number of deaths	140	(6.0%)	116	(5.0%)
On study	139	(6.0%)	116	(5.0%)
Cardiac/arrhythmic	48	(2.1%)	26	(1.1%)
Cardiac/non-arrhythmic	18	(0.8%)	17	(0.7%)
Non-vascular	49	(2.1%)	53	(2.3%)
Vascular/non-cardiac	24	(1.0%)	20	(0.9%)
On treatment	65	(2.8%)	54	(2.3%)
Cardiac/arrhythmic	31	(1.3%)	17	(0.7%)
Cardiac/non-arrhythmic	7	(0.3%)	9	(0.4%)
Non-vascular	15	(0.6%)	19	(0.8%)
Vascular/non-cardiac	12	(0.5%)	9	(0.4%)
Beyond study (a)				
Cardiac/non-arrhythmic	1		0	

(a) Data no longer collected systematically

Reviewer's comment:
It is import to remember that the Amendment 3 was not enacted until January 2007 when the Steering Committee classified the deaths. Therefore, many deaths were classified 2 years after they occurred. Essentially the primary cause of death was determined by the treating physician who was the Investigator and only a few autopsies were performed (9.8%).

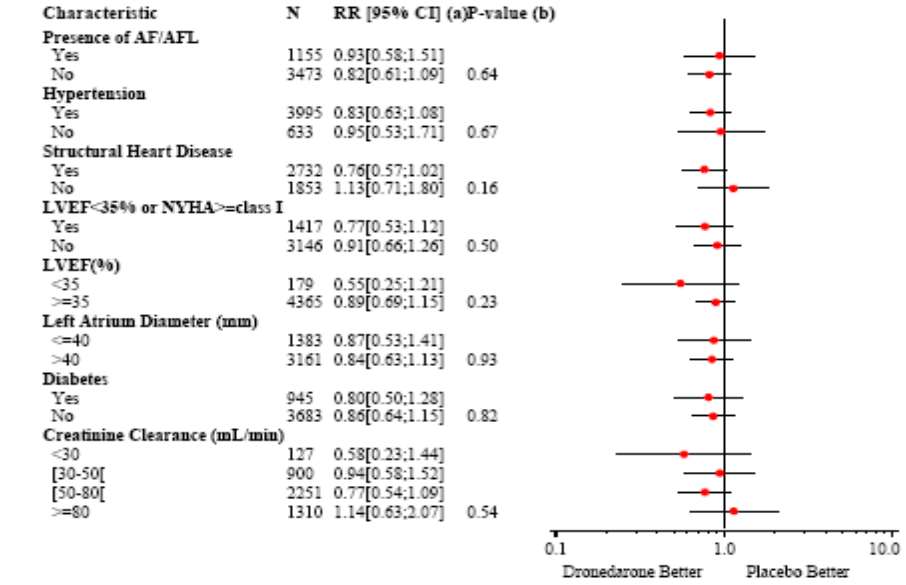
Baseline covariates and selected baseline medications were compared to test their possible influence. This is shown in the following figures.

Figure 6: Relative risk (dronedarone 400 mg BID versus placebo) estimates with 95% confidence intervals according to selected baseline characteristics - death from any cause



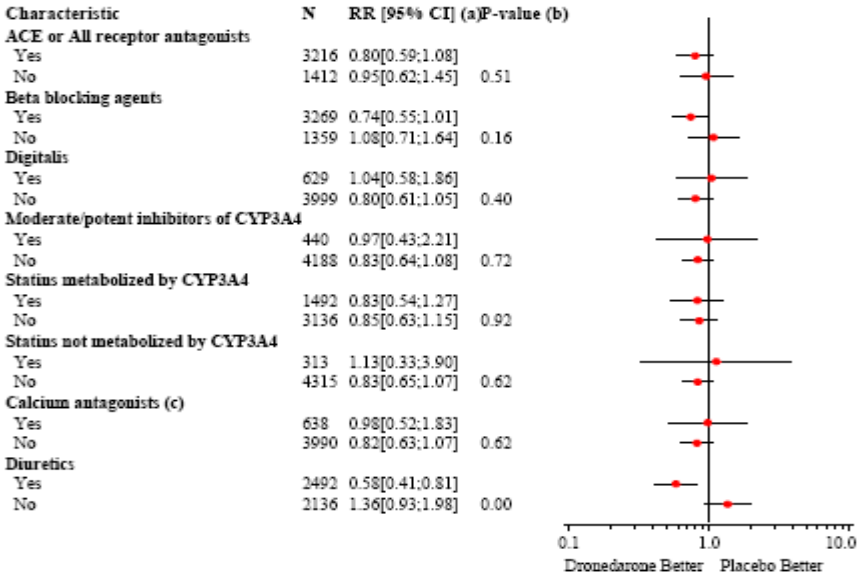
a Determined from Cox regression model
b P-value of interaction between baseline characteristics and treatment based on Cox regression model

Figure 7: Relative risk (dronedarone 400 mg BID versus placebo) estimates with 95% confidence intervals according to selected baseline characteristics – death from any cause



a Determined from Cox regression model
b P-value of interaction between baseline characteristics and treatment based on Cox regression model

Figure 8: Relative risk (dronedarone 400 mg BID versus placebo) estimates with 95% confidence intervals according to selected baseline medications for the time from randomization to death from any cause - All randomized patients



a Determined from Cox regression model
b P-value of interaction between baseline characteristics and treatment based on Cox regression model
c Calcium antagonists with heart rate lowering effects restricted to diltiazem, verapamil and bepridil

According to the pre-specified hierarchical procedure for testing the secondary endpoints, no further testing of the CV hospitalization or CV deaths should be performed because the first secondary endpoint, all death, was not statistically significant (p=0.176). This review shows the analyses of the CV hospitalization and CV deaths as exploratory, only for the completeness of clinical evaluation.

Cardiovascular hospitalization: The on-study analysis of the time from randomization to the first cardiovascular hospitalization demonstrated that dronedarone significantly decreases by 25.5% the cumulative incidence of cardiovascular hospitalization compared with placebo ($p=9 \times 10^{-9}$). This is shown in the following table.

Table 21: Analysis of time from randomization to first cardiovascular hospitalization

	Placebo (N= 2327)	Dronedarone 400mg BID (N= 2301)
Number of events, n	859	675
Median survival [95% CI](day)	NA	NA
Cumulative incidence of events at 6 months [95% CI]	0.195 [0.178 ; 0.211]	0.141 [0.127 ; 0.155]
Cumulative incidence of events at 1 year [95% CI]	0.289 [0.270 ; 0.307]	0.217 [0.200 ; 0.234]
Cumulative incidence of events at 2 years [95% CI]	0.399 [0.376 ; 0.421]	0.326 [0.304 ; 0.348]
Log-rank test p-value	9E-9	
Relative risk [95% CI]a	0.745 [0.673; 0.824]	

PGM= SR33589/EFC5555/CSR 02/BS/PGM RPT/611ATHSurv ana.sas OUT= OUTPUT/611ATH AnaHosp.html (21APR2008 - 15:15)
a Determined from cause-specific Cox regression model

The decrease in the number of cardiovascular hospitalizations with dronedarone group was mainly due to a reduction in AF and other supraventricular rhythm disorders. There was a trend for fewer hospitalizations for worsening congestive heart failure, myocardial infarction or unstable angina, and TIA/stroke in the dronedarone group compared with the placebo group. Hospitalizations for major

bleeding, syncope, or ventricular arrhythmia events (including ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation, and other ventricular arrhythmias) were similar between the treatment groups shown in the following table.

Reviewer's comment:
It is interesting that even though it is a derivative of amiodarone, dronedarone did not seem beneficial for improving hospitalizations for ventricular arrhythmias or syncope.

Table 22: Number of patients with a first cardiovascular hospitalization

	Placebo (N=2327)		Dronedarone 400 mg BID (N=2301)	
Any cardiovascular hospitalization	859	(36.9%)	675	(29.3%)
Atherosclerosis related (if not otherwise specified)	8	(0.3%)	11	(0.5%)
Myocardial infarction or unstable angina	61	(2.6%)	48	(2.1%)
Stable angina pectoris or atypical chest pain	41	(1.8%)	45	(2.0%)
Syncope	24	(1.0%)	21	(0.9%)
TIA or stroke (except intracranial hemorrhage)	35	(1.5%)	28	(1.2%)
Atrial fibrillation and other supraventricular rhythm disorders	457	(19.6%)	296	(12.9%)
Non-fatal cardiac arrest	2	(<0.1%)	3	(0.1%)
Cardiovascular surgery except cardiac transplantation	23	(1.0%)	21	(0.9%)
Implantation of a pacemaker, ICD or any other cardiac device	29	(1.2%)	32	(1.4%)
Transcutaneous coronary, cerebrovascular or peripheral procedure	31	(1.3%)	27	(1.2%)
Blood pressure related (hypotension, hypertension; except syncope)	21	(0.9%)	21	(0.9%)
Cardiovascular infection	0	(0%)	4	(0.2%)
Major bleeding (requiring two or more units of blood or any intracranial hemorrhage)	24	(1.0%)	21	(0.9%)
Pulmonary embolism or deep vein thrombosis	3	(0.1%)	10	(0.4%)
Worsening CHF, including pulmonary edema or dyspnea of cardiac origin	92	(4.0%)	78	(3.4%)
Ventricular extrasystoles	1	(<0.1%)	1	(<0.1%)
Ventricular tachycardia (non-sustained and sustained VT)	6	(0.3%)	6	(0.3%)
Ventricular fibrillation	1	(<0.1%)	1	(<0.1%)
Other ventricular arrhythmia	0	(0%)	1	(<0.1%)

Reviewer's comment:
The above table does show a decrease in hospitalizations for atrial fibrillation and other supraventricular rhythm disorders but frequently in the United States patients are not hospitalized for AF/AFL or simply have an Emergency Room visit.

Reviewer's comment:
According to the pre-specified hierarchical procedure for testing the secondary endpoints, no further testing of the CV hospitalization or CV deaths should be performed because the first secondary endpoint, all death, was not statistically significant (p=0.176). This review shows the analysis of the CV deaths as exploratory, only for the completeness of clinical evaluation.

Cardiovascular death: In the following table it is shown that dronedarone decreased by 30.2% the incidence of cardiovascular death compared with placebo.

Table 23: Unadjusted analysis of time from randomization to cardiovascular deaths

	Placebo (N= 2327)	Dronedarone 400mg BID (N= 2301)
Number of events, n	94	65
Median survival [95% CI](day)	NA	NA
Cumulative incidence of events at 6 months [95% CI]	0.012 [0.008 ; 0.017]	0.007 [0.003 ; 0.010]
Cumulative incidence of events at 1 year [95% CI]	0.024 [0.018 ; 0.030]	0.016 [0.011 ; 0.021]
Cumulative incidence of events at 2 years [95% CI]	0.042 [0.033 ; 0.051]	0.033 [0.024 ; 0.041]
Log-rank test p-value	0.0252	
Relative risk [95% CI]a	0.698 [0.509; 0.958]	

a Determined from cause-specific Cox regression model

The significance for CV deaths appeared to be largely driven by Russia. The analysis of time from randomization to CV death by country as shown in the following table was prepared by Dr. Freidlin.

Table 24: Analysis of time from randomization to CV death in ATHENA, by country
(All randomized patients. Countries with large number of patients and events)

Country	Number of patients	Number of CV deaths	RR	P-value
Argentina	94	4	0.99	0.99
Belgium	33	3	1.96	0.58
Canada	148	2	1.08	0.96
Czech Republic	172	7	0.73	0.68
Germany	323	8	1.05	0.95
Hong Kong	38	3	0.42	0.48
Morocco	20	2	1.54	0.76
Poland	198	6	1.01	0.99
Russia	907	49	0.57	0.055
South Africa	54	5	0.80	0.80
Taiwan	35	4	0.93	0.94
United States	1255	47	0.64	0.13

It appears that the reduction of cardiovascular death with dronedarone 400 mg BID was mainly due to a reduction in sudden cardiac deaths and stroke shown in the following table.

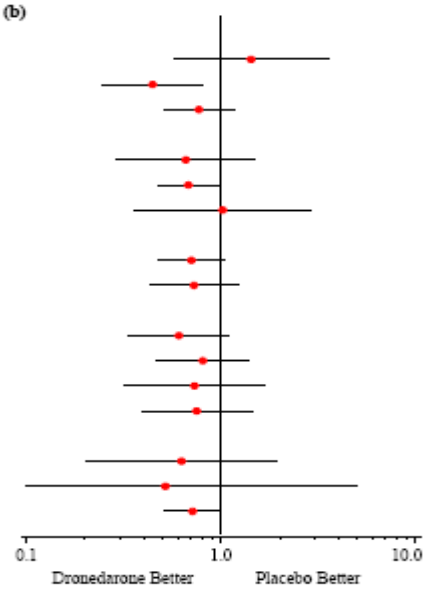
Table 25: Number of patients with cardiovascular death according to pre-specified main reason

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
Any cardiovascular death	94 (4.0%)	65 (2.8%)
Aortic dissection/aneurysm	0 (0%)	1 (<0.1%)
CHF	10 (0.4%)	13 (0.6%)
Cardiogenic shock	2 (<0.1%)	5 (0.2%)
Death during a cardiovascular transcutaneous interventional procedure or cardiovascular surgical intervention	2 (<0.1%)	0 (0%)
Hemorrhage (except cardiac tamponade)	5 (0.2%)	6 (0.3%)
Myocardial infarction or unstable angina (including complications of MI, except arrhythmias)	7 (0.3%)	5 (0.2%)
Pulmonary or peripheral embolism	6 (0.3%)	2 (<0.1%)
Stroke	18 (0.8%)	11 (0.5%)
Sudden cardiac death (e.g unwittnessed death or documented asystole)	35 (1.5%)	14 (0.6%)
Unknown cause	6 (0.3%)	6 (0.3%)
Ventricular fibrillation	2 (<0.1%)	2 (<0.1%)
Ventricular tachycardia (non-sustained and sustained vt)	1 (<0.1%)	0 (0%)

A comparison of dronedarone with placebo for cardiovascular death was made with baseline covariates and selected baseline medications to test their possible influence. In the following figure it is shown that there was no interaction for most covariates.

Figure 9: Relative risk of dronedarone 400 mg BID versus placebo according to selected baseline characteristics – cardiovascular death

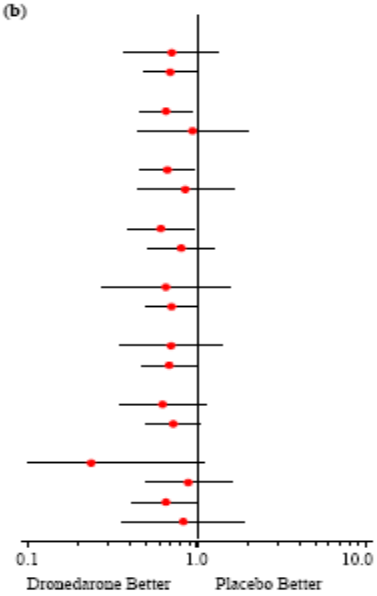
Characteristic	N	RR [95% CI] (a)	P-value (b)
Age (years)			
<65	873	1.42 [0.57;3.54]	
[65-75[	1830	0.44 [0.25;0.80]	
>=75	1925	0.77 [0.50;1.17]	0.08
Weight (Kg)			
<=60	505	0.66 [0.29;1.50]	
]60-100[	3571	0.68 [0.47;0.98]	
>=100	552	1.02 [0.36;2.91]	0.76
Gender			
Male	2459	0.70 [0.47;1.05]	
Female	2169	0.73 [0.43;1.21]	0.93
Gender and Age (years)			
M and age<75	1542	0.61 [0.34;1.10]	
M and age>=75	917	0.81 [0.46;1.40]	
F and age<75	1161	0.73 [0.32;1.69]	
F and age>=75	1008	0.75 [0.39;1.43]	0.92
Race			
Asian/oriental	304	0.63 [0.20;1.91]	
Black	50.0	0.52 [0.05;4.97]	
Caucasian	4137	0.71 [0.51;1.00]	0.99



a Determined from Cox regression model
b P-value of interaction between baseline characteristics and treatment based on Cox regression model

Figure 10: Relative risk of dronedarone 400 mg BID versus placebo estimates according to selected baseline characteristics – cardiovascular death

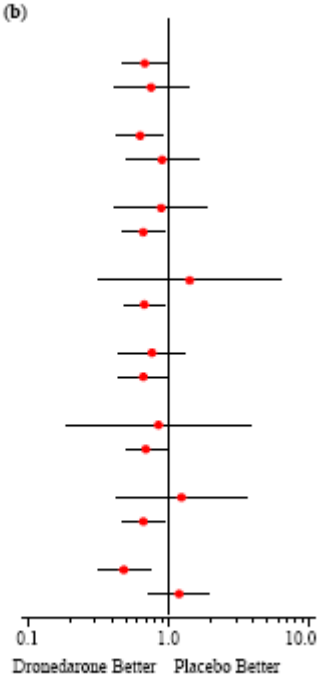
Characteristic	N	RR [95% CI] (a)	P-value (b)
Presence of AF/AFL			
Yes	1155	0.71 [0.38;1.35]	
No	3473	0.70 [0.48;1.00]	0.97
Hypertension			
Yes	3995	0.66 [0.46;0.93]	
No	633	0.94 [0.45;1.98]	0.39
Structural Heart Disease			
Yes	2732	0.67 [0.47;0.96]	
No	1853	0.85 [0.44;1.64]	0.52
LVEF<35% or NYHA>=class I			
Yes	1417	0.61 [0.39;0.95]	
No	3146	0.81 [0.51;1.27]	0.39
LVEF(%)			
<35	179	0.66 [0.28;1.56]	
>=35	4365	0.71 [0.50;1.00]	0.84
Left Atrium Diameter (mm)			
<=40	1383	0.70 [0.36;1.40]	
>40	3161	0.69 [0.48;0.98]	0.94
Diabetes			
Yes	945	0.63 [0.35;1.13]	
No	3683	0.73 [0.50;1.06]	0.68
Creatinine Clearance (mL/min)			
<30	127	0.24 [0.05;1.10]	
[30-50[	900	0.89 [0.50;1.59]	
[50-80[	2251	0.66 [0.42;1.03]	
>=80	1310	0.83 [0.36;1.90]	0.35



a Determined from Cox regression model
b P-value of interaction between baseline characteristics and treatment based on Cox regression model

Figure 11: Relative risk of dronedarone 400 mg BID versus placebo according to selected baseline characteristics – cardiovascular death

Characteristic	N	RR [95% CI] (a)	P-value (b)
ACE or AII receptor antagonists			
Yes	3216	0.68 [0.47;0.98]	
No	1412	0.75 [0.41;1.38]	0.78
Beta blocking agents			
Yes	3269	0.63 [0.43;0.92]	
No	1359	0.90 [0.50;1.62]	0.31
Digitalis			
Yes	629	0.89 [0.42;1.89]	
No	3999	0.66 [0.47;0.94]	0.48
Moderate/potent inhibitors of CYP3A4			
Yes	440	1.41 [0.32;6.32]	
No	4188	0.67 [0.49;0.93]	0.34
Statins metabolized by CYP3A4			
Yes	1492	0.76 [0.45;1.30]	
No	3136	0.66 [0.45;0.98]	0.67
Statins not metabolized by CYP3A4			
Yes	313	0.85 [0.19;3.79]	
No	4315	0.69 [0.50;0.95]	0.78
Calcium antagonists (c)			
Yes	638	1.24 [0.43;3.57]	
No	3990	0.66 [0.48;0.93]	0.27
Diuretics			
Yes	2492	0.48 [0.31;0.74]	
No	2136	1.19 [0.72;1.95]	0.01



a Determined from Cox regression model
b P-value of interaction between baseline characteristics and treatment based on Cox regression model
c Calcium antagonists with heart rate lowering effects restricted to diltiazem, verapamil and bepridil

6.1.5 Clinical Microbiology

NA

6.1.6 Efficacy Conclusions

In ATHENA study, dronedarone was not statistically superior to placebo in preventing death from any cause (p=0.176). Therefore, a claim for preventing death from any cause cannot be included in the labeling.

Relative to a claim for preventing CV death, there are some important issues.

1. According to the pre-specified hierarchical procedure to control global type 1 error at the 5% level, the secondary efficacy endpoint of CV death can be tested only if the first secondary endpoint, death from any cause, is statistically significant at the 5% level. As death from any cause was not statistically significant (p=0.176), the secondary endpoint of CV death should not be tested at all. The analysis for CV death is shown in this review only as exploratory for the completeness of clinical evaluation.
2. There are some issues with the reliability of classifications of CV deaths and the robustness of p=0.03 for the CV death.

For example, in ATHENA, 12 patients with unknown cause of death were classified as having CV death. If 6 placebo patients with unknown cause of death are reclassified as having non-CV death, then the analysis of CV death in ATHENA becomes non-significant: p=0.07 (log-rank test) or p=0.09 (Wilcoxon test). Even if only 4 placebo patients with unknown cause of death are reclassified as non-CV death, then the analysis for CV death in ATHENA already becomes non-significant: p=0.05 (log-rank test) or p=0.065 (Wilcoxon test).

In the ATHENA Study, with a nominal p-value of only p=0.03 for CV mortality and many other issues mentioned above, the statistical significance based on this p-value is inconclusive and could be due to data dredging. Therefore, an additional study is needed to determine whether this finding is real.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety evaluation was reviewed as presented by the Sponsor. Also, many case reports for death and hospitalizations were reviewed by the Medical Reviewer. The efficacy endpoint was death and hospitalizations so there is an overlap between safety and efficacy.

Reviewer's comment:
Unfortunately this Medical Reviewer (a clinician) did not agree with the Investigator (usually the treating physician) as to the designated cause of death in some of the reviewed cases. For instance, a bleeding esophageal cancer is not a vascular death in a cardiovascular trial. Also, hospital records were not located for those who were hospitalized once or more and then later died.

7.1.1 Deaths

The following table provides the deaths in the randomized and treated population, including cardiovascular and non-cardiovascular deaths. These deaths were not adjudicated by a committee but designated by the Investigator (the treating physician) as to a pre-specified reason. In very few instances was an autopsy performed.

Table 26: Overview of deaths over time

	Placebo (N=2313)		Dronedarone 400 mg BID (N=2291)	
All deaths				
On Study	139	(6.0%)	116	(5.1%)
On Treatment	65	(2.8%)	54	(2.4%)
Beyond study period (a)	1	(<0.1%)	0	(0%)
CV deaths				
On Study	94	(4.1%)	65	(2.8%)
On Treatment	50	(2.2%)	37	(1.6%)
Beyond study period (a)	1	(<0.1%)	0	(0%)
Non CV deaths				
On Study	45	(1.9%)	51	(2.2%)
On Treatment	15	(0.6%)	17	(0.7%)

(a) Data no longer collected systematically

Reviewer's comment:
It is interesting that there is an increase in non CV deaths with dronedarone. As stated above, the designation of what was a CV death was according to a check list by the investigating individual clinician.

In the two treatment groups the incidence of serious adverse events with an outcome of death during the emergent period was similar for the randomized, treated population (placebo: 30 of 2313, 1.3%; dronedarone: 37 of 2291, 1.6%). None of the patients in the placebo group experienced respiratory failure whereas it occurred in 4 patients (0.2%) in the dronedarone group. Pneumonia occurred in 3 patients (0.1%) in the placebo group and in 1 patient (<0.1%) in the dronedarone group. Septic shock occurred in 3 patients (0.1%) in the placebo group and none in the dronedarone group.

Reviewer's comment:
It is interesting that the definition of respiratory failure is not provided. Was this congestive heart failure? Pneumonia is common in this age group and this is the reason both the influenza and pneumococcal vaccine are recommended. We have no information on this aspect of the included patients' health care.

7.1.2 Other Serious Adverse Events

According to the Sponsor the incidence of treatment-emergent serious adverse events was similar in the 2 treatment groups. The most frequently reported events were infections, gastrointestinal disorders, and neoplasms both benign and malignant. Pneumonia was reported in more patients on placebo (45 of 2313, 1.9%) than dronedarone (32 of 2291, 1.4%).

A serious adverse event of torsades de pointes was experienced in one patient on dronedarone. The patient's was in the low normal range. The episode of torsades de pointes was recorded while the patient was in the intensive care unit. The patient suffered anoxic encephalopathy with confusion being the main symptom

Acute renal failure occurred in four patients in the placebo group and 14 in the dronedarone group. Twelve patients recovered in the dronedarone group without permanent drug discontinuation. Two patients on dronedarone did not have the drug permanently discontinued and they died one from congestive heart failure and one from acute renal failure. This patient had a low ejection fraction at baseline and a history of chronic renal failure. Treatment with an ACE inhibitor had been discontinued 6 months before death. Two patients in the placebo group with acute renal failure recovered without permanent study drug discontinuation. One patient recovered after permanent study drug discontinuation. The other patient did not permanently discontinue the study drug and died from chronic obstructive pulmonary disease.

7.1.3 Dropouts and Other Significant Adverse Events

More patients in the dronedarone group (12.7%) withdrew from treatment due to an adverse event compared with placebo (8.1%). In the dronedarone group there was a higher incidence of

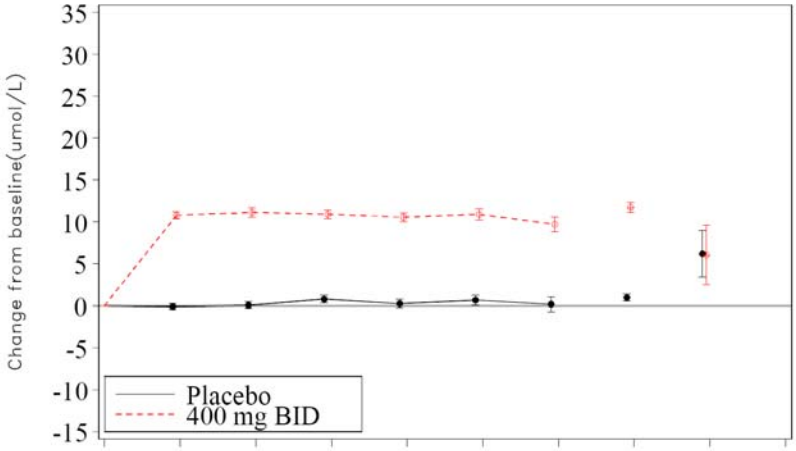
gastrointestinal disorders which included diarrhea, nausea, and vomiting. Also, among the dronedarone patients, there was a higher incidence of withdrawing because of investigation which included ECG QT prolongation and increased blood creatinine.

Patients on dronedarone also withdrew because of fatigue and not feeing well. Dronedarone patients had a higher incidence of withdrawing for a rash, urticaria, and pruritus. Reasons for withdrawal in the dronedarone group included bradycardia, heart failure, ventricular extrasystoles, and palpitations. There was a higher incidence in the dronedarone group of both benign and malignant neoplasms. Reasons for withdrawing in the dronedarone group included anorexia and hyperkalemia.

7.1.4 Laboratory Findings

There was a significant difference between the patients on dronedarone and placebo in serum creatinine as is shown in the following figure.

Figure 12: Mean changes from baseline (+/- SEM) of creatinine over time



Number of patients	B	D14	M3	M6	M12	M18	M24	EOT	F10+
Placebo	2306	2153	1999	1861	1660	1208	614	2267	131
400 mg BID	2282	2083	1952	1826	1655	1207	603	2203	172

A potentially clinically serious adverse event (PCSA) occurred more frequently in the dronedarone group compared to the placebo group regardless of the baseline as shown in the following table.

Table 27: Number (%) of patients with post-baseline PCSA in renal function

Parameter	Baseline status	PCSA criteria	Placebo (N=2313)	Dronedarone 400 mg BID (N=2291)
Creatinine	Missing	>= 150 umol/L	1 / 7 (14.3 %)	2 / 9 (22.2 %)
	>= 150 umol/L	>= 150 umol/L	79 / 98 (80.6 %)	68 / 79 (86.1 %)
	< 150 umol/L	>= 150 umol/L	156 / 2192 (7.1 %)	332 / 2167 (15.3 %)
	Whatever baseline status	>= 150 umol/L	236 / 2297 (10.3 %)	402 / 2255 (17.8 %)
Urea	Whatever baseline status	>= 17 mmol/L	84 / 2293 (3.7 %)	106 / 2255 (4.7 %)

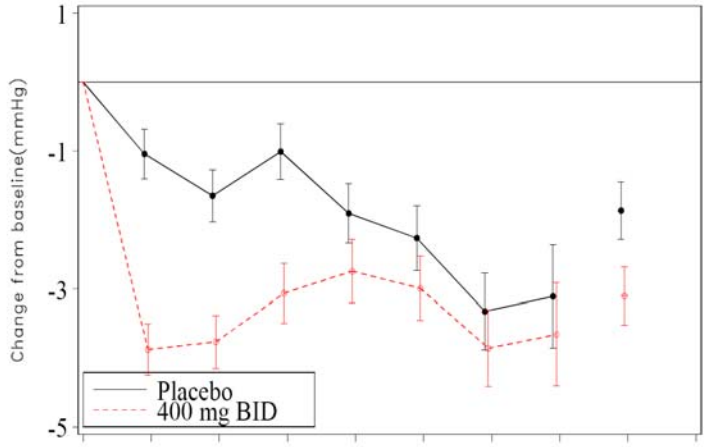
Denominator refers to patients with post baseline value for the parameter

Digoxinemia: Adverse events that led to treatment discontinuation associated with digoxinemia were reported by the Investigators. Two patients in the placebo group had adverse events associated with digoxin; one had anorexia and weight loss, the other digoxin intoxication. Four patients on dronedarone had serious adverse events; 1 an elevated serum digoxin level, and three cases of digoxin intoxication. There was only one patient on dronedarone that had permanent treatment discontinuation because of digoxin intoxication.

7.1.5 Vital Signs

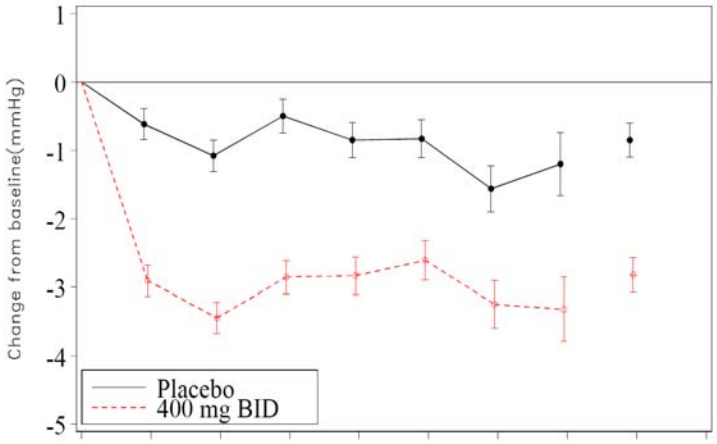
It is interesting that both the systolic and diastolic blood pressures decreased in the patients on dronedarone as shown in the following figures.

Figure 13: Mean changes from baseline (+/-SEM) of systolic blood pressure over time



Number of patients	B	D7	D14	M3	M6	M12	M18	M24	EOT
Placebo	2313	2186	2204	2023	1893	1689	1240	633	2274
400 mg BID	2290	2136	2141	1982	1847	1686	1224	627	2213

Figure 14: Mean changes from baseline (+/-SEM) of diastolic blood pressure over time



Number of patients	B	D7	D14	M3	M6	M12	M18	M24	EOT
Placebo	2313	2186	2204	2023	1893	1689	1240	633	2274
400 mg BID	2290	2136	2141	1982	1847	1686	1224	627	2213

7.1.6 Electrocardiograms (ECGs)

There was a greater percentage of patients in the dronedarone group with potentially significant clinically adverse events with heart rate decreases, prolonged PR interval, QT ≥500 ms, and QTcB parameters as is shown in the following table.

Table 28: Number (%) of patients with post baseline PCSA for 12-lead ECG parameters

Parameter	PCSA criteria	Placebo (N= 2313)	Dronedarone 400 mg BID (N= 2291)
Heart rate	# <= 50 bpm and decrease >= 15 bpm versus baseline	79 / 1869 (4.2 %)	208 / 1955 (10.6 %)
	# >= 120 bpm and increase >= 15 bpm versus baseline	5 / 1869 (0.3 %)	6 / 1955 (0.3 %)
PR interval	# >= 200 ms and increase >= 20 ms versus baseline	484 / 1869 (25.9 %)	777 / 1953 (39.8 %)
QRS interval	>= 120 ms	392 / 1869 (21.0 %)	369 / 1955 (18.9 %)
QT interval	>= 500 ms	62 / 1869 (3.3 %)	237 / 1955 (12.1 %)
QTc Bazett	431-450 ms (m), 451-470 ms (f) - borderline	443 / 1869 (23.7 %)	481 / 1955 (24.6 %)
	> 450 ms (m), > 470 ms (f) - prolonged	359 / 1869 (19.2 %)	549 / 1955 (28.1 %)
	>=500 ms	79 / 1869 (4.2 %)	130 / 1955 (6.6 %)
	## Increase in [30 - 60] ms versus baseline	427 / 1619 (26.4 %)	561 / 1607 (34.9 %)
	## Increase > 60 ms versus baseline	154 / 1619 (9.5 %)	261 / 1607 (16.2 %)

For patients with missing baseline assessment, only their post baseline assessments are taken
Patients with missing baseline assessment are not taken into account
Denominator refers to patients with post baseline value for the parameter
Only 12-lead ECG in normal sinus rhythm are considered

In the dronedarone group 4 (0.2%) prolonged ECG QT interval was reported as an adverse event compared 1 (<0.1%) of the patients in the placebo group. This QT prolongation lead to treatment discontinuation in 33 (1.4%) of the patients on dronedarone and 12 (0.5%) of the patients on placebo.

7.2 Adequacy of Patient Exposure and Safety Assessments

Dronedarone, if approved, will be utilized on a chronic basis. There is very little information available beyond a year or so of use. Ultimately we do not know if the side effects as seen with amiodarone will develop or the endocrine, teratogenicity, and carcinogenicity concerns as expressed by Dr. Hausner in her review and seen in animal models.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The ATHENA Study confirms the adverse events seen in the earlier NDA 21-913 of gastrointestinal disorders, EKG QT prolongation, and increased blood creatinine.

7.4 General Methodology

The ATHENA Study was in accomplished in a population that was not as sick at the ANDROMEDA Study; therefore, a difference in the death rates is seen in the two studies.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor has proposed that the dronedarone dosage is 400 mg twice daily and is to be given with the morning and evening meal. The Agency recommended to the Sponsor early in the development program that various doses be available.

According to Dr. Kumi's original review for NDA 21-913, healthy elderly males have exposures that are about 40 % higher relative to healthy young males; elderly females have exposures that are approximately 30 % higher relative to elderly males; and healthy Asian (Japanese) males have exposures that are about 100 % higher relative to healthy male Caucasians. Also, Dr. Kumi stated in his earlier review that a clear dose-response relationship was shown for QT prolongation in healthy subjects.

8.2 Drug-Drug Interactions

The following table is from Dr. Kumi's original review for NDA 21-913.

Table 29: PK/PD drug-drug interaction information

Drug	Classification	Effect of co-administration		
		PD (either or both drugs)	Dronedarone	Other Drug
	Miscellaneous			
digoxin	PGP substrate	NA	NA	↑ 2.5 fold
pantoprazole	decrease gastric pH	NA	↔	NA
theophylline	CYP1A2 substrate	NA	↔	↓ 20 %
	CYP3A function			
rifampicin	inducer	None	↓ 80 %	NA
dilitiazem	weak inhibitor	↑ repolarization time	↑ 60 %	NA
nifedipine	weak inhibitor	Lowered blood pressure	↑ 20 %	NA
grapefruit juice	moderate inhibitor	NA	↑ 3-fold	NA
ketoconazole	strong inhibitor	↑ PR, no effect on QT	↑ ≥ 9-fold	NA
verapamil	Substrate, inhibitor	↑ repolarization time	↑ 40 %	↑ 40 %
nisoldipine	substrate	↔	↔	↑ 100 %
simvastatin	substrate	↔	↔	↑ 4-fold
ethinylestradiol	substrate	NA	NA	↑ 25 %
levonorgestrel	substrate	NA	NA	↑ 18 %
	CYP2C9 function			
losartan	substrate	↑ heart rate	↔	↔
S-warfarin/R-warfarin	substrate	↑ INR by 7 %	↔	↑ AUC 11 %
	CYP2D6 function			
metoprolol	Substrate	↓ cardiac contractility	NA	↑ 60 -150 %
propranolol	substrate	↓ HR, DBP, SBP	↔	↑ 16 to 33 %

8.3 Special Populations

Dronedarone has not been studied in the pediatric population. It is contraindicated with Class 4 and probably Class 3 patients in congestive heart failure (CHF). Also, patients with severe liver failure probably should not take dronedarone.

8.4 Pediatrics

A waiver for pediatric studies at this time has been granted.

8.5 Advisory Committee Meeting

An Advisory Committee Meeting is to be held March 18, 2009.

Please Note: The Sponsor emphasizes in their briefing package to the Advisory Committee the post hoc analysis for stroke although this endpoint was not prespecified and was not submitted in the NDA.

8.6 Literature Review

Articles which were pertinent were reviewed.

8.7 Postmarketing Risk Management Plan

To be decided after the Advisory Committee Meeting March 18, 2009.

8.8 Other Relevant Materials

NA

9 OVERALL ASSESSMENT

9.1 Conclusions

The ATHENA Study which is reviewed in this NDA 22-425 is a large prospective study in patients with AF/AFL accomplished by individual treating physicians throughout the world. The primary endpoint, the composite of death from any cause or CV hospitalization, was highly statistically significant. However, the efficacy of the prevention of death from any cause was not established (p=0.176). The need to hospitalize these patients varies from physician to physician and country to country. Most importantly, the study investigates a population which is different from the prior ANDROMEDA Study which had a statistically significantly (25 vs. 12, p=0.027) higher rate of death from any cause in the patients on dronedarone. The patients in the ATHENA trial were not as sick as those in the ANDROMEDA Study. We have tried to summarize the differences in the two trials in our following table.

Table 30: Differences between ANDROMEDA and ATHENA studies at randomization

	ANDROMEDA		ATHENA	
Regions	Europe		World, Eastern Europe, USA	
	Placebo	**Dronedarone**	**Placebo**	**Dronedarone**
Age	Mean 68	Mean 69	69% were 75+	69% were 75+
AF/AFL	28%	24%	25%	24%
1st episode	48%	43%		
Paroxysmal	11%	19%		
Persistant	12%	11%	0	0
Permanent	29%	28%	0	0
NYHA				
Class I	0	0	8%	9%
Class II	37%	41%	17%	16%
Class III	59%	57%	5%	4%
Class IV	4%	2%	0	0
Ejection fraction	Wall motion index Mean 0.86	Mean 0.90	<35% 4% >35% 96%	4% 96%
Creatinine level				
<50	42%	44%	24%	21%
>50	58%	56%	76%	79%

Inclusion Criteria	**ANDROMEDA**	**ATHENA**
	Older than 18	75+ without risk factors, 70+ with risk factors
	Class II-IV NYHA	Within 6 months EKG with NSA & AF/AFL
	Wall Motion Index ≤1.2, (LVEF ≤ 35%)	
Exclusion Criteria	**ANDROMEDA**	**ATHENA**
	Acute pulmonary edema within 12 hours	Permanent AF
	MI within 7 days preceding randomization	NYHA Class IV within last 4 weeks
	Any illness other than CHF	GFR < 10 mL/min

Other information provided recently by the Sponsor on January 28, 2009, at the Agency's request, provides additional pertinent information regarding the ANDROMEDA study in patients with AF/AFL. The following table shows that dronedarone statistically significantly increased risk of death from any cause in patients with history of AF in ANDROMEDRA study.

Table 31: Analysis of time from randomization to death from any cause up to 16 January 2003; All patients with a history of AF

	Placebo (N= 126)	**Dronedarone 400mg BID (N= 114)**
Number of events, n	6	14
Median survival [95% CI](day)	NA	NA
Cumulative incidence of events at Day 30 [95% CI] Cumulative incidence of events at Day 90 [95% CI] Cumulative incidence of events at Day 180 [95% CI]	0.009 [0.000 ; 0.025] 0.099 [0.020 ; 0.178] 0.099 [0.020 ; 0.178]	0.067 [0.019 ; 0.115] 0.156 [0.079 ; 0.233] 0.156 [0.079 ; 0.233]
Log-rank test p-value Relative risk [95% CI][a]	0.0444 2.573 [0.988; 6.697]	

[a] Determined from cause-specific Cox regression model

The following table from the ANDROMEDA Study reveals that dronedarone statistically significantly (p=0.0046) increased the risk of cardiovascular death in patients with history of AF. It is important to remember that in ANDROMEDA study deaths and hospitalizations were adjudicated.

Table 32: Analysis of time from randomization to cardiovascular death up to 16 January 2003; All patients with a history of AF

	Placebo (N= 126)	**Dronedarone 400mg BID (N= 114)**
Number of events, n	3	14
Median survival [95% CI](day)	NA	NA
Cumulative incidence of events at Day 30 [95% CI] Cumulative incidence of events at Day 90 [95% CI] Cumulative incidence of events at Day 180 [95% CI]	0.009 [0.000 ; 0.025] 0.040 [0.000 ; 0.087] 0.040 [0.000 ; 0.087]	0.067 [0.019 ; 0.115] 0.156 [0.079 ; 0.233] 0.156 [0.079 ; 0.233]
Log-rank test p-value Relative risk [95% CI][a]	0.0046 5.053 [1.452; 17.585]	

[a] Determined from cause-specific Cox regression model

In the NDA, in the Investigator's Brochure, and in the Advisory Committee Briefing Package, the Sponsor stated that in the ANDROMEDA Study, the increase of mortality on dronedarone could be because of discontinuations of ACE inhibitors or AII receptor antagonists. However, the following information contradicts this sponsor's conclusion. In response to the FDA request, the Sponsor has submitted the following information regarding ACE or AII receptor Antagonists:

"In the ANDROMEDA study 36 patients in the placebo group and 61 patients in the dronedarone group never took or interrupted ACE inhibitors or AII receptor antagonists. In this subpopulation 2 patients died in the placebo group compared to 15 in the dronedarone group. The hazard ratio of 5.1 appears to be higher in this subpopulation compared to the overall ANDROMEDA population with a hazard ratio of 2.3 (95% confidence interval: 1.1 – 4.2), however the 95% confidence intervals overlap. This observation of an apparent increase in the mortality rate in dronedarone treated patients who never took or interrupted ACE inhibitors or AII receptors antagonists as compared to placebo

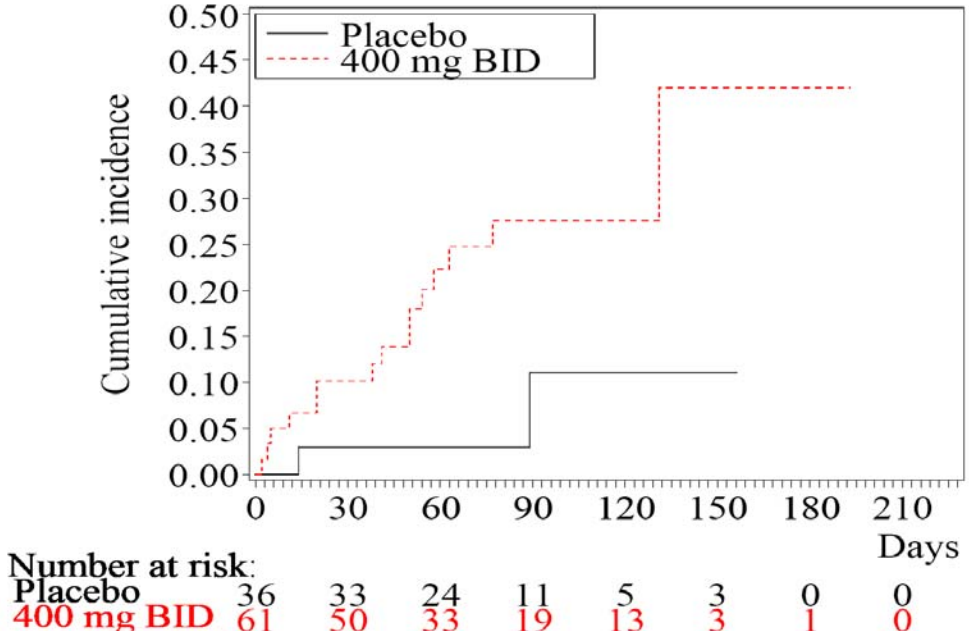
patients challenge the hypothesis that a misinterpretation of the increase in creatinine could have caused the excess of mortality observed in ANDROMEDA."

Table 33: Unadjusted analysis of time from randomization to death from any cause during the on treatment period - All patients who never took or interrupted concomitant ACE inhibitors or AII receptors antagonists (EFC4966/ANDROMEDA)

	Placebo (N= 36)	**Dronedarone 400mg BID (N= 61)**
Number of events, n	2	15
Median survival (95% CI) (days)	NA	NA
Cumulative incidence of events at 30 days [95% CI]	0.029 [0.000 ; 0.086]	0.101 [0.024 ; 0.178]
Cumulative incidence of events at 90 days [95% CI]	0.110 [0.000 ; 0.271]	0.276 [0.149 ; 0.402]
Cumulative incidence of events at 180 days [95% CI]	0.110 [0.000 ; 0.271]	0.421 [0.147 ; 0.694]
Log-rank test p-value	0.0164	
Relative Risk [95% CI] [a]	5.065 [1.157 ; 22.177]	

[a] Determined from Cox regression model, adjusted on studies
Note: protocols : EFC4966/ANDROMEDA

Figure 15: Kaplan-Meier cumulative incidence curves of time to death from any cause up to 16 January 2003 – all patients never took or interrupted ACE or ARB (EFC4966/ANDROMEDA)



9.1.1 Efficacy Conclusions

In ATHENA study, the primary composite endpoint of death from any cause or CV hospitalization was highly statistically significant. However, the efficacy of the prevention of death from any cause was not established (p=0.176). Therefore, a claim for preventing death from any cause cannot be included in the labeling.

The composite endpoint was driven mostly by the other component, CV hospitalizations. Note that the need to hospitalize these patients varies from physician to physician and country to country. Most importantly, the study investigates a population which is different from the prior ANDROMEDA Study, NDA 21-913, which had a statistically significantly (25 vs. 12, p=0.027) higher rate of death from any cause in the patients on dronedarone. Also, the patients in this ATHENA trial were not as sick as those in the prior ANDROMEDA Study.

Relative to a claim for preventing CV death, there are some important issues.

1. According to the pre-specified hierarchical procedure to control global type 1 error at the 5% level, the secondary efficacy endpoint of CV death can be tested only if the first secondary endpoint, death from any cause, is statistically significant at the 5% level. As death from any cause was not statistically significant (p=0.176), the secondary endpoint of CV death should not be tested at all. The analysis for CV death is shown in this review only as exploratory for the completeness of clinical evaluation.

2. There are some issues with the reliability of classifications of CV deaths and the robustness of p=0.03 for the CV death.

For example, in ATHENA, 12 patients with unknown cause of death were classified as having CV death. If 6 placebo patients with unknown cause of death are reclassified as having non-CV death, then the analysis of CV death in ATHENA becomes non-significant: p=0.07 (log-rank test) or p=0.09 (Wilcoxon test). Even if only 4 placebo patients with unknown cause of death are reclassified as non-CV death, then the analysis for CV death in ATHENA already becomes non-significant: p=0.05 (log-rank test) or p=0.065 (Wilcoxon test).

In the ATHENA Study, with a nominal p-value of only p=0.03 for CV mortality and many other issues mentioned above, the statistical significance based on this p-value is inconclusive and may be due to data dredging. Therefore, an additional study is needed to determine whether this finding is real.

These reviewers are concerned regarding the safety of dronedarone. There is a continuum in patients with AF/AFL, they go in and out of congestive heart failure. We feel that the safety of dronedarone presents a problem that the label alone may not be able to cover. The prior studies for rhythm and rate control did establish that patients stay in normal sinus rhythm a little longer than placebo but their heart rate on dronedarone when exercising is not within the ACC Guidelines.

9.2 Recommendation on Regulatory Action

This is to be decided after the Advisory Committee Meeting, March 18, 1009.

9.3 Recommendation on Postmarketing Actions

This is to be decided after the Advisory Committee Meeting, March 18, 1009.

9.4 Labeling Review

This will be accomplished after above Advisory Committee Meeting.

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/s/

Gail Moreschi
2/18/2009 12:02:36 PM
MEDICAL OFFICER

Abraham Karkowsky
2/18/2009 04:34:46 PM
MEDICAL OFFICER
I have no major disagreements with the conclusions contained in this review. Additional comments can be fiound in the CDTL memo dated February 18, 2009.

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/s/

Valeria Freidlin
2/18/2009 12:22:53 PM
BIOMETRICS

James Hung
2/18/2009 12:59:00 PM
BIOMETRICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 22-425	Submission Date(s): 06/27/2008, 07/31/2008, 10/27/08, 11/03/08, 12/03/2008, and 12/10/2008
Relevant IND(s)	49,484
Submission Type; Code	N_000
PDUFA Goal Date	April 30, 2009 (extended from January 30, 2009 by major amendment received on December 3, 2008)
Brand Name (proposed)	MULTAQ
Generic Name	Dronedarone hydrochloride
Formulation; Strength(s)	Tablet (film-coated); 400 mg
Class/Indication	Anti-arrhythmic/ in patients with a history of, or current atrial fibrillation or atrial flutter, for the reduction of the risk of cardiovascular hospitalization or death.
Applicant	Sanofi-Aventis
Reviewer	Robert O. Kumi, Ph.D.
Secondary Reviewer	Elena Mishina, Ph.D.
OCP Division	1
OND Division	Cardiovascular and Renal Products
Briefing Date	Not Applicable: A briefing was not held

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1 Executive Summary

Background

NDA 22-425, MULTAQ (dronedarone hydrochloride), is proposed for patients with a history of, or current atrial fibrillation or atrial flutter, for the reduction of the risk of cardiovascular hospitalization or death. Dronedarone hydrochloride was previously submitted as NDA 21-913 for a similar patient population but with a different indication. The Action Letter for NDA 21-913 was issued on August 29, 2006 and listed deficiencies that included clinical pharmacology and biopharmaceutics comments. NDA 22-245 was initially submitted as an amendment to NDA 21-913 and referred to as a "Complete Response" to the Action Letter. The Agency determined that a new indication was being sought, thus, a new NDA was required. An advisory committee will be held for Multaq in late February 2009, as dronedarone is a new molecular entity.

Dronedarone is a benzofuran derivative in the same class as amiodarone, an approved anti-arrhythmic agent. Dronedarone is an anti-arrhythmic agent that has electrophysiological properties associated with all four Vaughan-Williams classes. If approved, Multaq will be marketed as a 400 mg strength tablet. The proposed dronedarone dosage is 400 mg twice daily; each dose should be given with the morning and evening meal. The applicant conducted a fairly comprehensive clinical development program for dronedarone in NDA 21-913 and the findings are applicable to NDA 22-425. Two new clinical pharmacology studies were included in NDA 22-425; these studies were conducted in patients (impaired hepatic function and impaired renal function) and included healthy subjects as controls. Dronedarone was administered orally in these studies. In addition, three in vitro metabolism studies were conducted. This review addresses the clinical pharmacology/biopharmaceutics information related to the complete response and relevant new clinical pharmacology information.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the information submitted to NDA 22-425. The clinical pharmacology and biopharmaceutics information provided in NDA 22-425 is acceptable. Please refer to previous NDA 21-913 for detailed labeling recommendations; an additional labeling comment is listed below. NDA 22-425 includes updated labeling in the required Prescription Drug Labeling format.

New Labeling Comment Regarding Impaired Hepatic Function

Based on the findings of the Hepatic Impairment study, patients with moderately impaired hepatic function should be monitored closely for adverse events when receiving dronedarone. This recommendation is based on the fact that these patients had numerically higher plasma concentrations than subjects with normal hepatic function after receiving the proposed dosing regimen (400 mg dronedarone BID). The exposure values in these patients were highly variable and tended to be relatively higher suggesting that some patients may achieve supra-therapeutic dronedarone concentrations. There is no exposure-response information to support the safe use of dronedarone that could result in supra-therapeutic dronedarone concentrations. Based on the available pharmacokinetic information, dronedarone should be contraindicated in patients with severe hepatic impairment, unless there is clinical experience with these patients, supporting its safe use.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Previously, the applicant conducted a fairly comprehensive clinical pharmacology and biopharmaceutics for dronedarone hydrochloride (NDA 21-913). The current NDA 22-425 includes five new studies involving the assessment of the effect of hepatic function, creatininemia, and in vitro metabolism.
Additional studies were submitted in NDA 22-425, including reanalysis of population pharmacokinetic data using "modern approaches" and reanalysis of other pharmacokinetic studies. These additional studies were not reviewed as they did not provide any new information.

Key Clinical Pharmacology and Biopharmaceutics Findings and Information

Intrinsic Factors (Special Populations): Impact of Impaired Hepatic Function
Following repeated administration (7 days) of dronedarone 400 mg twice daily (proposed regimen), dronedarone exposure in patients with moderate hepatic impairment was not statistically significantly different (at the 95 % confidence interval) from that in subjects with normal hepatic function (Table 1).

Table 1: Statistical comparisons of dronedarone PK measures in hepatic impairment study

PK Measure	Ratio Estimate or p-value	95 % Confidence Interval
Cmax	1.20	0.63 – 2.28
AUC	1.32	0.75 – 2.33
Half-life	P = 0.37	NA

Plasma concentrations were generally more variable and numerically higher in patients with impaired hepatic function, relative to subjects with normal hepatic function (Table 2).

Table 2: Dronedarone Mean (CV %) pharmacokinetic measures in hepatic impairment study

PK Measure	Hepatic impaired patients (n =8)	Healthy Subjects (n = 8)
Cmax (ng/mL)	134 (93)	90.4 (44)
Tmax* (h)	2.5 [1 – 5]	3.5 [2 – 6]
AUC (ng h/mL)	618 (71)	395 (37)

* Median [range] reported for Tmax

Patients with moderate hepatic impairment had a relatively high degree of variability (CV above 70 %) and numerically higher exposure than subjects with normal hepatic function.

Pharmacodynamics (Creatininemia)/Pharmacokinetics: Impact of Impaired Renal Function
Following repeated administration (14 days) of dronedarone 400 mg twice daily to elderly subjects with normal renal function and different degrees of renal impairment (mild and moderate)

- Creatinine plasma concentrations increased over the first three days, peaking on Day 5
- Creatinine plasma concentrations decreased to baseline level three days after treatment discontinuation (Day 17)

- The magnitude of creatinine changes was independent of renal function
- Dronedarone plasma concentrations were similar across renal function strata (Table 3)

Table 3: Dronedarone PK measures in healthy males in renal impairment study

PK Parameter	Normal n=6	Mild n=7	Moderate n=6
C_{max} (ng/mL)	169 ± 64.9 (38) [156]	152 ± 43.8 (29) [146]	151 ± 60.5 (40) [141]
t_{max} (h)	4.00 (4.00 , 6.00)	4.00 (2.00 , 6.00)	4.00 (4.00 , 6.00)
$AUC_{0-\tau}$ (h.ng/mL)	1440 ± 545 (38) [1330]	1160 ± 213 (18) [1140]	1270 ± 583 (46) [1160]

Tabulated values are Mean ± SD (CV%) [Geometric Mean] except for t_{max} where values are Median (Min, Max)

In Vitro Metabolism

- SR35021, the major metabolite of dronedarone, is metabolized primarily by CYP3A and by CYP2D6 to a minor extent; other non-CYP enzymes may also be involved in SR35021 metabolism
- Dronedarone and SR35021 have a low potential to inhibit CYP2B6 enzymatic activity, based on I/Ki calculations (I*/Ki < 0.1). The apparent Ki for SR35021 was 56.9 µM and that for dronedarone was 12.0 µM
- Dronedarone and SR35021 have a low potential to inhibit CYP2C8 enzymatic activity, based on I/Ki calculation (I*/Ki < 0.1). The apparent Ki for SR35021 was 36.6 µM and that for dronedarone was above 100 µM;

* I represents in vivo Cmax: 0.467 µM for SR33589 (260 ng/mL) and 0.360 µM for SR35021 (180 ng/mL); Ki represents inhibition constant.

Signatures

Primary Clinical Pharmacology Reviewer Robert O. Kumi

Acting Team Leader Elena Mishina

CC: NDA 22-425 Mishina Uppoor Mehta Kumi (HFD 860)

2 QUESTION BASED REVIEW

This clinical pharmacology and biopharmaceutical review for NDA 22-425 employs an abridged version of the 'Question Based Review' (QBR) since most QBR elements were addressed in the original dronedarone application (ND 21-913). Please refer to NDA 21-913 for information on human pharmacokinetics and bioavailability of dronedarone. The QBR elements addressed in detail in this Clinical Pharmacology Review are Intrinsic Factors (effect of impaired hepatic function) Pharmacodynamics (related to creatininemia and renal function), and Extrinsic factors (in vitro metabolism). In all, five studies were reviewed.

2.1 What are the general attributes of dronedarone hydrochloride?

Regulatory History

The clinical pharmacology information provided in NDA 21-913 was deemed acceptable by the office of clinical pharmacology; however, the following comments were to be conveyed to the sponsor, as appropriate.

Comments to Sponsor

- Please indicate when results from the hepatic impairment study, POP5820, will be submitted to the Agency. Without this information, the product labeling will be restrictive in this patient population
- You have not adequately addressed the issue of dose-response in the target population; therefore dosage adjustment is not feasible during dronedarone therapy.
- You have not provided sufficient permeability information to support dronedarone designation as BCS 2. Please provide all available information that demonstrate dronedarone is a high permeability compound.
- The dissolution methodology is acceptable, however, we do not agree with your dissolution specification. Based on the data provided the following specification is more appropriate: 1) Not less than (b) (4) and not more than (b) (4) is dissolved within 30 minutes 2) Q = (b) (4) at 90 minutes
- In future submissions, any concentrations and/or subjects that have been excluded from the analysis should be maintained in the datasets. For this analysis, the sponsor identified 123 concentrations (from 10 subjects) as outliers and excluded these observations from the dataset.

Ultimately, the 29 August 2006 Action Letter for NDA 21-913 included the comments related to permeability and dissolution only. The unaddressed comments were directly or indirectly addressed fully or in part in NDA 22-245. Currently, the Office on New Drug Quality Assessment (ONDQA) is responsible for dissolution evaluations; whereas, OCP determines BCS classification. New dissolution information was included in NDA 22-425; no new permeability information was provided, thus there was no need for additional OCP evaluation. For the remaining comments: 1) The POP5820 study was included in the new NDA, 2) dose-response, though desirable, was not conducted for the new indication, and 3) The comment related to population PK analysis can be forwarded to the Applicant in the Action Letter for NDA 22-425.

2.2 What are the general clinical pharmacology characteristics of dronedarone?

The clinical pharmacology program for dronedarone was comprehensive and evaluated previously for NDA 21-913.

Design Features of Clinical Study

One clinical efficacy study, EFC5555 (ATHENA), was conducted to support the proposed indication. ATHENA was a double-blind, well-controlled study of 2327 placebo and 2301 patients receiving dronedarone for a mean duration of 21 months. According to the applicant, the study population mirrors the AF/AFL population for which the drug is targeted. The primary endpoint was time to first hospitalization for cardiovascular reasons or death.

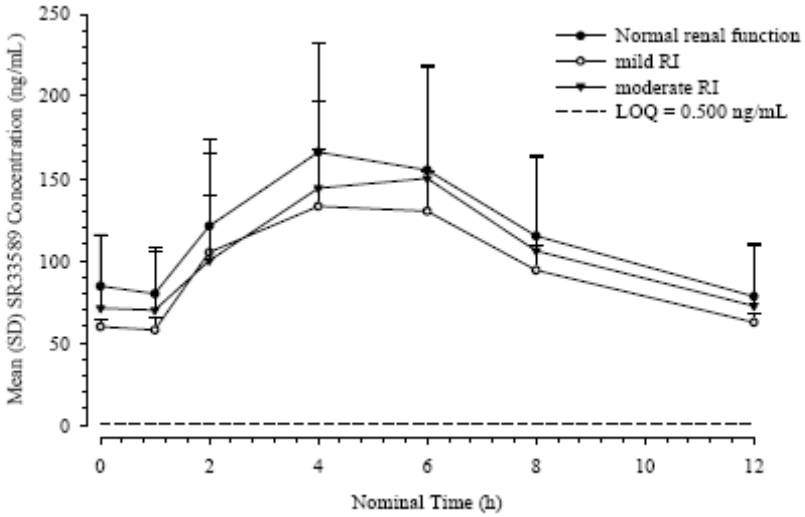
Pharmacodynamics (Creatininemia)/Pharmacokinetics

This study confirmed the previous observation of plasma creatinine increase under dronedarone treatment. The effect of dronedarone treatment on plasma creatinine did not appear to be related to kidney function, and the effect stabilized after about 3 to 5 days of treatment. Plasma creatinine returned to baseline about 3 days after discontinuation of dronedarone treatment. Dronedarone exhibits similar pharmacokinetic parameter values in steady-state conditions irrespective of the population (subjects with normal renal function and subjects with mild and moderate renal impairment) studied. These results are consistent with the very minor urinary excretion of dronedarone and SR35021.

<u>Dronedarone Pharmacokinetics</u>

The mean dronedarone plasma concentration-time profiles for subjects with normal renal function and impaired renal function are depicted in the figure below.

Figure 1: Mean dronedarone plasma concentration-time profile in renal impairment study



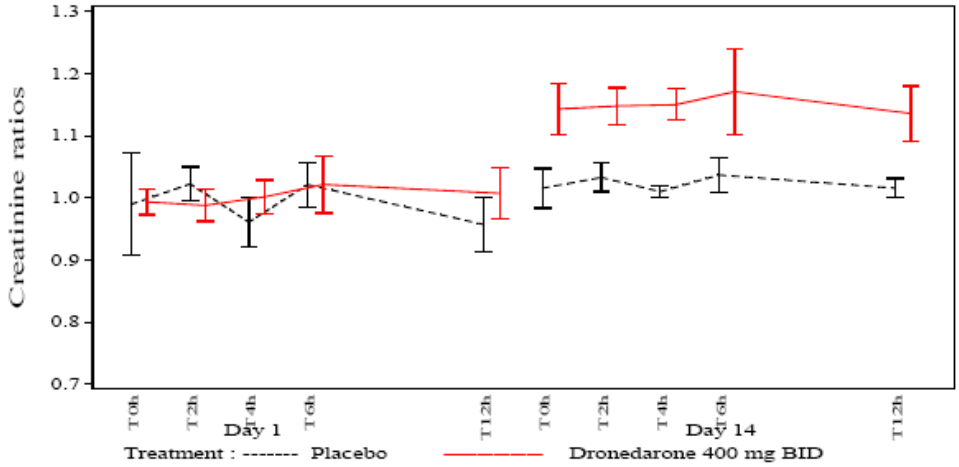
The report did not include a formal statistical comparison of PK measures across the treatment groups as such a comparison was not one of the stated study objectives. However, based on the current study results, renal impairment will not alter dronedarone PK. This finding is expected as dronedarone is excreted to a minimal extent renally, and a previous study had demonstrated that the degree of renal impairment did not alter dronedarone PK.

Dronedarone Pharmacodynamics (PD)

There was no difference in creatinine ratios among renal function strata; thus, the findings for moderate renal impairment can be extrapolated to subjects with normal renal function and mild renal impairment. By inspection, the following figure suggests that for subjects with moderate renal impairment:

- there is no difference in creatinine ratios (baseline vs. given Day) between placebo and dronedarone on Day 1
- there is a difference in the creatinine ratios between placebo and dronedarone on Day 14

Figure 2: Time-matched ratios vs. baseline in creatinine concentration on Day 1 and Day 14 (moderate renal impairment)



The clinical relevance of the 10 to 20 % increase in plasma creatinine concentrations is unclear according to the Medical Reviewer. However, the clinical studies and labeling provide specific instructions related to dronedarone and creatinine. In essence, these instructions indicate that: a) creatininemia is reversible upon discontinuation of dronedarone and b) creatininemia should not lead to discontinuation of ACE inhibitors or other compounds that are known to increase plasma creatinine concentration.

Three key findings related to the time course of effect (creatininemia) were:

1) The maximum PD effect (plasma creatinine concentration) was reached on Day 5.
2) Plasma creatinine concentrations returned to baseline levels three days after the last study drug intake.
3) Plasma concentrations exhibited a similar time course as creatinine concentrations.

2.3 What intrinsic factors affect dronedarone exposure (Effect of moderate hepatic impairment)

Patients with moderately impaired hepatic function had numerically higher (~ 25 %) plasma concentrations than subjects with normal hepatic function after receiving the proposed dosing regimen (400 mg dronedarone BID). However, exposure values were highly variable and tended to be higher in patients, suggesting that some patients may achieve supra-therapeutic dronedarone concentrations. Consequently, patients with moderately impaired hepatic function who receive dronedarone should be monitored closely for adverse events. There are no PK data on patients with severe hepatic impairment. According to the Medical Reviewer, the degree of hepatic impairment was not documented in the clinical studies. Patients with severe hepatic impairment should not receive dronedarone in the absence of clinical experience with these patients or

exposure-response data, supporting its safe use. As expected, SR35021 exposure decreased (approximately 50 %) in patients compared with healthy subjects, as dronedarone is primarily hepatically cleared. These decreases were statistically significant for Cmax, but not AUC.

The table below summarizes the PK data obtained in the hepatic impairment study.

Table 4: Dronedarone Pharmacokinetic measures in hepatic impairment study (400 mg BID)

PK Parameter Mean (CV %)	Healthy Subjects, N=8	Hepatically Impaired Patients, N=8
	First Administration – Day 1	
Cmax (ng/mL)	134 (93)	219 (72)
Tmax (h)	2.5 [1 – 5]	3.5 [2 – 6]
AUC_{0-12}	618 (71)	395 (37)
	Repeated Administration – Day 7	
Cmax (ng/mL)	219 (72)	143 (25)
Tmax (h)	3.5 [2 – 6]	4.5 [2 – 5]
AUC_{0-12}	1820 (71)	1040 (22)

The following two tables summarize the exposure comparisons for dronedarone (Table 5) and SR35021 (Table 6) in the hepatic impairment study. As noted, there is no statistical difference in dronedarone exposure between subjects with normal hepatic function and those with moderate hepatic function. For SR35021, there is a trend towards decreased exposure for patients with moderate hepatic function, relative to subjects with normal function, because SR35021 is formed by hepatic processes. It should be noted that the statistical comparisons were done at the 95 % confidence interval rather than the recommended 90 % confidence interval.

Table 5: Statistical comparisons of dronedarone PK measures in hepatic impairment study (400 mg BID regimen)

Parameter	Ratio Estimate or p-value	95 % Confidence Interval
Cmax	1.20	0.63 – 2.28
AUC_{0-12}	1.32	0.75 – 2.33
T1/2	P = 0.37	NA
Unbound AUC	1.88	1.10 – 3.22

Table 6: SR30621 Geometric mean ratios and associated confidence intervals under fasted and fed conditions

Parameter	Ratio Estimate or p-value	95 % Confidence Interval
Cmax	0.44	0.25 – 0.79
AUC_{0-12}	0.53	0.28 – 1.01
T1/2	P = 0.04	NA
Unbound AUC	0.62	0.38 – 1.03

2.4 What extrinsic factors affect dronedarone or SR35021 pharmacokinetics (In vitro metabolism)

SR35021 was metabolized by CYP3A primarily and CYP2D6 to a lesser extent; there was also evidence that other non-CYP enzymes may be involved in SR35021 metabolism. Neither dronedarone nor SR35021 demonstrated the potential to inhibit CYP2C8 or CYP2B6 metabolism

<u>SR35021 Metabolism</u>

Study MIH0138 investigated SR35021 metabolism via microsomes, Supersomes and hepatocytes using standard in vitro techniques. In the microsome study, where SR35021

was incubated with active and inactive microsomes with or without NADPH, the following was observed (Table 7):

- No NADPH-dependent metabolism of SR35021 at either 0.2 µM (100 ng/mL) or at 2 µM (1000 ng/mL)
- Inactive microsomes did not deplete SR 35021 to as great a degree as active microsomes

Together these findings suggest that SR35021 metabolism involves microsomes, however, the metabolism is not solely dependent on CYP enzymes that require NADPH for activity

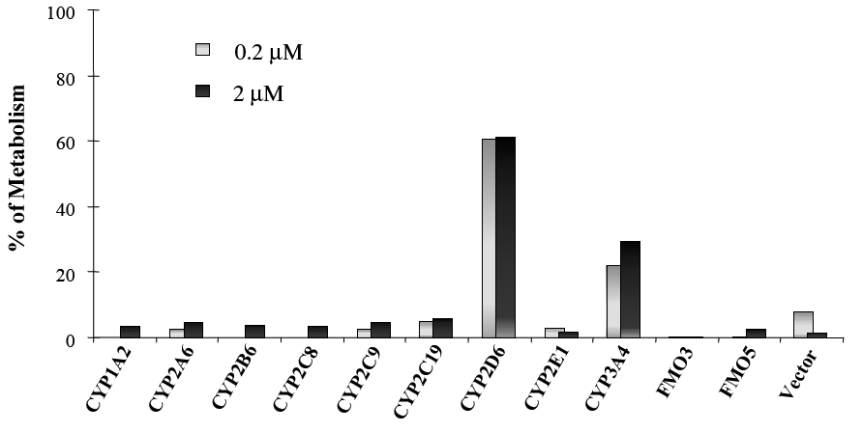
Table 7: Metabolism of SR35021 in human liver microsomes (Standard Conditions*)

Microsome Preparation	SR35021 Nominal (µM)	SR35021 Observed (µM)		Percent of Control (%)
		Control [a] (-NADPH)	Reaction [a] (+NADPH)	
Active	0.2	0.155	0.148	95.5
	2	1.27	1.27	100
Inactive[b]	0.2	0.201	0.200	99.5
	2	2.31	2.35	102

[a] Mean of duplicate preparations
[b] Microsomes were inactivated by heat
* 0.25 mg/mL protein, 37°C for 30 min

With Supersomes™ (Human cDNA Expressed CYP Isoforms), CYP2D6 and CYP3A metabolized SR35021 at both reaction mixture concentrations of 0.2 and 2 µM (figure below). Other CYP and non-CYP enzymes had minimal impact on SR35021 metabolism.

Figure 3: SR35021 metabolism by Supersomes



Additional studies were conducted with hepatocytes +/- specific enzyme inhibitors: quinidine for CYP2D6 and ketoconazole for CYP3A. Based on the inhibition results, the contribution of CYP2D6 and CYP3A to SR35021 metabolism was approximately 6 and 22 %, respectively.

CYP2B6 and CYP2C8 Inhibition Potential of dronedarone and SR35021

Standard procedures for determining inhibition potential were used. For CYP2C8 the probe substrate was paclitaxel and for CYB2B6 the probe substrate was bupropion. Ki values and proposed inhibition mechanisms for the two enzymes are summarized in the following table.

Table 8: Effect of SR33589* / SR35021* on Bupropion Hydroxylation in Human Liver Microsomes

Compound	Inhibition Model	Apparent Ki µM	I/Ki	Likelihood of inhibition
	Paclitaxel for CYP2C8			
Dronedarone	Not reported	> 100	< 0.01	Low
SR35021	Noncompetitive	36.6	0.0	Low
	Bupropion for CYP2B6			
Dronedarone	Mixed	12.0	0.039	Low
SR35021	Mixed	56.9	0.006	Low

* Concentrations: 0.467 µM for SR33589 or dronedarone (260 ng/mL) and 0.360 µM for SR35021 (180 ng/mL).

Reviewer note on Dronedarone and SR35021 concentrations

The dronedarone concentrations exceed therapeutic concentrations by more than 10-fold.

Based on current FDA guidelines (I/Ki), the inhibition data indicate that SR33589 and SR35021 have a low potential to significantly inhibit the clearance of drugs metabolized by CYP2B6 or CYP2C8. All I/Ki values are less than 0.1

2.5 What assay was used to measure dronedarone and SR35021 plasma concentrations in clinical pharmacology studies?

The standard, previously validated LC/MS/MS dronedarone assay used in NDA 21-913 was utilized in the clinical pharmacology studies for NDA 22-425. Within study assay validation was also conducted and the assay performances were acceptable. Please refer to individual study reviews in Appendix for additional details.

3 Labeling Comments

Please refer to the clinical pharmacology review for NDA 21-913 for detailed labeling recommendations. The only additional labeling comment for NDA 22-425 is related to cautionary use in patients with moderate hepatic impairment and contraindication in patients with severe hepatic impairment (see Recommendations Page 3)

4 APPENDIX

4.1 Proposed Labeling

4.2 Individual Study Reviews

4.2.1 Effect of Pharmacokinetics and safety of dronedarone after repeated oral doses for 7 days in patients with moderate hepatic impairment in comparison with healthy matched subjects - Non-randomized, non placebo-controlled, open-labeled, 2 parallel-group study (POP5820)

INVESTIGATORS	Kenneth C. Lasseter, MD and Thomas C. Marbury, MD
STUDY SITE	Clinical Pharmacology Associates, Miami, FL and Orlando Clinical Research Center, Orlando, FL
STUDY PERIOD	July, 2004 – April, 2005

Objectives (per applicant):

Primary

To assess the pharmacokinetics of dronedarone and its metabolite, SR35021, in patients with moderate hepatic impairment after repeated oral doses of dronedarone for 7 days given in fed conditions compared with healthy sex-, age- and weight-matched subjects.

Secondary

- To assess the pharmacodynamics of dronedarone based on ECG parameters and on vital signs (HR and BP)
- To assess the clinical and laboratory tolerability of dronedarone in patients with moderate hepatic impairment and in healthy subjects

Study Design

This was a multicenter, comparative, non-randomized, non-placebo-controlled, open-labeled, 2 parallel-group and repeated oral dose study. Dronedarone was administered initially as repeated 400 mg once daily (OD) doses. Based on an interim safety and PK evaluation, additional subjects and patients with moderate hepatic impairment (Child Pugh Class B) were included and treated with 400 mg once daily (OD), or 400 mg twice daily (BID). All subjects received a standardized meal (fed conditions)

Reviewer Note

This review is focused on the pharmacokinetic information; specifically, the 400 mg BID regimen, as this is the proposed dronedarone dosage. However, once daily information is included in this review for completeness.

Subject Demographics

The subject demographics are summarized in Table 9. Twenty six subjects were enrolled; however, twenty-four subjects completed the study: the eight at the 400 mg OD dose and 18 at the 400 mg BID dose. Two subjects in the 400 mg BID dose group discontinued the study: one healthy subject due to a treatment emergent adverse events or TEAEs (No. 840002103) and one patient with hepatic impairment due to investigator/subject request (No. 840001003).

Table 9: Subject Demographic Data

Parameter (unit)	Statistics/ Category	Dronedarone 400 mg OD		Dronedarone 400 mg BID		Overall
		Healthy subjects (N=4)	Hepatic impairment (N=4)	Healthy subjects (N=9)	Hepatic impairment (N=9)	(N=26)
Age (yrs)	N	4	4	9	9	26
	Mean (SD)	51.3 (4.8)	52.5 (3.4)	53.4 (8.7)	54.0 (6.9)	53.2 (6.7)
	Min - Max	45 - 55	48 - 56	46 - 69	45 - 65	45 - 69
Weight (kg)	N	4	4	9	9	26
	Mean (SD)	80.45 (14.66)	82.25 (16.90)	74.81 (11.41)	76.33 (14.49)	77.35 (13.31)
	Min - Max	67.0 - 96.3	67.3 - 99.5	57.3 - 90.0	53.2 - 100.0	53.2 - 100.0
Height (cm)	N	4	4	9	9	26
	Mean (SD)	178.0 (12.4)	168.0 (6.8)	166.8 (9.0)	169.8 (8.0)	169.7 (9.2)
	Min - Max	160 - 188	160 - 175	152 - 180	156 - 183	152 - 188
BMI (kg/m^2)	N	4	4	9	9	26
	Mean (SD)	25.40 (4.04)	28.90 (4.01)	26.82 (2.99)	26.44 (3.86)	26.79 (3.55)
	Min - Max	19.5 - 28.4	24.7 - 33.6	20.6 - 30.1	18.4 - 31.9	18.4 - 33.6
Gender	Male (N,%)	3 (75.0)	3 (75.0)	5 (55.6)	5 (55.6)	16 (61.5)
	Female (N,%)	1 (25.0)	1 (25.0)	4 (44.4)	4 (44.4)	10 (38.5)
Race	Black (N,%)	0 (0)	0 (0)	1 (11.1)	0 (0)	1 (3.8)
	Caucasian (N,%)	1 (25.0)	2 (50.0)	2 (22.2)	8 (88.9)	13 (50.0)
	Other (N,%)	3 (75.0)	2 (50.0)	6 (66.7)	1 (11.1)	12 (46.2)

PGM= SR33589B/POP5820/CSR/BS/PGM RPT/i4demo.sas OUT= OUTPUT/I4 demo1.html (09AUG2005 - 12:53)

Blood (Pharmacokinetic) sampling times

Blood samples were collected at the following times on the specified days:

- Day 1 and Day 7: predose and 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours
- Day 2, 4, 5 and 6: predose
- Day 7: predose and then 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48 and 72 hours on Day 7 after repeated administration of dronedarone 400 mg OD or BID.

Plasma unbound concentrations of dronedarone and SR35021 were assessed in blood (plasma) collected at the following times on the specified days:

- Day 1 and Day 7: predose and 2, 4, 6, 12 and 24 hours after repeated administration of dronedarone 400 mg OD
- Day 1 and Day 7: predose and 2, 4, 6, 12 hours on after repeated administration of dronedarone 400 mg BID

Formulation

Dronedarone, 400 mg tablets; Batch number: CL-04530

Bioanalytical methods

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as illustrated in Table 10.

Table 10: Performance of Dronedarone and SR35021 Assays (DOH0036)

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.50 to 300 ng/mL range^	Satisfactory
Between day Precision	CV data were not provided	Cannot be assessed
Accuracy	The majority of QC samples were within 15 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the to 0.50 to 300 ng/mL range^	Satisfactory
Between day Precision	CV data were not provided	Satisfactory
Accuracy	The majority of QC samples were within 15 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

^ Neither r nor R^2 values were provided; however, based on the validation report the assay is linear over the evaluated range
*The validation report for the assay included chromatograms that suggest the assay was specific

Unbound concentrations of dronedarone and SR35021 in human plasma dialysate were determined by equilibrium dialysis (turboflow extraction) and LC/MS-MS method. The assay performance was acceptable for both compounds and had the following characteristics:

- LOQ = 10 pg/mL
- Linear range: 10 to 500 pg/mL; r > 0.98
- The majority of QC samples were within 15 % of nominal concentration

Pharmacokinetics

The following dronedarone and SR35021 pharmacokinetic measures were estimated:

- Day 1: Cmax, tmax, AUC_{0-24} for OD regimen or AUC_{0-12} for BID regimen
- Day 7: Ctrough, Cmax, tmax, AUC_{0-24} for OD regimen, or AUC_{0-12} for BID regimen, t1/2z, and CL_{0-24}/F, Vdz/F for dronedarone only
- accumulation ratio (Rac) (Day 7/Day 1) for dronedarone and SR35021, calculated based on AUC_{0-24} for OD regimen and AUC_{0-12} for BID regimen, as well as Cmax
- metabolic ratio (Rmet: ratio of SR35021/dronedarone AUCs) after single and repeated administrations
- Day 1 and on Day 7: unbound fractions of dronedarone and SR35021 concentration were assessed; unbound AUC_{0-12} for BID regimen and unbound AUC_{0-24} for OD regimen

Statistical methods

Standard pharmaco-statistical methods were used to evaluate the effect of impaired hepatic function on dronedarone and SR35021 pharmacokinetics. The subjects with normal hepatic function served as the reference treatment group and subjects with impaired hepatic function

were the treatment group. The population and day effects were assessed separately for each dronedarone dose level with a linear mixed effect model:

PK parameter = Population +Day + Population*Day + Subject (Population) +
Error with random term for Subject and fixed term otherwise.

Cmax and AUCs were log-transformed before analysis. For these parameters, population ratio estimates and 95% CIs were computed within the above model framework, and then these estimates were converted to a ratio of geometric means by antilog transformation. It is noted that 95 % confidence intervals (CIs) rather than 90 % CIs (typical) were used to compare drug exposure (geometric mean estimates and associated CIs).

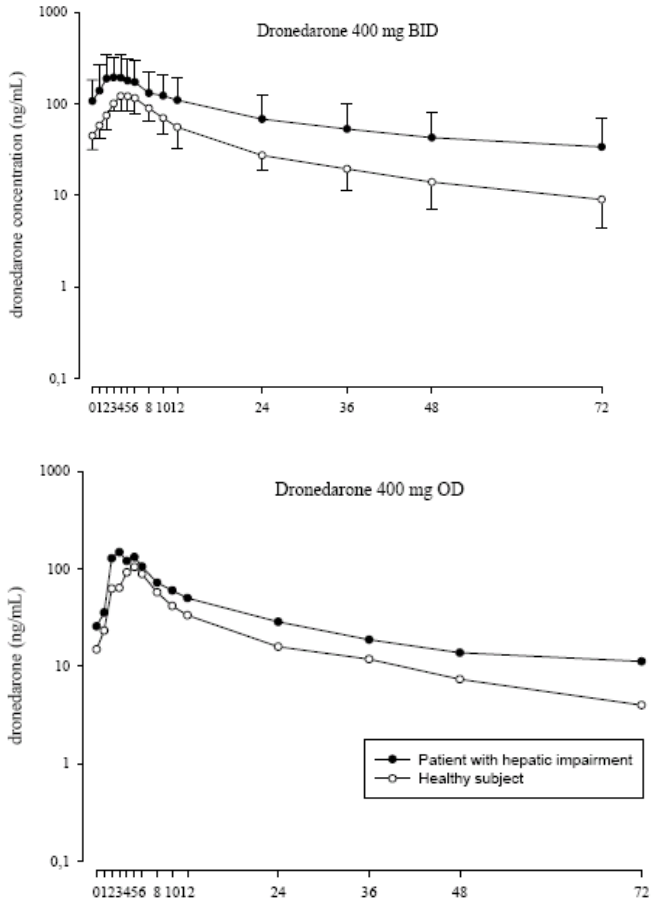
Additional statistical analyses were conducted to describe dronedarone and SR35021 PK.

Results

Dronedarone Pharmacokinetics

The mean dronedarone plasma concentration-time profiles in the two study groups are shown in Figure 4.

Figure 4: Mean dronedarone plasma concentration-time profiles following 400 mg BID dosing (upper panel) and 400 mg OD (lower panel) under fed conditions- filled circles (hepatic impairment) and open circles (healthy)



Dronedarone PK measures are summarized in Table 11 and the PK measures are statistically compared in Table 12. As noted previously, this review focuses on the 400 mg BID results.

Table 11: Dronedarone pharmacokinetic measures in hepatic impairment study

PK parameter Mean (CV%)	Dronedarone 400 mg OD		Dronedarone 400 mg BID	
	Hepatic impaired patient n=4	Healthy subject n=4	Hepatic impaired patient n=8	Healthy subject n=8
	First administration – Day 1			
C_{max} (ng/mL)	99.6 (31)	90.0 (52)	134 (93)	90.4 (44)
t_{max} (h)[a]	3 [2 ; 5]	5 [3 ; 5]	2.5 [1 ; 5]	3.5 [2 ; 6]
AUC [d] (ng.h/mL)	778 (26)	531 (50)	618 (71)[b]	395 (37)
Unbound fraction %[c]	0.279 (26)	0.255 (5)	0.498 (26)	0.337 (15)
Unbound AUC[d] (ng.h/mL)	2.15 (36)	1.35 (48)	2.77 (59)	1.30 (32)
	Repeated administration – Day 7			
C_{max} (ng/mL)	167 (23)	126 (63)	219 (72)	143 (25)
t_{max} (h)[a]	4 [2 ; 5]	3 [1 ; 5]	3.5 [2 ; 6]	4.5 [2 ; 5]
AUC [d] (ng.h/mL)	1510 (38)	1010 (60)	1820 (71)	1040 (22)
$t_{1/2Z}$ (h)	28.3 (44)	24.9 (21)	43.2 (35)	38.0 (62)
Unbound fraction %[c]	0.291 (29)	0.251 (32)	0.515 (27)	0.356 (15)
Unbound AUC[d] (ng.h/mL)	4.25 (38)	2.20 (58)	8.70 (59)	3.66 (22)

[a]: median [Min ; Max] values, [b]: n=7, [c]: mean values of unbound fractions observed at each sampling time in each day, [d]: AUC = AUC_{0-24} for the OD regimen and AUC_{0-12} for the BID regimen

Table 12: Statistical comparisons of dronedarone PK measures in hepatic impairment study

Parameter	Dronedarone 400 mg OD		Dronedarone 400 mg BID	
	Ratio Estimate or p-value	95% C.I.	Ratio Estimate or p-value	95% C.I.
C_{max}	1.63	[0.40 ; 6.73]	1.20	[0.63 ; 2.28]
AUC[a]	1.81	[0.53 ; 6.14]	1.32	[0.75 ; 2.33]
$t_{1/2z}$	p=0.79	-	p=0.37	-
Unbound AUC[a]	2.01	[0.69 ; 5.87]	1.88	[1.10 ; 3.22]

[a]: AUC = AUC_{0-24} for the OD regimen and AUC_{0-12} for the BID regimen

The comparisons (impaired hepatic function vs. normal hepatic function) indicate the following:

- there was a non statistically significant increase by 20 percent and 30 percent in dronedarone Cmax and AUC_{0-12}, respectively
- Dronedarone t1/2z was not different
- Dronedarone plasma unbound fractions were statistically significantly increased ~ 2-fold

Reviewer Comment on Interpretation of PK comparisons

- The data indicate that there was a high variability in exposure, particularly in subjects with impaired hepatic function (CV 71 % vs. 25 % after repeated administration). This finding coupled with the relatively wide confidence intervals suggests that some patients with impaired hepatic function may be at an additional risk for experiencing adverse events associated with dronedarone administration. There is limited information on dronedarone exposure-response, thus the ramifications of hepatic impairment cannot be clearly delineated currently.

- The change in unbound fractions is unlikely to be clinically significant due to relatively small magnitude of the change 0.32 to 0.52 %.

Metabolic ratio
The metabolic ratio, Rmet, observed on Day 7 after repeated BID oral administration of dronedarone was lower in patients with hepatic impairment (0.33 to 0.36) compared with healthy subjects (0.71 to 0.99). The finding is expected as less hepatically-generated metabolite will be formed in patients with impaired hepatic function relative to those with normal hepatic function.

Accumulation ratio
The accumulation ratios were pooled for the two subject groups (populations) because the population term did not have a statistically significant effect. As summarized in the following table, both patients with moderate hepatic impairment and healthy subjects had statistically significant increases in exposure upon 7-day repeat dosing: 75 % increase for Cmax and 193 % increase for AUC.

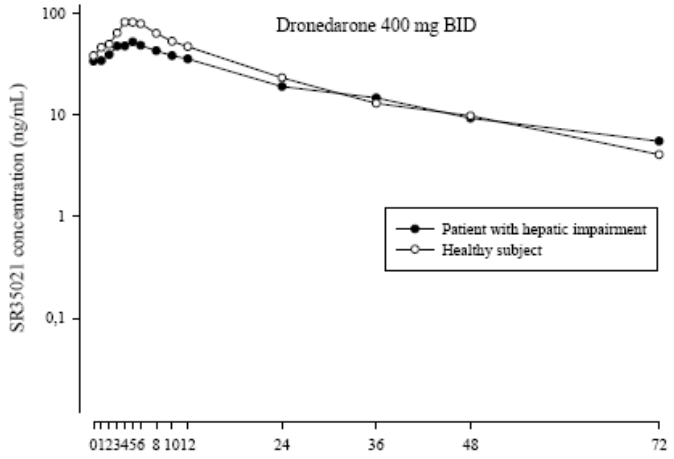
Table 13: Accumulation Ratio in Hepatic Impairment Study (Pooled across populations)

Parameter	Dronedarone 400 mg OD		Dronedarone 400 mg BID	
	R_{ac} estimate	95% C.I.	*R_{ac} estimate*	95% C.I.
C_{max}	1.32	[0.80 ; 2.16]	1.75	[1.36 ; 2.26]
AUC[a]	1.74	[1.30 ; 2.32]	2.93	[2.36 ; 3.63]

[a]: AUC = AUC_{0-24} for the OD regimen and AUC_{0-12} for the BID regimen

SR35021 Pharmacokinetics
The mean SR35021 plasma concentration-time profiles are depicted in the following figure.

Figure 5: Mean SR35021 plasma concentration-time profile following administration of dronedarone 400 mg BID in hepatic impairment study



The PK measures for SR35021 are summarized in the following two tables. Based on the statistical comparisons (Table 15) for the BID regimen, relative to subjects with normal hepatic function, subjects with impaired hepatic function had:

- a statistically significantly lower Cmax

- a statistically significantly longer half-life
- tended to have lower AUC

Table 14: SR30521 PK measures in hepatic impairment study

PK parameter Mean (CV%)	Dronedarone 400 mg OD		Dronedarone 400 mg BID	
	Hepatic impaired patient n=4	Healthy subject n=4	Hepatic impaired patient n=8	Healthy subject n=8
	First administration – Day 1			
C_{max} (ng/mL)	24.3 (46)	51.7 (40)	22.1 (46)	46.6 (27)
t_{max} (h)[a]	4.5 [4 ; 6]	5 [4 ; 6]	4 [2 ; 5]	5 [3 ; 6]
AUC[d] (ng.h/mL)	218 (41)	398 (35)	162 (38)	240 (30)
Unbound fraction %[c]	1.48 (12)	1.20 (18)	2.02 (24)	1.70 (11)
Unbound AUC[d] (ng.h/mL)	3.12 (33)	4.56 (22)	3.08 (33)	4.01 (27)
	Repeated administration – Day 7			
C_{max} (ng/mL)	38.4 (30)	59.6 (52)	54.5 (63)	94.1 (25)
t_{max} (h) [a]	5.5 [3 ; 6]	4 [2 ; 6]	5 [3 ; 12]	5 [4 ; 6]
AUC[d] (ng.h/mL)	468 (22)	712 (45)	502 (68)	732 (26)
$t_{1/2Z}$ (h)	25.1 (27)	25.4 (28)	35.5 (57)	21.4 (26)
Unbound fraction %[c]	1.48 (9)	1.20 (25)	2.08 (25)	1.77 (13)
Unbound AUC[d] (ng.h/mL)	6.89 (20)	7.79 (32)	9.22 (56)	12.7 (14)
Rmet	0.36 (57)	0.99 (66)	0.33 (67)	0.71 (14)

a: median [Min ; Max] values, b: n=7, c: mean values of unbound fractions observed at each sampling time in each day, [d]: AUC = AUC_{0-24} for the OD regimen and AUC_{0-12} for the BID regimen

Table 15: SR30621 Geometric mean ratios and associated confidence intervals under fasted and fed conditions

Parameter	Dronedarone 400 mg OD		Dronedarone 400 mg BID	
	Ratio Estimate or p-value	95% C.I.	Ratio Estimate or p-value	95% C.I.
C_{max}	0.59	[0.24 ; 1.43]	0.44	[0.25 ; 0.79]
AUC[a]	0.62	[0.31 ; 1.25]	0.53	[0.28 ; 1.01]
$t_{1/2z}$	p=0.98	-	p=0.04	-
Unbound AUC[a]	0.78	[0.48 ; 1.27]	0.62	[0.38 ; 1.03]

[a]: AUC = AUC_{0-24} for the OD regimen and AUC_{0-12} for the BID regimen

There was no difference in the accumulation ratio (AUC or Cmax) between the two populations (data not shown).

Applicant's Safety Summary

There were no deaths or serious adverse events (AEs) reported during the study. One healthy subject discontinued study drug on Day 1, due to non-serious treatment emergent AEs (blurred vision, hyperhydrosis, tremor, asthenia, dry mouth, headache), reported 3.5 hours after the first 400 mg dose of the BID regimen. Few potentially clinically significant abnormalities (PCSAs) were observed in hematology and in vital signs, at both doses and in both populations. No PCSAs of delta QTcB/QTcF >60 ms were recorded. PCSAs in QTcB/QTcF >450 ms (males) or >470 ms (females) were recorded mainly in patients with hepatic impairment taking 400 mg

BID. The mean values of QTc intervals at baseline were higher in patients compared with healthy subjects. Diarrhea

Recommendations/Conclusions

- Average steady state of dronedarone and SR35021 was reached after 3 to 6 treatment days for both populations (patients with moderate hepatic impairment and healthy subjects) receiving the proposed 400 mg BID regimen
- Based on the 95 % confidence interval, non-statistically significant increases of 1.2- to 1.3-fold in dronedarone Cmax and AUCs were observed after single and repeated dronedarone 400 mg BID administration in patients with moderate hepatic impairment, compared with healthy subjects. However, exposure values were highly variable in patients, suggesting that some patients may achieve supra-therapeutic dronedarone concentrations. Consequently, patients with moderately impaired hepatic function and severe hepatic dysfunction should be monitored closely for adverse events; potentially, subjects with impaired hepatic function should not receive dronedarone, unless there's clinical experience with these patients, supporting its safe use.
- SR35021 exposure decreased approximately 50 % (Cmax and AUCs) in patients compared with healthy subjects; however, these decreases were statistically significant, for Cmax, but not AUC.
- Dronedarone plasma unbound fractions were slightly higher in patients compared with healthy subjects, with a 2-fold increase in unbound AUCs. However, the change in the unbound fraction did not appear clinically significant
- Dronedarone t1/2z was not different in patients compared with healthy subjects, with a mean dronedarone t1/2z of 38 to 43 hours in the BID regimen for both populations.
- SR35021 plasma unbound fraction remained approximately similar for the 2 populations, for each dose regimen.
- After repeated oral administration of dronedarone 400 mg BID, the accumulation ratio was about 1.8 and 2.9, respectively, for dronedarone Cmax and AUC0-12 across both populations, and 2.1 and 3.1, respectively, for SR35021.

4.2.2 A randomized, double-blinded, placebo-controlled, two parallel group study to assess the effect before, during, and after treatment with 400 mg BID of oral dronedarone for 14 days on creatininemia in elderly male subjects (PDY5850)

INVESTIGATORS	Kenneth C. Lasseter, MD and Thomas C. Marbury, MD
STUDY SITE	Clinical Pharmacology Associates, 2060 N.W. 22nd Avenue, Miami, FL 33142, USA
STUDY PERIOD	November 2004 – January, 2008

Objectives (per applicant):

Primary objective
To evaluate the effect of oral dronedarone compared with placebo on the pharmacodynamics of creatininemia during and after drug administration in elderly subjects.

Secondary objectives
- To assess the effect of oral dronedarone compared with placebo on plasma/urine markers of the RAAS and associated factors including PRA, aldosterone, angiotensin II, cortisol, urea, uric acid, NMN, sodium, and potassium in elderly subjects.
- To document the plasma concentrations of dronedarone and SR35021 during and after treatment
- To assess the relationship between plasma concentrations of dronedarone and/or SR35021 in conjunction with creatininemia.

Study Design
This was a multi-center, randomized, placebo-controlled, double-blinded study, with a 3-day placebo run-in period followed by a 14-day repeated dosing of dronedarone or placebo. Thirty-three elderly male subjects were enrolled and divided into three strata according to their creatinine clearance (CLcr) calculated at screening with the Cockroft and Gault formula:
- CLcr >30 to 50 mL/min- subjects with moderate renal impairment
- CLcr >50 to 80 mL/min- subjects with mild renal impairment
- CLcr >80 mL/min- subjects with normal renal function

Additionally some subjects received placebo. All subjects received standardized meals.

Subject Demographics
Subject demographics are presented in the following table. Of the 33 randomized subjects, 29 completed the study. Two subjects recruited at the New Orleans center discontinued after Hurricane Katrina (Subjects No. 840002001 and No. 840002002), and 2 other subjects withdrew consent (Subjects No. 840001027 and No. 840001006).

Table 16: Subject Demographic Data

Parameter (unit)	Statistics/ Category	Strata(*)					
		Normal		Mild		Moderate	
		Placebo (N=4)	Dronedarone 400 mg BID (N=6)	Placebo (N=4)	Dronedarone 400 mg BID (N=7)	Placebo (N=4)	Dronedarone 400 mg BID (N=8)
Age (Yrs)	N	4	6	4	7	4	8
	Mean (SD)	66.8 (1.5)	66.3 (1.0)	74.5 (4.4)	69.6 (4.4)	71.5 (5.6)	72.5 (5.3)
	(Min , Max)	(65 , 68)	(65 , 68)	(69 , 78)	(65 , 78)	(66 , 79)	(65 , 79)
Weight (kg)	N	4	6	4	7	4	8
	Mean (SD)	88.43 (8.11)	88.40 (6.23)	75.70 (7.44)	70.00 (6.50)	72.33 (7.11)	63.29 (10.79)
	(Min , Max)	(80.5 , 97.3)	(79.5 , 98.2)	(66.4 , 84.1)	(63.6 , 81.8)	(64.1 , 81.2)	(50.0 , 81.2)
Height (cm)	N	4	6	4	7	4	8
	Mean (SD)	171.0 (8.0)	175.7 (4.1)	167.3 (4.6)	168.4 (5.4)	168.0 (6.3)	163.4 (8.6)
	(Min , Max)	(165 , 182)	(170 , 180)	(162 , 172)	(165 , 180)	(160 , 175)	(147 , 172)
BMI (kg/m2)	N	4	6	4	7	4	8
	Mean (SD)	30.24 (1.99)	28.64 (1.62)	27.06 (2.48)	24.73 (2.73)	25.76 (3.68)	23.77 (3.92)
	(Min , Max)	(28.1 , 32.9)	(26.9 , 31.3)	(24.4 , 29.8)	(21.0 , 29.3)	(22.2 , 29.1)	(17.8 , 28.3)
Gender	Male	4 (100.0%)	6 (100.0%)	4 (100.0%)	7 (100.0%)	4 (100.0%)	8 (100.0%)
Race	Black	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	2 (25.0%)
	Caucasian/White	1 (25.0%)	3 (50.0%)	0 (0.0%)	2 (28.6%)	1 (25.0%)	3 (37.5%)
	Other(Hispanic)	3 (75.0%)	3 (50.0%)	4 (100.0%)	5 (71.4%)	2 (50.0%)	3 (37.5%)

(*) Strata were defined at screening with creatinine clearance calculated from Cockroft and Gault formula as:
Moderate:]30 – 50 mL/min], Mild:]50 - 80 mL/min], Normal: >80 mL/min
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Blood (Pharmacokinetic) sampling times

Blood samples were drawn at the following times on the specified days:

- Day 1: predose, and 2, 4, 6, 12 hours postdose
- Days 2, 3, 4, 5, 7, 10, 12 predose
- Day 14: predose and 1, 2, 4, 6, 8, 12 hours postdose
- On Days 15 (24 hours), 16 (48 hours), 17 (72 hours), 18 (96 hours), 21 (168 hours), 24 (240 hours), 27 (312 hours), and 28 (336 hours).

Formulation

- Dronedarone 400 mg tablets; Batch numbers: CL-05232 and CL-09176
- Placebo tablets; Batch numbers: CL-04404, CL-08265 and CL-08546

Bioanalytical methods

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay was the same as that used in POP5820 and the assay performance was acceptable (data not included in this review).

Pharmacokinetics

The following plasma pharmacokinetic (PK) parameters were determined for dronedarone and SR35021 by non-compartmental analysis: Cmax, tmax, and AUC_{0-12}.

Statistical methods

Pharmacodynamics

- Analysis of primary endpoint:
  - time-matched ratios of plasma creatinine concentrations at Day 1 (single dose) and Day 14 (repeated doses) versus baseline (Day –1) were calculated
  - ratios versus baseline in trough concentrations during treatment and follow-up periods.

These parameters were then analyzed as log-transformed data, using a linear mixed effects model that included terms for subject as random effect, for treatment, stratum, time (or day) and treatment-by-time (or treatment by- day) interactions as fixed effects. Point estimates and 95% confidence intervals (CIs) of differences between treatment means of dronedarone versus placebo were computed and converted to ratios of geometric means.

- Analysis of secondary endpoints:
  - plasma urea, uric acid, ^{1}N-methylnicotinamide, plasma renin activity, aldosterone, cortisol, and angiotensin II, time-matched ratios were calculated, and analyzed for differences
  - ratios of listed endpoints versus baseline in trough concentrations during treatment and follow up.

These parameters were analyzed in the same manner as the primary endpoint.

Pharmacokinetics

Dronedarone and SR35021 plasma concentrations were summarized using descriptive statistics.

Pharmacokinetic/Pharmacodynamic relationship

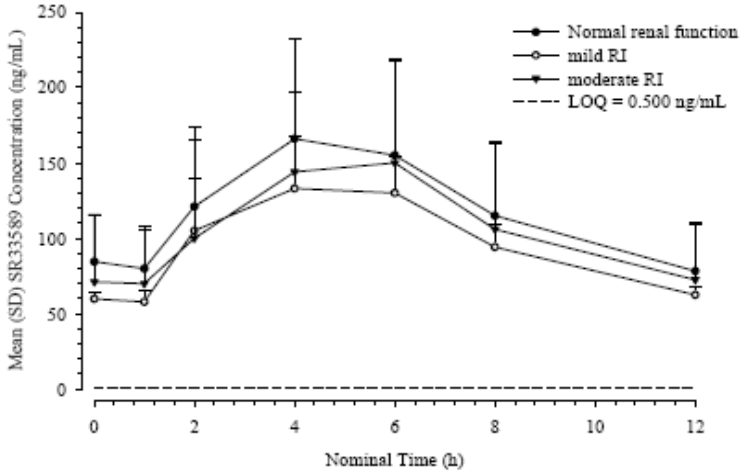
The relationship between dronedarone or SR35021 plasma concentrations and creatinine plasma concentrations was investigated, by day, stratum, and overall.

Results

Dronedarone Pharmacokinetics

The mean dronedarone plasma concentration-time profiles for subjects with normal renal function and impaired renal function are depicted in the figure below.

Figure 6: Mean dronedarone plasma concentration-time profile under fasted and fed conditions



The report did not include a formal statistical comparison of PK measures across the treatment groups; as such a comparison was not one of the stated study objectives. However, by inspection the data (table below) suggest renal impairment will not alter dronedarone PK. This finding is expected as dronedarone is not excreted renally; furthermore, a previous study in NDA 21-913 had demonstrated that the degree of renal impairment did not alter dronedarone PK. It is noted that dronedarone affects tubular secretion, thereby increasing plasma creatinine concentrations.

Table 17: Dronedarone PK measures on Day 14 in subjects with normal, mild, and moderately impaired renal function

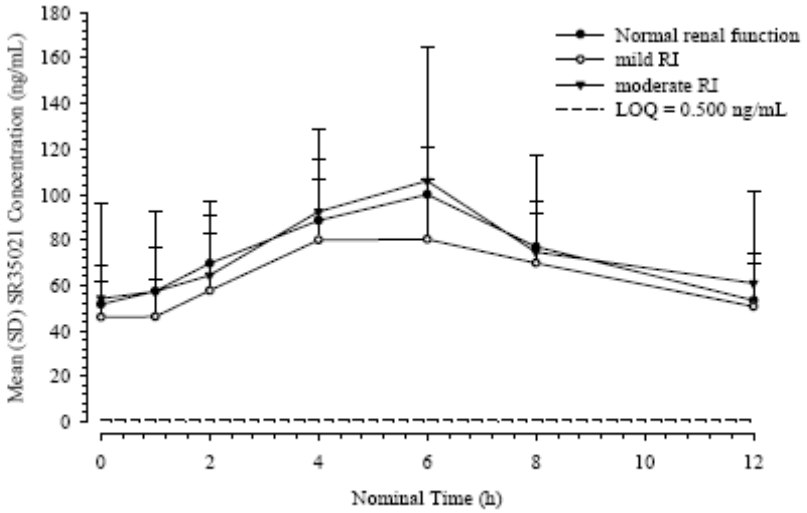
PK Parameter	Normal n=6	Mild n=7	Moderate n=6
C_{max} (ng/mL)	169 ± 64.9 (38) [156]	152 ± 43.8 (29) [146]	151 ± 60.5 (40) [141]
t_{max} (h)	4.00 (4.00 , 6.00)	4.00 (2.00 , 6.00)	4.00 (4.00 , 6.00)
$AUC_{0-\tau}$ (h.ng/mL)	1440 ± 545 (38) [1330]	1160 ± 213 (18) [1140]	1270 ± 583 (46) [1160]

Tabulated values are Mean ± SD (CV%) [Geometric Mean] except for t_{max} where values are Median (Min, Max)

SR35021 Pharmacokinetics

The mean SR35021 plasma concentration time profile under fasted and fed conditions is depicted in the following figure.

Figure 7: Mean SR35021 plasma concentration-time profile under fed and fasted conditions



SR35021 PK measures in the study are shown in the table below. As observed with dronedarone, SR35021 PK were not altered by renal function.

Table 18: SR30521 PK measures in renal impairment study

PK Parameter	Normal n=6	Mild n=7	Moderate n=6
C_{max} (ng/mL)	100 ± 20.8 (21) [98.5]	88.5 ± 23.9 (27) [85.6]	103 ± 52.4 (51) [92.8]
t_{max} (h)	6.00 (4.00 , 6.00)	6.00 (4.00 , 8.00)	4.00 (4.00 , 6.00)
AUC_{0-12} (h.ng/mL)	898 ± 243 (27) [873]	786 ± 245 (31) [751]	907 ± 489 (54) [806]

Tabulated values are Mean ± SD (CV%) [Geometric Mean] except for t_{max} where values are Median (Min, Max)

Dronedarone Pharmacodynamics (PD)

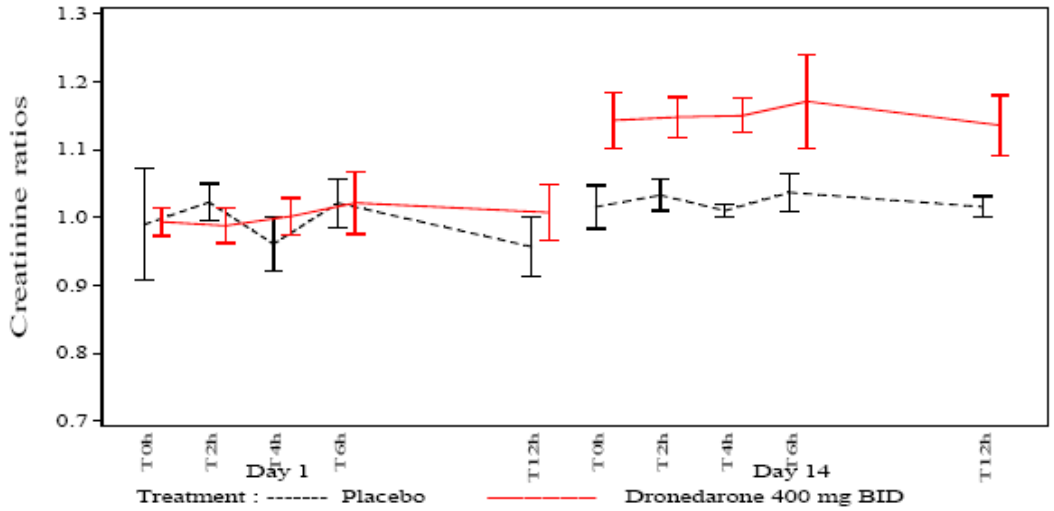
Primary PD Criteria: Plasma creatinine concentrations

The following observations were made based on a comparison of 400 mg BID vs. placebo

- On Day 14: Over the 12 hour period there was an increase in plasma creatinine concentration time-matched ratios versus baseline for dronedarone 400 mg BID (p <.001); the ratio of dronedarone versus placebo was 1.117 across strata (stratum effect not significant).
- On Day 1: No statistically significant difference existed
- Day 1 to Day 14: trough plasma creatinine concentration ratios versus baseline for dronedarone 400 mg BID (p <.001); the ratio of dronedarone versus placebo was 1.084 across strata (stratum effect not significant).

The listed findings are depicted and highlighted in the following figure.

Figure 8: Time-matched ratios vs. baseline in creatinine concentration on Day 1 and Day 14 (moderate renal impairment)



Secondary criteria:

The report notes that differences were evident between the dronedarone and placebo groups during pretreatment, suggesting that the results related to secondary pharmacodynamic measures should be viewed with caution.

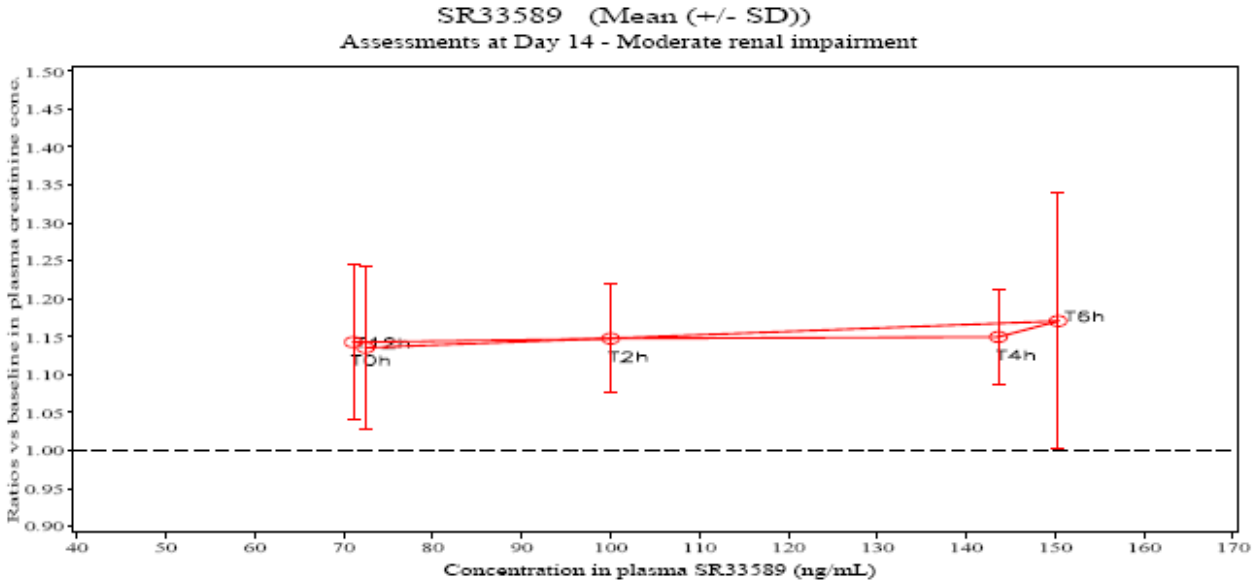
Reviewer Note on Secondary Criteria

Due to the reports stated limitations regarding secondary parameters, this reviewer decided to exclude findings related to the secondary parameters from this review.

Pharmacokinetic/pharmacodynamic (PK/PD) results: Onset/Offset of Primary PD effect
Some key PK/PD findings were as follows:

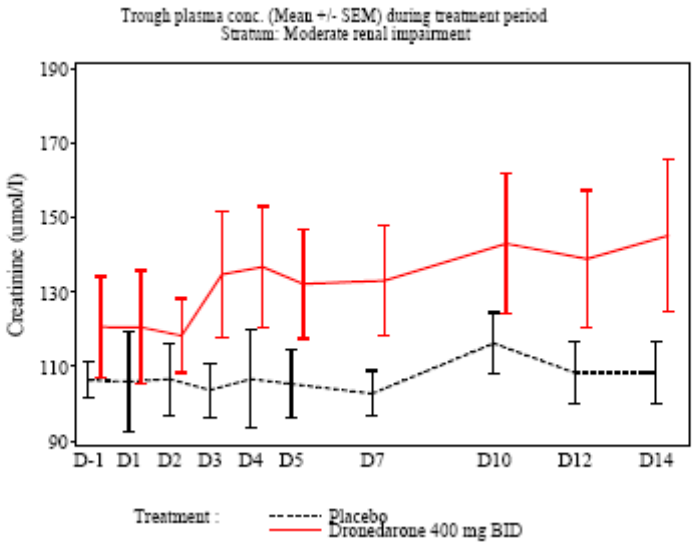
- On Day 14 when PK and PD steady-state had been achieved, the maximal pharmacodynamic effect occurred at 12 hours postdose, later than the tmax of plasma dronedarone and SR35021 concentrations (4 and 6 hours postdose, respectively). In essence this finding suggests that hysteresis occurs: within a dosing interval, the pharmacodynamic effect on plasma creatinine concentrations lagged behind plasma drug concentrations; however, graphically, the hysteresis was negligible as shown in the figure below.

Figure 9: Time-matched ratios in plasma creatinine concentration vs. dronedarone concentration on Day 14 (



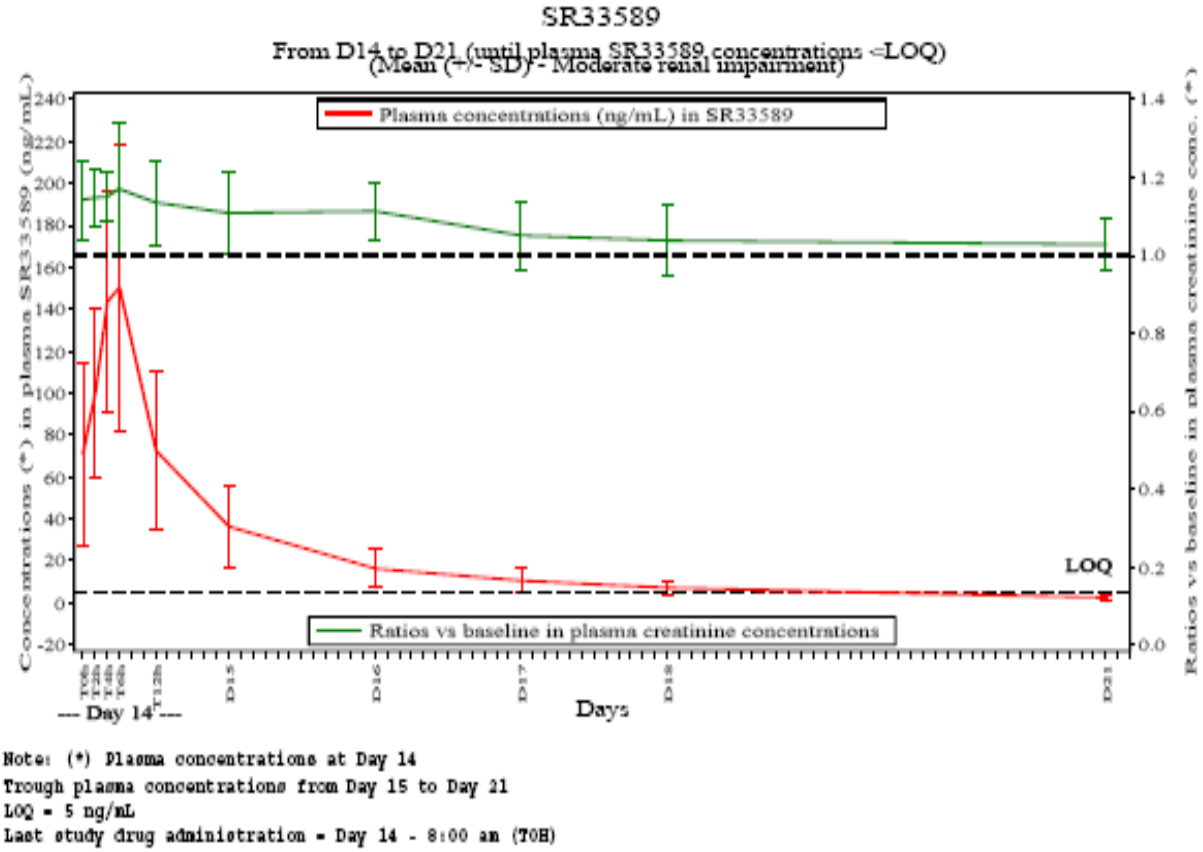
- The maximum pharmacodynamic effect (plasma creatinine concentration) was reached on Day 5.

Figure 10: Trough plasma creatinine concentration during treatment period (moderate renal impairment)



- Plasma creatinine concentrations returned to baseline levels three days after the last study drug intake. (Figure 11). The upper panel (green line) shows change in plasma creatinine concentration as a function of time; lower panel (red line) is plasma concentration-time profile for dronedarone

Figure 11: Trough plasma creatinine concentration and plasma concentrations following last dronedarone dose (moderate renal impairment)



- On Day 17, remaining concentrations of dronedarone and SR35021 were similar irrespective of the studied population and were lower than trough concentrations (data not shown).

Applicant's Safety Summary

No deaths, SAEs, or TEAEs leading to treatment discontinuation were reported during the study. Overall, TEAEs were reported in 8/21 (38.1%) subjects in the dronedarone 400 mg BID group and in 5/12 (41.7%) subjects in the placebo group. Only a few potentially clinically significant abnormalities (PCSAs) in clinical laboratory parameters and vital signs were recorded in both treatment groups and in all strata.

No subjects had QTc ≥500 ms. Overall, PCSAs of QTc >450 ms were recorded in 6/21 subjects in the dronedarone group,distributed across all strata and associated in 2 cases with a QTc change from baseline >60 ms, versus 2/12 subjects in the placebo group.

Recommendations/Conclusions

- This study confirmed the previous observation of plasma creatinine increase under dronedarone treatment. The effect of dronedarone treatment on plasma creatinine did not appear to be related to kidney function, and stabilized after about 3 to 5 days of treatment. Plasma creatinine returned to baseline about three days after discontinuation of dronedarone.
- Dronedarone and SR35021 exhibit similar pharmacokinetic parameter values in steady-state conditions irrespective of the population studied (normal renal function and subjects with mild and moderate renal impairment). These results are consistent with the very minor urinary excretion of dronedarone and SR35021.

4.2.3 Determination of the Cytochrome P450 (CYP) Isoforms Involved in the Oxidative Metabolism of SR35021 in vitro (MIH0138)

PROTOCOL #	MIV0159
Investigator	Carolyne Lieu
STUDY SITE	Sanofi Aventis, Malvern, Pennsylvania
STUDY PERIOD	October 2004 - February 2005

Objective (per applicant)

To determine the cytochrome P450 (CYP) isoforms involved in the oxidative metabolism of SR35021 and to assess the contribution from relevant CYP isoforms to overall hepatic metabolism using *in vitro* techniques.

Study Design

Standard procedures for in vitro metabolism studies were used. Microsome preparations were prepared from human liver or insect cells transfected with human CYP cDNA, or cryopreserved human hepatocytes. SR35021 was mixed with pooled microsomes. The SR35021 (primary metabolite of dronedarone) concentrations were between 0.2 and 2 µM (100 ng/mL and 1000 ng/mL). Two sets of studies were conducted.

1. Metabolism of SR35021 by individual cDNA expressed isoforms (Supersomes™): Reaction mixtures containing microsomes with a single expressed CYP isoform and SR35021.
2. Inhibition of SR35021 metabolism in human hepatocytes: Suspension cultures containing human hepatocytes, SR35021 and CYP selective inhibitors.

The isoforms investigated were CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A. The experiments included appropriate controls to ensure that the enzyme system was viable (e.g. selective CYP substrates, inactive microsomes and system +/- NADPH). SR35021 concentrations were determined by a validated LC/MS-MS method.

Compounds

- SR35021, batch number APS-15-15-1
- CYP enzyme substrates and inhibitors were obtained from commercial sources

Results

All control systems demonstrated that the system was functional (data are not included in this review).

Microsomes

Key findings from the initial study are summarized as follows (see table below):

- NADPH-dependent metabolism of SR35021 was not observed at either 0.2 µM (100 ng/mL) or 2 µM (1000 ng/mL) concentration.
- Inactive microsomes did not deplete SR 35021 to as great a degree as active microsomes

Together these findings suggest that SR35021 metabolism involves microsomes; however, the metabolism is not solely dependent on CYP enzymes that require NADPH for activity.

Table 19: Metabolism of SR35021 in human liver microsomes (Standard Conditions*)

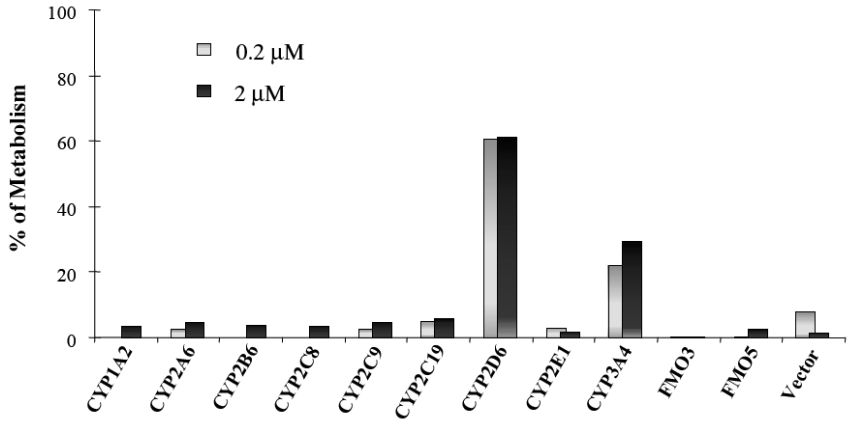
Microsome Preparation	SR35021 Nominal (µM)	SR35021 Observed (µM)		Percent of Control (%)
		Control [a] (-NADPH)	Reaction [a] (+NADPH)	
Active	0.2	0.155	0.148	95.5
	2	1.27	1.27	100
Inactive[b]	0.2	0.201	0.200	99.5
	2	2.31	2.35	102

[a] Mean of duplicate preparations
[b] Microsomes were inactivated by heat
* 0.25 mg/mL protein, 37°C for 30 min

Supersomes

Supersomes™ (Human cDNA Expressed CYP Isoforms) expressing CYP2D6 and CYP3A metabolized SR35021 at both reaction mixture concentrations of 0.2 and 2 µM (figure below). Other CYP enzymes had minimal impact on SR35021 metabolism.

Figure 12: SR35021 metabolism by Supersomes

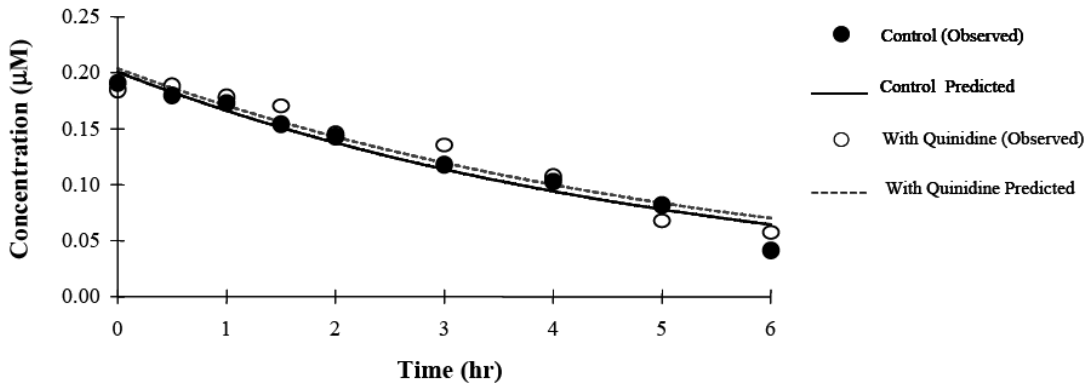


Hepatocytes +/- specific CYP2D6 inhibitor, quinidine

Significant metabolism (data are not included in this review) of 0.2 and 2 µM SR35021 (approximately 80 and 70 %, respectively) was observed in hepatocyte suspensions when

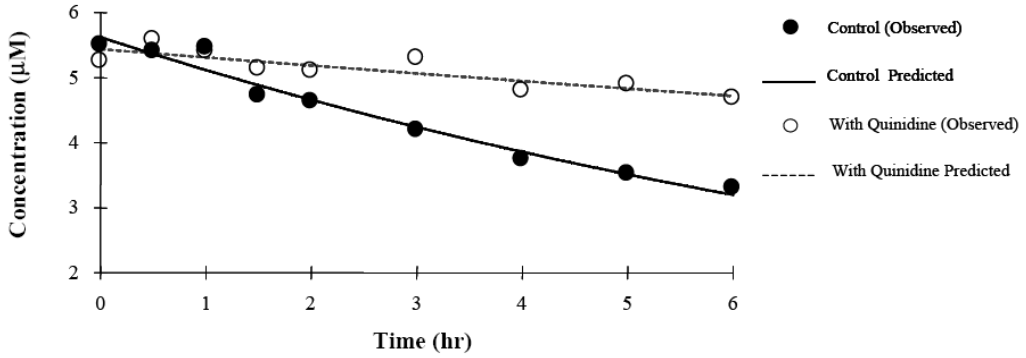
incubated for 6 hr at 37º C. However, quinidine (10 µM), a selective inhibitor of CYP2D6, did not inhibit this metabolism as shown in the following figure. Approximately 6 % of the metabolism could be attributed to CYP2D6

Figure 13: Metabolism of 0.2 µM SR35021 incubated with or without 10 µM quinidine in human hepatocytes



In contrast, bufuralol metabolism, selective for CYP2D6 activity and used as a positive control, showed the hepatocyte cultures were metabolically active and were inhibited by 10 µM quinidine as shown in the figure below.

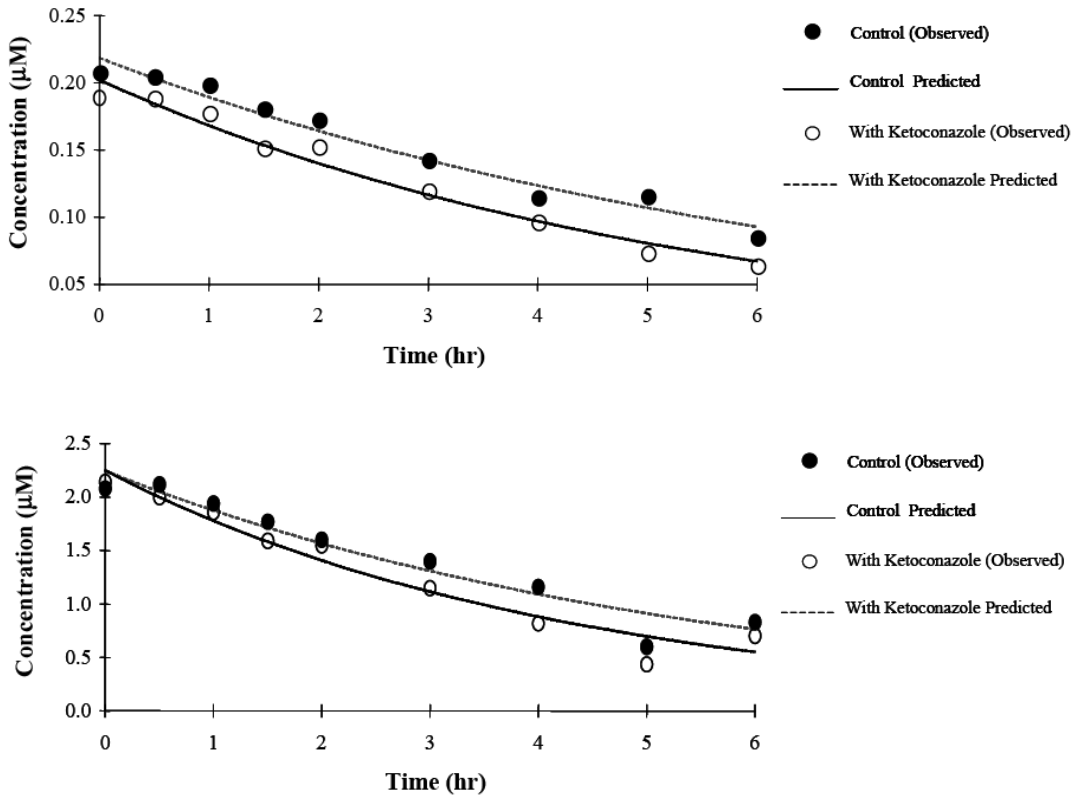
Figure 14: Metabolism of bufuralol incubated with or without 10 µM quinidine in human hepatocytes



<u>Hepatocytes +/- specific CYP3A inhibitor, ketoconazole</u>

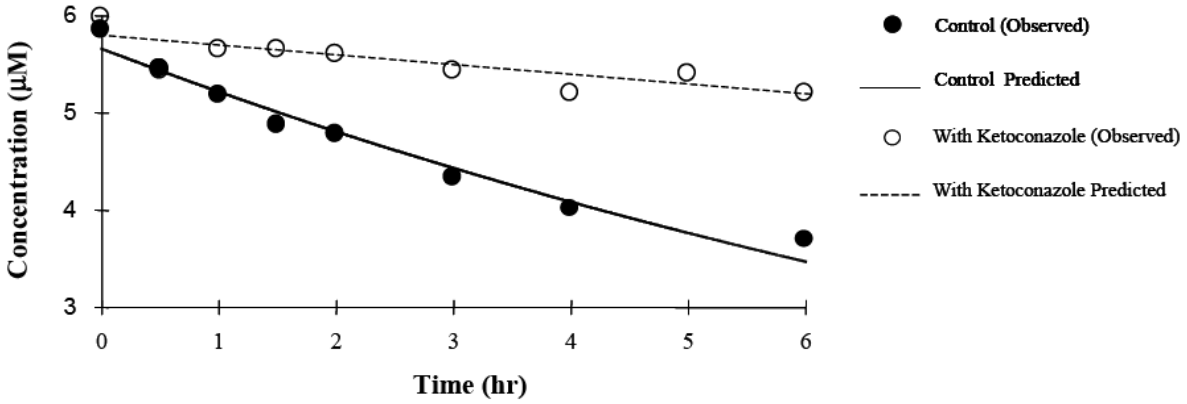
Significant metabolism (data are not shown in this review) of 0.2 and 2 µM SR35021 (~70%) was observed in hepatocyte suspensions when incubated for 6 hr at 37ºC. Metabolism of SR35021 in human hepatocyte suspensions containing 1 µM ketoconazole is depicted in the following figure. Based on the inhibition results, the contribution of CYP3A to SR35021 metabolism was approximately 22 %.

Figure 15: Metabolism of SR35021 incubated with or without 1 µM ketoconazole (0.2 µM in upper panel and 2.0 µM in lower panel) in human hepatocytes



Midazolam metabolism, selective for CYP3A activity and used as a positive control, showed the hepatocyte cultures were metabolically active and were inhibited by 1 µM ketoconazole (see following figure)

Figure 16: Metabolism of midazolam incubated with or without 1 µM ketoconazole in human hepatocytes



Recommendations/Conclusions

- NADPH-dependent metabolism of SR35021 was not observed in human liver microsomes, however some NADPH-independent (non-CYP) metabolism was observed.
- CYP2D6 and CYP3A metabolized SR35021 at approximate rates of 6 and 20 % respectively. These results suggest that CYP3A is the major CYP enzyme involved in SR35021 metabolism, but other (non-CYP) enzymes may be involved.

4.2.4 Investigating the Potential for SR33589 and SR35021 (N-debutyl metabolite) to Inhibit Cytochrome P450 2B6 (CYP2B6) Using Human Liver Microsomes in vitro (MIH0441)

Investigator	Steven Ross
STUDY SITE	Sanofi Aventis, Malvern, Pennsylvania
STUDY PERIOD	June – July 2006

Objective (per applicant)

To determine if SR33589 (dronedarone) or SR35021 inhibited the human liver cytochrome P450 (CYP) enzyme CYP2B6 using in vitro methods.

Study Design

Standard procedures for in vitro metabolism studies were used. SR35021 or SR33589 (dronedarone) were mixed with pooled hepatic microsomal fractions (Source: BD Biosciences, Inc.). Microsomes were incubated with the CYP2B6 isoform selective substrate, bupropion, with or without SR33589 or SR35021 or selective inhibitor, for 10 min at 37°C, followed by the addition of an NADPH-generating system in timed sequence and incubated for 15 min. The amount of hydroxybupropion formed was quantified using an LC-MS/MS method for CYP2B6 activity. Appropriate control systems were used to ensure system viability and suitability.

The supplies used in the study are tabulated below.

Table 20: Concentrations of Stock Solutions, Solvents Used In CYB2B6^ Study and Vendors for Chemicals

Isoform	Chemicals	Concentration [a] (mM)	Solvent used [b]	Vendor (location)
CYP2B6	Bupropion	10	MeOH:H_2O (1:1)	Sigma (St. Louis, MO)
	Hydroxybupropion	10	MeOH:H_2O (1:1)	BD Biosciences (Woburn, MA)
	[$^{13}C_6$]-Bupropion	10	MeOH:H_2O (1:1)	IsoSciences (King of Prussia, PA)
	mAb-2B6	10 mg/mL	25 mM Tris	BD Biosciences (Woburn, MA)

[a] Concentrations shown are primary concentrated stock solutions and may not be representative of the working stock concentration; [b] The solvent used to prepare the working stock solution may differ from the solvent used for the preparation of the primary concentrated stock solution.

^ mAb-2B6* is an inhibitor monoclonal antibody

Compounds

- SR33589B, batch number CL-05754
- SR35021A, batch number A-BGD- 040020-P2

Results

As shown in Table 21, SR33589 and SR35021 (200 µM; 111 µg/mL for SR33589, 100 µg/mL for SR35021) inhibited CYP2B6 (defined as ≥30% inhibition relative to control values). Consequently apparent Ki values were determined for inhibition of CYP2B6 in microsome reaction mixtures.

Table 21: Effect of SR33589 and SR35021 on Bupropion Hydroxylation in Human Liver Microsomes

CYP Selective Substrate Assay	Percent of Control Activity		
	SSR33589 (200 µM)	SR35021 (200 µM)	mAb-2B6 (0.025 mg/mL)
CYP2B6 Bupropion hydroxylation	5.65	<1.94[a]	4.64

[a] Below the LLOQ (0.01 µM) of this assay.

Reviewer note on Dronedarone and SR35021 concentrations

The above mentioned concentrations exceed therapeutic concentrations by more than 10-fold thus the findings from the study are not likely to be clinically relevant.

The apparent Ki values for SR33589 and SR35021 inhibition of CYP2B6 in human liver microsome reaction mixtures are tabulated in the following table.

SR Compound	Inhibition Model	Apparent Ki (µM)	I/Ki
SR33589	Mixed	12.0	0.0389
SR35021	Mixed	56.9	0.00633

In the equation, (I) refers to plasma concentrations for SR33589 or SR35021. The highest plasma C_{max} observed in humans at steady state after 400 mg BID dosing across several studies are 0.467 µM for SR33589 (260 ng/mL) and 0.360 µM for SR35021 (180 ng/mL). Based on current FDA guidelines (I/Ki), the inhibition data indicate that SR33589 and SR35021 have a low potential to significantly inhibit the clearance of drugs metabolized by CYP2B6. Inhibition is likely to occur when I/Ki approaches values equal to or greater than 0.1.

CONCLUSION

Neither dronedarone nor SR35021 are likely to inhibit the metabolism of CYP2B6 substrates.

4.2.5 Investigating the potential of SR33589 and SR35021 to inhibit the cytochrome p450 isoform CYP2C8 using pooled human liver microsomes (HLM's) in vitro (MIH0460)

PROTOCOL #	MIV0159
Investigator	Carolyne Lieu
STUDY SITE	Sanofi Aventis, Malvern, Pennsylvania
STUDY PERIOD	October 2004 - February 2005

Objective (per applicant)

To investigate the potential of both SR33589 and its N-debutyl metabolite, SR35021 to inhibit the in vitro enzyme activity of the human hepatic cytochrome P450 isoform, CYP2C8.

Study Design

Standard procedures for in vitro metabolism studies were used. Pooled human liver microsomes (n = 50), obtained from Xenotech, LLC, were co-incubated with the CYP2C8 substrate, paclitaxel, with or without SR33589 or SR35021 or quercetin. Quercetin is a specific CYP2C8 inhibitor. NADPH was added to start the metabolic reaction and incubation allowed to proceed for an additional 15 min. IC50's for SR33589 and SR35021were determined using paclitaxel at a single concentration of 5 µM which approximates its apparent Km value. The concentrations of both SR35021 and SR33589 used in the determination of the IC50 value were 0, 0.01, 0.1, 0.5, 1, 5, 10, 50 and 100 µM. The Ki value for SR35021 was determined using paclitaxel at 1, 2.5, 5, 10 and 25 µM. Each concentration of paclitaxel was incubated with 0.5, 1, 5, 25, 50 and 100 µM SR35021. The amount of the metabolite 6α-hydroxypaclitaxel, which is formed in the CYP2C8 enzyme reaction from paclitaxel, was quantified using a validated LC-MS/MS method. The apparent Ki value for SR35021 inhibition of CYP2C8 was determined by non-linear regression. Appropriate controls were performed concomitantly and included.

Table 22: Concentrations of Stock Solutions, Solvents Used In This Study and Vendors for Chemicals

Chemicals	Stock solution concn (mM) *	Solvent used in assay	Vendor
Paclitaxel	5	MeOH	Sigma-Aldrich
6α-Hydroxypaclitaxel	0.25	MeOH	Cypex
Quercetin	5	DMSO	Sigma-Aldrich

* : Concentrations shown refer to concentrated stock solutions that may not be representative of the working stock solutions.

Compounds

SR33589B and SR35021A, mono-hydrochloride salts, batch numbers: CL-05754 and A-BGD-040020-P2, respectively.

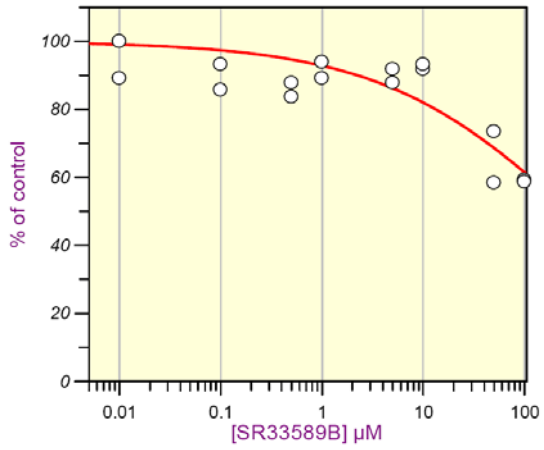
Results

The IC50 values of the specific inhibitor, quercetin were in the range of 2.97 to 5.3 µM in the SR33589 and SR35021 experiments. Thus, the specific inhibitor of CYP2C8, quercetin was effective in reducing the formation of 6α- hydroxypaclitaxel, under the experimental conditions used in this study.

IC50 determination

As shown in the figure below, no Ki value was determined for SR33589 as the estimated IC50 value was greater than 100µM (55.5 µg/mL). This exclusion appears reasonable as in vivo dronedarone concentrations are 100 fold lower (< 1 µM) at the proposed dosage.

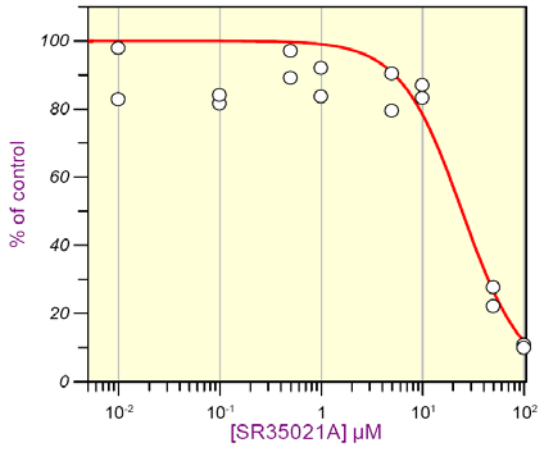
Figure 17: Plot of % inhibition of control substrate vs. dronedarone concentration



IC_{50} > 100 µM

As shown in the following figure, the estimated IC50 value for SR35021 was less than 100 µM. Therefore, the inhibition of CYP2C8 activity was characterized by determining the apparent Ki value.

Figure 18: Plot of % inhibition of control substrate vs. SR35021 concentration



IC_{50} 24.4 µM

The estimated apparent Ki value for SR35021 was found to be 36.6 µM. Subsequently,

SR35021 was determined to inhibit CYP2C8 activity with an estimated IC50 value of 24.4 μM. According to the report, the inhibition was best described by the non-competitive model. Using the I/Ki model [plasma concentrations of 0.360 μM (180 ng/mL for SR35021)], SR35021 has a low potential to inhibit the metabolism of CYP2C8 substrates. The I/Ki value for SR35021 was ~ 0.0001, demonstrating a low potential to inhibit CYP2C8 metabolism.

CONCLUSION

- Neither SR33589 nor SR35021 have a potential to inhibit the metabolism of CYP2C8 substrates.
- The estimated apparent CYP2C8 Ki value for SR35021 was 36.6 μM and > 100 μM for dronedarone.

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/s/

Robert Kumi
1/30/2009 03:27:54 PM
BIOPHARMACEUTICS

Elena Mishina
1/30/2009 03:32:59 PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-425**
DOCUMENTS REVIEWED:	**complete response to non-approvable letter**
DATE RECEIVED BY CENTER:	**June 26, 2008**
PRODUCT:	**Multaq® (dronedarone hydrochloride tablets)**
INTENDED CLINICAL POPULATION:	**patients with atrial fibrillation or atrial flutter**
SPONSOR:	**Sanofi**
REVIEW DIVISION:	**Division of Cardio-Renal Drug Products**
PHARM/TOX REVIEWER:	**Elizabeth Hausner, D.V.M.**
PHARM/TOX SUPERVISOR:	**Charles Resnick, Ph.D.**
DIVISION DIRECTOR:	**Norman Stockbridge, M.D., Ph,D.**
PROJECT MANAGER:	**Russell Fortney**

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EXECUTIVE SUMMARY

Background

Dronedarone is a benzofuran derivative structurally similar to amiodarone and demonstrating electrophysiologic characteristics of all 4 Vaughan-Williams classes of anti-arrhythmic compounds. Dronedarone was originally presented in NDA 21913 for treatment of atrial fibrillation (AF) or atrial flutter (AFL).

The Division issued a "non-approvable" letter for NDA 21913, for both clinical and non-clinical reasons. The clinical reasons for non-approval included an unfavorable risk: benefit relationship. The potential symptomatic improvement offered by the drug was also weighed against the nonclinical issues of carcinogenicity, teratogenicity, and endocrine effects (thyroid gland and female cyclicity). The complete response to these concerns was filed under NDA 22425 with a new indication of treating patients with AF/AFL or with a history of such events to reduce the risk of cardiovascular hospitalization or death. The proposed dose is 400 mg twice a day.

Summary of Non-Clinical Concerns

Endocrine Effects

Thyroid effects: Because of dronedarone's similarity to amiodarone, thyroid hormone levels were measured in several toxicology studies. There were changes in circulating hormone levels, sometimes statistically significant, in both rats and dogs. Thyroid tumors were not seen in the carcinogenicity study. The findings were discussed in detail in the review for NDA 21913.

Reproductive toxicology: The sponsor and I agree that the drug is teratogenic. This is a labeling issue. Another issue was the apparent effect on female cyclicity. This was manifested in a number of toxicology studies in which the drug-treated females were paused in diestrus. Other studies showed an increase in the frequency of irregular cycles and lack of cycles. Ovarian and uterine weights were affected in several studies. These findings were discussed in detail in the review for NDA 21913.

No non-clinical material was submitted to address the endocrine issues. According to the Clinical Safety Summary, the sponsor gathered clinical data to assess thyroid hormone effects of dronedarone. This data is in the clinical section of this submission and will be addressed by the medical officer.

Carcinogenicity

The Exec CAC considered the following findings to be drug-related: histiocytic sarcoma in male mice, mammary adenocarcinomas in female mice and hemangiomas in male rats. The minutes of the Executive CAC meeting are on file under IND 49484.

The sponsor's Clinical Safety Summary for NDA 22425 contains the following comments on the carcinogenicity studies:

- A slight increased incidence of adenocarcinoma was observed in the mammary gland of female mice, at the highest dose only, with no effect in male mice or in rats of either sex. The slightly raised incidence is associated with a modest increase in prolactinemia, explaining the small mammary gland response. In addition, the tumors themselves are those classically noted for the mouse, and are histologically different from those in humans. This mechanism of tumors is acknowledged to be specific to rodents with no relevance to humans.
- A slight increase in histiocytic sarcoma was observed in mice at the highest dose level, but not in rats of either sex. The low incidence lies within historical values of the National Toxicology Program, and there was no increase in the frequency of other lymphoreticular tumors in both carcinogenicity studies. In addition, no analogous tumor is known to occur in man.
- Dronedarone induced an increased incidence of benign vasoproliferative lesions in the mesenteric lymph nodes in rats and female mice, at the highest dose only. In the literature, venous or lymphatic obstruction is known to lead to vascular transformation of lymph nodes. Dronedarone has been shown to accumulate preferentially in the mesenteric lymph nodes and to induce locally accumulation of foamy macrophages in rats, a species particularly susceptible to this type of effect. The physical presence of foamy macrophages in the mesenteric lymph nodes could be sufficient to alter local blood flow and thus induce vascular lesions. Hemangiomas are not precancerous changes and do not transform into malignant hemangiosarcomas in either animals or man. Both lesions are extremely rare in humans at the level of lymph nodes. Overall, the proliferative vascular changes seen in the rat are considered to be reactive-proliferative, rare in occurrence and innocuous, therefore not relevant for man.

To support their assertion of a lack of clinical significance of the carcinogenicity findings, the sponsor submitted two studies measuring circulating prolactin levels in mice following dronedarone administration, an immunohistochemistry study to show differences in blood flow to mesenteric lymph nodes (for reasons noted in the sponsor's statement above) and an autoradiography study that focused on the amount of drug-associated radioactivity found in lymph nodes.

Neither study designed to demonstrate altered blood flow supported that hypothesis. It was reported that the tumor incidences seen in the dronedarone studies were within the background range of the NTP studies reported in Haseman et al. The referenced publication is Haseman et al. "Use of dual control groups to estimate false positive rates in laboratory animal carcinogenicity studies." Fundamental and applied Toxicology: 573-584 (1986). There is a question of the relevance of the Charles River SD rats and CD-1 mice used in the historical studies to the SD(IOPS Caw) rats (different strain) and the CD-1 mice (genetic drift from time and geography) used almost 20 years later.Slightly

more recent databases from Charles River do indicate that that the incidences of hemangioma, hemangiosarcoma and histiocytic sarcoma in the dronedarone studies were within historical control ranges albeit for SD rats.

Increased prolactin was hypothesized to be the cause of the mammary tumors reported in the mice and presented as a mechanism irrelevant to humans. The sponsor showed increases in serum prolactin levels in the mice that persist for at least 28 days. The total duration of elevated prolactin is not clear. Antipsychotic drugs that increase prolactin in rodents via binding to the D2 dopaminergic receptor have also been shown to increase prolactin in humans.

The sponsor has shown only modest binding (IC50>10 μM) of dronedarone to the D2 dopaminergic receptor. No information was provided for receptor binding of the major metabolites.

The sponsor did not demonstrate in the non-clinical section of the submission that prolactin does not increase in humans treated with dronedarone.

The current published clinical literature has numerous articles discussing epidemiologic and other data that support increased prolactin as a factor involved in carcinogenesis. The sponsor's proposed mechanism for the mammary tumors can't be dismissed out of hand as irrelevant to human health.

The questions of alteration of thyroid homeostasis and effects on female cyclicity were reported to have been addressed clinically and as such will be evaluated by the medical officer.

Recommendations

A. Recommendation on approvability: From a non-clinical view, the drug could be approved despite the lack of data to support the carcinogenicity findings as not clinically important. This depends upon the evaluation of the risk: benefit relationship in view of the new indication.

B. Recommendations for additional nonclinical studies: 1) receptor binding studies for the parent drug and main metabolites, and 2) data to show that the tumors are not clinically relevant, although this may not necessarily be non-clinical data.

C. Recommendations on labeling

Under "**NONCLINICAL TOXICOLOGY, Carcinogenesis, Mutagenesis, Impairment of Fertility**,"

the statement :

> "In 2 year-oral carcinogenicity studies, the highest dronedarone dose administered for 24 months was 70 mg/kg/day in rat and 300 mg/kg/day in mice.
> Observations were increased incidence of mammary gland tumors in female mice, histiocytic sarcomas in mice and hemangiomas at the mesenteric lymph node level in rats, all at the highest tested dose only (corresponding to an exposure of 5 to 10 times that of the human therapeutic dose). Hemangiomas are not precancerous changes and do not transform into malignant hemangiosarcomas in either animals or man.
> None of these observations was considered relevant for humans."

should be replaced with :

> "In studies in which dronedarone was administered to rats and mice for up to 2 years at doses of up to 70 mg/kg/day and 300 mg/kg/day, respectively, there was an increased incidence of histiocytic sarcomas in dronedarone-treated male mice (300 mg/kg/day or 5X MRHD based on AUC comparisons), mammary adenocarcinomas in dronedarone-treated female mice (300 mg/kg/day or 8X MRHD based on AUC comparisons) and hemangiomas in dronedarone-treated male rats (70 mg/kg/day or 5X MRHD based on AUC comparisons). "

The statement:

"Dronedarone had no genotoxic effects, based on one *in vivo* micronucleus test in mice and four *in vitro* tests: the Ames test with or without metabolic activation, a DNA repair test on rat hepatocytes, a gene mutation assay on hamster fibroblasts and a cytogenetic study of human lymphocytes."

should be replaced with:

"Dronedarone did not demonstrate genotoxic potential in the *in vivo* mouse micronucleus test, the Ames bacterial mutation assay, the unscheduled DNA synthesis assay, the HPRT gene mutation assay in Chinese Hamster V79 fibroblasts and an *in vitro* chromosomal aberration assay in human lymphocytes."

The statement :

"Dronedarone was not shown to alter fertility in animal studies up to 100 mg/kg/day"

should be replaced with:

" In fertility studies conducted with female rats, Dronedarone given prior to breeding and implantation caused an increase in irregular estrus cycles and cessation of cycling at doses ≥10mg/kg (equivalent to 0.12X the MRHD on a mg/m^2 basis)." Corpora lutea, implantations and live fetuses were decreased at 100 mg/kg (equivalent to 1.2X the MRHD on a mg/m^2 basis). There were no reported effects on mating behavior or fertility of male rats at doses of up to 100 mg/kg/day.

Under **"Pregnancy,"**

the paragraph that reads:

"MULTAQ can cause fetal harm when administered to pregnant women. In rats, dronedarone caused marked effects on embryo-fetal development at 100 mg/kg/day such as increased post-implantation losses, reduced fetal and placental weights and various external, visceral and skeletal malformations in most fetuses. At lower dosages, up to 50 mg/kg/day (corresponding to 4.5 times the recommended human therapeutic dose), dronedarone had no effects on the litters (with the exception of a transient minor effect on the bodyweight gain of the pups from D1 to D4 post-partum). Dronedarone had no adverse effects on the mothers and their litters up to 30 mg/kg/day. In rabbits, the high dose level (200 mg/kg/day, equivalent to 5X the MRHD on a mg/m^2 basis) did not induce any effects to fetuses."

Should be modified to read as follows:

> "Dronedarone was teratogenic in rats given oral doses ≥80 mg/kg (a dose equivalent to the maximum recommended human dose on a mg/m^2 basis), with fetuses showing external, visceral and skeletal malformations (cranioschisis, cleft palate, incomplete evagination of pineal body, brachygnathia, partially fused carotid arteries, truncus arteriosus, abnormal lobation of the liver, partially duplicated inferior vena cava, brachydactyly, ectrodactylia, syndactylia, anterior and/or posterior club feet). In rabbits, dronedarone caused an increase in skeletal abnormalities (anomalous ribcage and vertebrae, pelvic assymetry) at doses ≥20 mg/kg (the lowest dose tested and approximately half the MRHD on a mg/m^2 basis).

The section **13.2 Animal Toxicology and/or Pharmacology** is unnecessary and should be removed.

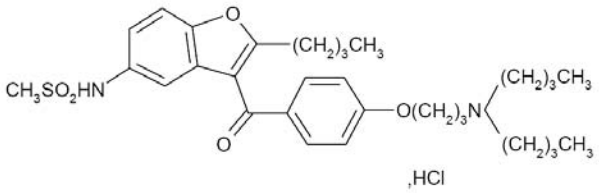
PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: 22425
Sponsor: Sanofi-Synthelabo
Agent: NA
Submission Type: complete response to non-approvable letter
Date of Submission: June 27, 2008
CDER Stamp Date: electronic submission

Reviewer: Elizabeth Hausner, D.V.M.
Division: Division of Cardio-Renal Drug Products
HFD #: 110
Review Completion Date: December 9, 2008

Drug:

Trade name: Multac®
Generic name: dronedarone
Code name: SR33589B
Chemical name:N-{2- butyl- 3-[4-(3- dibutylaminopropoxy) benzoyl] benzofuran- 5- yl}methanesulfonamide, hydrochloride.
CAS registry number: 141626-36-0
Molecular formula/molecular weight: $C_{31}H_{44}N_2O_5S,HCl$/ 593.2
Structure:



Pharmacologic Class: antiarrhythmic

Related INDs/NDAs/DMFs: Sanofi-Winthrop IND 49484
Sanofi-Synthelabo NDA 21913

Intended Clinical Population: patients with atrial fibrillation or atrial flutter for the reduction of the risk of cardiovascular hospitalization or death (new indication)

Clinical Formulation: 400 mg of dronedarone base with inactive ingredients of hypromellose, starch, crospovidone, poloxamer 407, lactose monohydrate, colloidal silicon dioxide, magnesium stearate

Route of Administration: oral

Prolactin Assay After a Single Oral Administration to Mice

Report number: DIV1142
Study location: Sanofi-Aventis Recherche and Developpement, Montpellier Cedex, France
GLP: statement included
QA: yes
Study dates: in-life started September 12, 2007
Test article: SR33589B, batch number CL-05754, purity 99.9% by HPLC
The chemical analysis form lists the potency of active drug as 93.42%
A conversion factor of 1.066 was used to correct for the salt form.
Animals: female mice, CD-1(ICR), 6-8 weeks of age at initiation of dosing

SR33589B was orally administered as a suspension in 0.6% methylcellulose aqueous solution to 20 female mice in a single gavage dose of 300 mg/kg/day, the high dose used in the mouse carcinogenicity study. A control group of females received the vehicle of methylcellulose (0.6% aqueous solution). For 9 days prior to the study the animals were habituated to gavage dosing (with water) and being placed in the anesthesia box.

Un-fasted animals were anesthetized with inhalant isoflurane, approximately 2 hours after drug administration (based on the Tmax in mice occurring at 2 hours). The blood was collected, the serum frozen and sent to Anilytics, Inc., Gaithersburg, MD. Animals were euthanized immediately after blood collection. The prolactin was measured by a radio-immunoassay (RIA) method. Prolactin concentrations in the test samples were determined from a standard curve generated under the same conditions. It was reported to be a species specific assay but no validation material was presented or referenced. No information was provided regarding the standard curve or the variability of the analysis itself.

Observations

- Mortality: twice a day and only once on the day of termination
- Clinical signs: at least once on day of dosing
- Serum prolactin levels at time of euthanasia.

Results

There was no unscheduled mortality. No clinical signs were reported.

There was a difference in the mean and median values for the control and treated groups that was significant at p<0.001 by the exact two-sided Wilcoxon test.

Table 1 - Descriptive statistics

Analysis Variable : Prolactin (Ng/mL)				
Dose (mg/kg)	**N Obs**	**Mean**	**Median**	**Std Dev**
0	20	52.78	37.66	42.93
300	20	211.10	195.07	69.22

Because hormonal assays are subject to profound variability, I have included in this section a copy of the sponsor's box plot of the results as well as the numerical description.

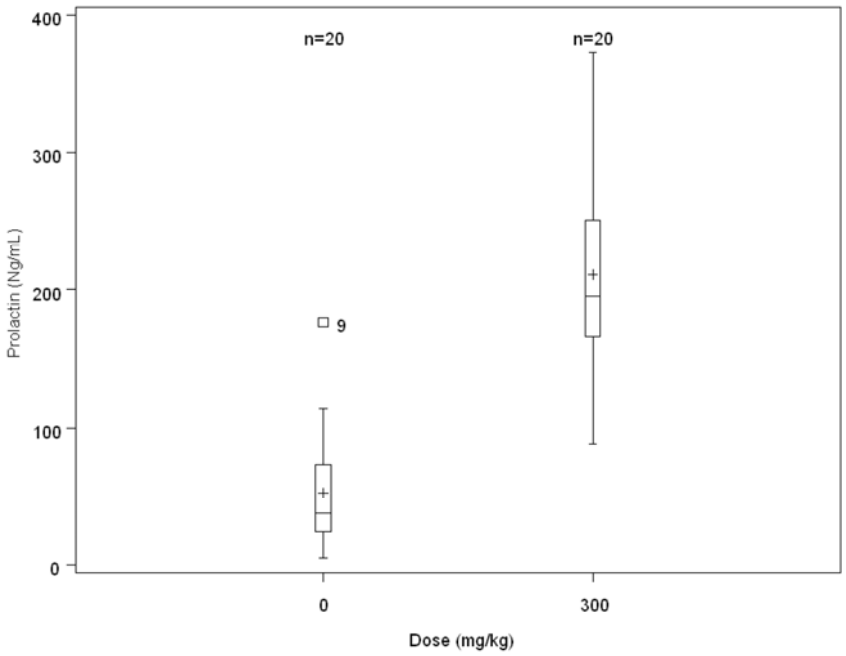


Figure 1 - Boxplots of the Prolactin per group

The means (+) are greater than the medians for both groups, that indicates a dissymmetry in the distributions. There is also an animal (n°9) that obtains a high value (177 Ng/mL) compared to its group results.

Prolactin Assay After a 28-day Oral Administration to Mice

Report number: DIV1123
Study location: Sanofi-Aventis Recherche and Developpement, Montpellier Cedex, France
GLP: statement included
QA: yes
Study dates: study started September 5, 2007
Test article: SR33589B, batch number CL-05754, purity 99.9% by HPLC
The chemical analysis form lists the potency of active drug as 93.42% and a "purity correction" of 93.80 is listed. A conversion factor of 1.066 was used to correct for the salt form.
Animals: female mice, CD-1(ICR), 6-8 weeks of age at initiation of dosing

SR33589B was orally administered as a suspension in 0.6% methylcellulose aqueous solution to 20 female mice at 300 mg/kg/day for 28 days. A control group of females (n=20) received the vehicle. Two hours after the administration on day 28, the animals were anesthetized, blood collected for serum analysis and the mice euthanized. The 300 mg/kg dose was chosen as it was the high dose of the mouse carcinogenicity study.

The sponsor also detailed procedures to minimize stress on the animals:

> Note: For the last 10 days of treatment, to minimize stress on the actual day of blood sampling, mice of both groups were daily administered with distilled water (0.25 mL) and placed in the anesthesia box for approximately 2 minutes for habituation.

It is unclear to me why the animals were gavaged with water as they already had at least 18 days of experience with daily gavage. The sponsor did not describe what steps were taken to minimize circadian/diurnal variation in the hormone assays.

Observations

- Mortality: twice daily and once on day of termination
- Signs: at least once a day
- Body weight: pre-study, then weekly
- Prolactin: Day 28, approximately 2 hours after drug administration, the mice were anesthetized with inhalant isoflurane. Blood was collected and frozen. The frozen samples were sent to Anilytics, Gaithersburg, MD. The serum was analyzed for prolactin using a radio-immunoassay (RIA). It was reported to be a species specific assay but no validation material was presented or referenced.
- Necropsy: Necropsy was performed only for mice found dead or euthanized moribund.
  This was reported to include macroscopic examination, preservation of grossly abnormal tissues and limited histological evaluation. The tissues collected are listed below.

Organ and tissues taken

Liver	Uterine horns/Cervix/Vagina
Spleen	Esophagus
Gallbladder	Stomach (non glandular)
Kidneys	Stomach (glandular)
Adrenal glands	Duodenum
Thymus	Jejunum
Heart	Colon
Lungs	Brain
Ovaries/Oviducts	Rectum (36F only)

Results

There was no unscheduled mortality in the control group. Two females from the treated group died prior to euthanasia. Female 28F showed signs of hunched posture on day 7 as well as 20% weight loss compared to her pre-study value. She appeared weak, cold to the touch and was recumbent by day 8. She was euthanized Day 8. According to the text, there were no significant gross lesions and the microscopic lesions suggested acute to chronic stress and under-nutrition. Histologic changes to support that were reported for the spleen, adrenals, thymus, brown fat and pancreas. There was more detail regarding the histologic findings in the appendices of the report. Something not mentioned in the main text was the presence of cardiac degeneration. The sponsor felt that the cause of death could not be determined. The other female, 36F, was found dead on day 17 without any premonitory signs reported. It was also reported that there were minimal gross or histologic changes which did not explain the cause of death. The appendix reported necrotizing pneumonia for female #36, also not mentioned in the main text. It was reported that the remaining animals did not display any clinical signs.

There were statistically significant differences in the rate of weight gain in the treated animals.

Prolactin assay after a 28-day oral administration to mice

Summary of Body Weight Changes

Sex = FEMALE

Dose mg/kg/d		Day (-1)-7	Day (-1)-14	Day (-1)-21	Day (-1)-27
Group 1 0	MEAN	0.68	0.61	1.23	1.57
	STD	1.22	1.34	1.75	2.03
	N	20	20	20	20
Group 2 300	MEAN	1.35 NS	1.85 *	3.10 *	2.88 *
	STD	2.15	1.60	1.58	1.38
	N	20	19	18	18

There was a statistically significant difference between the treated and control group median prolactin levels (Exact two-sided Wilcoxon p <0.001).

	Prolactin level (ng/mL)			
Dose (mg/kg)	N Obs	Mean	Median	Std Dev
0	20	81.13	68.46	60.29
300	18	190.61	193.49	64.64

The box and whisker plot is also shown for clarity.

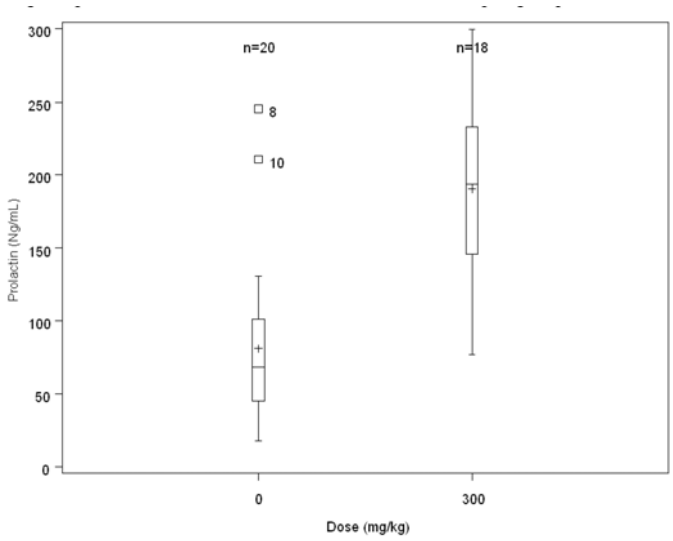


Figure 1 - Boxplots of the Prolactin per group

In control group, the mean (+) is greater than the median, that indicates a dissymmetry in the distributions. There are also two animals (n°8 and n°10) that obtain high values (respectively 245.76 Ng/mL and 210.48 Ng/mL) compared to their group results.

Study of the Potential Alteration of Blood Flow in Mesenteric Lymph Nodes after Repeated Oral Administrations of SR33589B to Female Sprague-Dawley Rats.

Study number: 070164
Report number: DIV1124
Study location: Oncodesign, Dijon Cedex, France
Study dates: initiated November 15, 2007
GLP: statement not found
QA: no
Test article: SR33589B batch CL-07444, purity 94.53%
Diltiazem batch 7Y05431, purity 99.8%
Vehicle: 0.6% aqueous methylcellulose solution
Animals: female Sprague-Dawley rats

The purpose of this study was to analyze the possible alteration of blood or lymph flow in mesenteric lymph nodes induced by repeated oral administration of dronedarone to female SD rats. Diltiazem was used "as a vasodilator that would potentially produce changes in the blood supply to the mesenteric lymph nodes."

Sixty healthy female SD rats were assigned to 3 groups of 20 rats according to body weight. The treatment schedules were:

- Group 1: 20 rats received 1 daily oral administration of vehicle for 28 consecutive days
- Group 2: 20 rats received 1 daily oral administration of SR33589B at 100 mg/kg/day for 28 days
- Group 3: 20 rats received 1 daily oral administration of diltiazem at 100 mg/kg/day for 28 days

Blood volume in mesenteric lymph nodes was studied by detecting a hydrophilic dye (Patent Blue V) using HPLC/UV analysis. The change in quantity of Patent Blue V in mesenteric lymph nodes could reflect a change in blood volume in the lymph nodes.

Functionality and permeability of the lymph node blood vessels was determined with two dyes: Hoescht and dextran-FITC (fluorescein isothiocyanate linked to a specified size of dextran).

Density of vessels was evaluated by detecting the RecA-1 antigen expressed on rat endothelial cells by immunohistochemical methods. Detection of CD68 antigen (a glycosylated protein expressed mostly on macrophages) was used to determine macrophage infiltration in lymph nodes.

The study design is summarized in the sponsor's table below.

Group	No. rats	Test substance	Treatment dose (mg/kg/day)	Adm. route	Volume of administration (mL/kg)	Number of rats included in the assessment of mesenteric lymph nodes functionality	
						Patent Blue V level determination	RecA-1 and CD68 immunodetection
1	20	Vehicle	-	PO	5	10	10
2	20	SR33589B	100	PO	5	9	9
3	20	diltiazem	100	PO	5	9	9

The rats were anesthetized, the mesenteric lymph nodes exteriorized and Patent Blue V was injected into the tail vein. Determination of Patent Blue V uptake was done by extracting the dye from the lymph nodes and assessing by HPLC/UV methods using an internal standard (tartrazine).

The other designated rats were anesthetized, the mesenteric lymph nodes exteriorized and the rats given IV boluses of Hoecsht dye followed 30 seconds later by Dextran-FITC. The lymph nodes for each animal were embedded in the same block for analysis. For each block (each animal), 3 slides were prepared. Each set of 3 slides was analyzed as summarized by the sponsor below:

Section	Marker	Evaluation	Technique
1	Hoechst dye / Dextran-FITC dye	Blood perfusion and vessels permeability (5) / Effective vascular volume and functional vessels (6)	Fluorescence: blue / Fluorescence: green
2	RecA-1	Vessel density	Immunohistochemistry
3	CD68	Macrophages detection	Immunohistochemistry

Vessel permeability and functionality assessment: pictures of the lymph nodes were taken with a fluorescence microscope. The images were converted to a binary black and white image followed by objective quantification with a computer program.

Vessel density determination by immunohistochemistry: RecA-1 detection
Immunohistochemical (IHC) procedures were followed. For each section, a single area was analyzed (semi-quantitative analysis). One representative pictures was taken for each rat.

Macrophage infiltration detection by immunohistochemistry: CD68 detection
Standard IHC techniques were used. For each section, a single area was analyzed (semi-quantitative analysis). One representative picture was taken per rat.

Analysis of RecA-1 and CD-68 immunodetection: Blindly analyzed by a consultant pathologist for Oncodesign

A grade (semi-quantitative analysis) was determined for each slide using the following scale:

- 0: no staining.
- 1: low staining.
- 2: low to intermediate staining.
- 3: intermediate staining.
- 4: strong staining.
- 5: very strong staining.

For each group the mean grade was calculated.

For the detection of vessels in mesenteric lymph nodes, the percentage of post-capillary veins was also determined.

For the detection of macrophages in mesenteric lymph nodes, a grade was determined for the cortical and for the medullary zones.

Other Observations

Moribundity, clinical signs and behaviour: each day
Body weights: twice a week
Necropsy: gross examination of heart, lungs, liver, spleen, kidneys and gastro-intestinal tract.

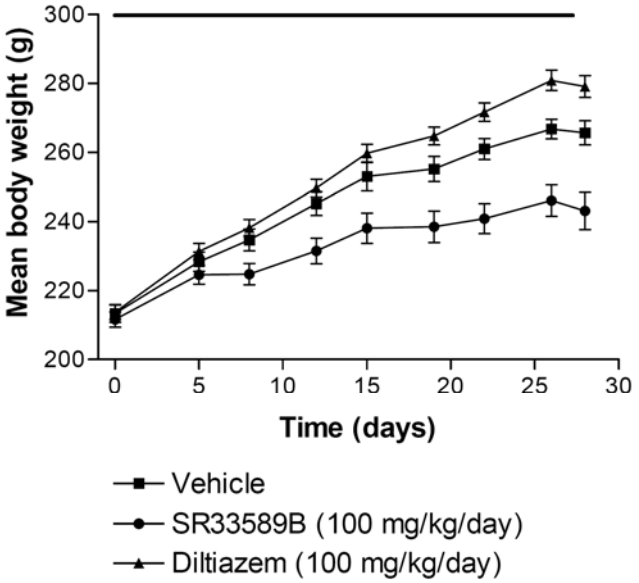
Results

Signs and Mortality

Two rats treated with SR33589B were found dead, one on Day 4 and the other on Day25. Two rats treated with diltiazem were found dead on Day 5 and day 6. The only significant necropsy findings reported for these animals were liquid in the lungs. The sponsor felt that the deaths were due to gavage accidents rather than directly due to test articles. No treatment related macroscopic changes were reported for any of the examined organs.

Body weight

All of the treatment groups showed mean weight gains. The rats treated with ditiazem showed the greatest rate of gain followed by the control group. Animals treated with SR33589B showed the lowest mean body weight gains.



Reviewer's Summary of Body Weight Gains

Day	vehicle	SR33589B 100 mg/kg/day	Diltiazem 100 mg/kg/day
0	213.4±11.5	211.6±9.9	213.7±9.4
12	245.2±15.4	231.5±16.2	249.7±10.8
28	265.7±15.8	243.1±22.8	279.1±13.4
Δday28-day0	52.3	31.5 (-40%)	65.4(+25%)

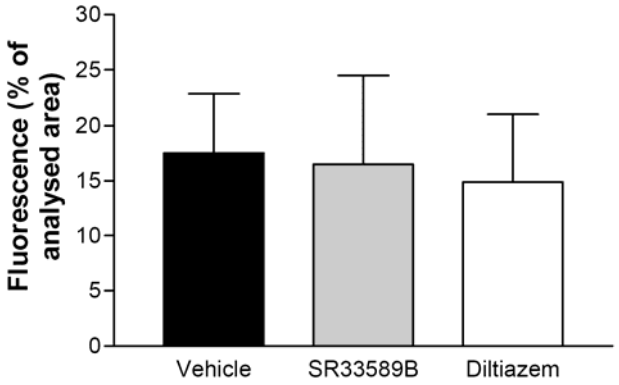
Numbers in parentheses are percent difference from control

Patent Blue V (HPLC-UV analysis)

The mean Patent Blue V quantity in mesenteric lymph nodes in rats treated with dronedarone and diltiazem was not statistically different from rats receiving the vehicle.

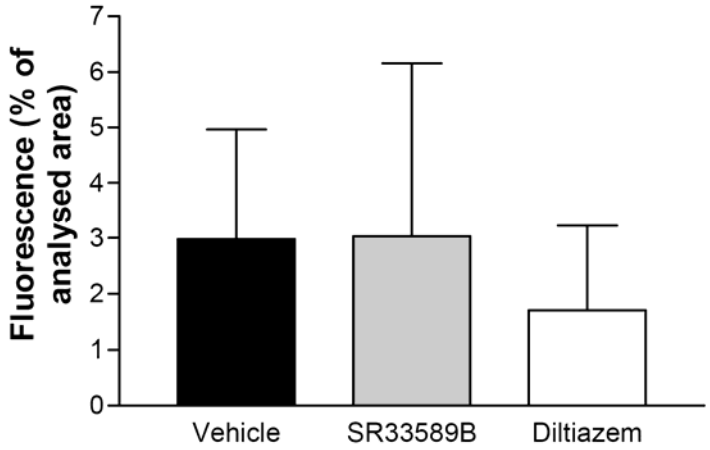
Hoecsht dye (perfusion)

There was no significant difference in the fluorescence detected in the analyzed areas of the mesenteric lymph nodes.



Dextran-FITC ("functionality")

There is a slight decrease in mean fluorescence for the diltiazem group but there are no significant differences between the different treatment groups.



The Hoecsht and Dextran-FITC results are consistent with each other, indicating that dronedarone had no influence on the functionality and permeability of the blood vessels.

RecA-1: vessel density

There was no significant difference in percentage of post-capillary veins between treatment groups.

Individual and mean±SD grade determined for vessel density assessment in mesenteric lymph nodes

vehicle	SR33589B 100 mg/kg/day	Diltiazem 100 mg/kg/day
3.1±1.1	3.3±0.5	2.7±0.7

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Individual and mean ±SD proportions of post capillary veins determined in mesenteric lymph nodes

vehicle	SR33589B 100 mg/kg/day	Diltiazem 100 mg/kg/day
42.0±15.6	51.6±12.5	53.4±10.6

CD68: macrophage infiltration

The sponsor presented mean±SD grade determined for the assessment of macrophage infiltration in the medullary zone of mesenteric lymph nodes. There was no significant difference reported for the treatment groups.

Mean±SD for macrophage infiltration of the medullary zone

vehicle	SR33589B 100 mg/kg/day	Diltiazem 100 mg/kg/day
3.6±0.6	3.6±0.6	3.6±0.5

The results for the cortical zones also showed no differences.

Mean±SD for macrophage infiltration of the cortical zone

vehicle	SR33589B 100 mg/kg/day	Diltiazem 100 mg/kg/day
2.3±1.2	2.4±1.1	2.8±1.1

The study was adequate and indicates that under the conditions of the study dronedarone had no detectable influence on permeability and functionality of vessels in mesenteric lymph nodes of female Sprague-Dawley rats. The study did not support the hypothesis of altered blood flow to the lymph nodes promoting carcinogenic changes.

Bacterial Reverse Mutation Test of Dronedarone Impurity on Salmonella Typhimurium (Ames test)

Study location: Sanofi-Synthelabo, Porcheville, France
Study number: FSRFU-HIS1692-EN-E01
Report Number: his1692
Study dates: experiment started July 20, 2005
GLP: statement included
QA: yes
Test article: SR 194090 (a dronedarone impurity), batch A-CRS-050018, purity 98.45%
Vehicle: DMSO
Note: either the vehicle was contaminated or there was column carryover.

Control of stock solutions	In the first and second tests for each dose level tested the stock solution in the DMSO was analyzed and found acceptable. In solvent control a presence of peak corresponding to retention time of SR194090 estimated at about 0.8 µg/mL to 0.2 µg/mL was noted. This does not jeopardize the scientific value of this study.

Concentrations tested:

Preliminary cytoxicity test (TA98 and TA100), plate incorporation test:
0, 50, 125, 250, 1250, 2500, 5000 µg/plate ±S9 mix

Mutagenicity test (TA98, TA100, TA102, TA1535, TA1537), plate incorporation and pre-incubation methods:
0, 50, 125, 250, 500, 1250, 2500, 5000 µg/plate ±S9 mix

Treatment duration was 48-72 hours.

S9 mix: prepared from the livers of male Sprague-Dawley rats treated with Aroclor 1254 (Moltox, Inc).

Positive controls:
Without S9: sodium azide (Na azide), 2-nitrofluorene, 9-aminoacridine, Mitomycin C
With S9: 2-aminoanthracene

Number of plates/concentration/test: 1(dose-range finding cytotoxicity test), 3(mutagenicity tests)
Number of independent mutagenicity tests: 2(one plate incorporation and one pre-Incubation) for all strains

In the dose-range finding study, precipitates were observed for both tester strains without S9 at concentrations ≥2500 µg/plate. Precipitation was reported for TA102 at concentrations ≥500 µg/plate both with and without S9 mix.

The sponsor provided criteria by which the acceptability of the assay was assessed and the criteria for a positive response.

Criteria for positive response:

- if, for at least one dose level, the induction factor is greater than 2 with the strains TA98, TA100 and TA102, and greater than 3 with the strains TA1535 and TA1537 (6).
- and the increase in the number of revertants is dose-related or observed at the highest dose level.
- and the values are out of the range of the historical negative control data.
- and the response is reproducible using the same experimental conditions.

4.6 Data acceptance criteria

- Mean number of revertants in negative controls has to be within the range of historical control values,
- Positive controls have to induce a marked increase in the number of revertant colonies for all strains, therefore confirming the sensitivity of the strains and the activity of S9-mix (AA),
- At least three non-cytotoxic dose levels.
- At least five analysable dose levels.

The positive controls produced appropriate responses. Under the conditions of the assay there were no positive responses to the test article in the bacterial strains tested. The presence of test article in the vehicle control cast some doubts about the adequacy of the study although the sponsor does not feel that the integrity of the data was compromised.

For the solvent control a presence of peak corresponding to retention time of SR194090 estimated at about 0.8 µg/mL to 0.2 µg/mL was noted. Possibly due to a technical failure, the origin of this presence still unclear but this does not jeopardize the scientific value of this study (see deviation in section (4.11)).

The range of historical controls was provided. Some of the present control results are slightly high compared to the mean values for the historical controls but are for the most part within the historical ranges.

In Vitro Gene Mutation Test of Dronedarone Impurity at the Locus TK in Mouse Lymphoma L5178Y Cells

Study location: Sanofi-Synthelabo, Porcheville, France
Study number: FSRFU-LYM0193-EN-E01
Report number: LYM0193
Study date: July 19, 2005
GLP: statement included
QA: yes
Test article: SR194090, an impurity of dronedarone, batch A-CRS-050018,
Vehicle: DMSO. Analysis did not reveal test article in the vehicle.

Concentrations tested (µg/ml)

Dose-range finding cytotoxicity test	
-S9 (3 hour exposure)	5-10-25-50-75-100-150
+S9 (3 hour exposure)	5-10-25-50-75-100-150
-S9 (24 hour exposure)	0.01, 0.05, 0.1, 0.5, 1, 2.5, 5
First test	
-S9 (3 hour exposure)	5, 10, 12.5, 15, 17.5, 20
+S9 (3 hour exposure)	25, 50, 55, 60, 65, 70
Second test	
-S9 (24 hour exposure)	0.5, 1, 2, 2.5, 3, 4
Complementary assays	
-S9 (3 hour exposure)	1, 2.5, 5, 7.5, 10, 12.5, 15
+S9 (3 hour exposure)	25, 30, 40, 50, 55, 60, 65, 70, 75, 80, 85

Positive controls: -S9 methylmethane sulfonate (MMS)
+S9 Cyclophosphamide (CP)

Number of cultures/concentrations 1: dose-range finding cytotoxicity test
2: mutagenicity tests

Number of independent assays: -S9 (3 hour exposure) : 2
+S9 (3-hour exposure) : 2
-S9 (24 hour exposure) : 1

Precipitation was seen at concentrations ≥150 µg/ml.

There were blips in the mutation frequency at the concentrations where relative total growth was decreased to appropriate levels. However, dose-responses were not apparent and significant increases were not apparent except under one set of conditions (second assay of 24 hours, -S9, shown below). There were several small increases in small colony count. The lack of consistent signals is suggestive that the findings are random occurrences rather than indications of genotoxicity. The results are shown below.

LYM0193 **First test in the absence of S9-mix (3-hour exposure)**

Compound		Day 0 factor	CE0 (%)	S (%)	RS (%)	SG	CE2 (%)	RTG (%)	Adj RTG (%)	MF ($\times 10^{-6}$)	Stat.	MI	MF small colonies ($\times 10^{-6}$)	MF large colonies ($\times 10^{-6}$)
solvent control	A	0.95	104.62	99.28	100.46	12.46	87.96	92		103.64		1.07	24.19	75.91
	B	1.05	93.52	98.30	99.47	11.31	116.02	110		89.49		0.92	37.50	47.41
	Totals	**1.00**	**98.82**	**98.82**	**100.00**	**11.89**	**100.43**	**100**	**100**	**97.04**		**1.00**	**32.13**	**60.59**
SR194090 5 µg/mL	A	1.06	90.68	95.71	96.85	10.15	84.09	71		55.12		0.57	25.31	28.55
	B	1.13	70.65	80.16	81.12	9.12	86.64	66		34.05		0.35	12.15	21.43
	Totals	**1.10**	**79.86**	**87.46**	**88.50**	**9.63**	**85.35**	**69**	**76**	**44.35**	**NS**	**0.46**	**18.60**	**24.93**
SR194090 10 µg/mL	A	0.94	45.98	43.38	43.90	6.45	94.99	51		70.29		0.72	36.90	33.97
	B	1.02	46.66	47.77	48.34	5.97	81.64	41		89.11		0.92	46.37	39.53
	Totals	**0.98**	**46.32**	**45.56**	**46.10**	**6.21**	**87.96**	**46**	**45**	**79.30**	**NS**	**0.82**	**41.44**	**36.69**
SR194090 12.5 µg/mL	A	0.82	15.85	12.95	13.10	2.02	90.68	15		162.47		1.67	93.68	60.66
	B	0.85	15.01	12.73	12.88	1.76	104.62	15		134.18		1.38	75.33	49.80
	Totals	**0.83**	**15.43**	**12.84**	**12.99**	**1.89**	**97.26**	**15**	**12**	**147.89**	**NS**	**1.52**	**84.18**	**55.06**
SR194090 15 µg/mL	A	0.67	3.00	2.00	2.02	0.32								
	B	0.57	6.51	3.72	3.77	0.40								
	Totals	**0.62**	**4.73**	**2.93**	**2.96**	**0.36**	**(1)**	**(1)**	**(1)**	**(1)**	**(1)**	**(1)**	**(1)**	**(1)**
SR194090 17.5 µg/mL	A	0.43	0.00	0.00	0.00	0.20								
	B	0.56	0.00	0.00	0.00	0.28								
	Totals	**0.50**	**0.00**	**0.00**	**0.00**	**0.24**	**(1)**	**(1)**	**(1)**	**(1)**	**(1)**	**(1)**	**(1)**	**(1)**
SR194090 20 µg/mL	A	0.32	0.00	0.00	0.00	0.21								
	B	0.29	0.33	0.10	0.10	0.32								
	Totals	**0.31**	**0.16**	**0.05**	**0.05**	**0.27**	**(1)**	**(1)**	**(1)**	**(1)**	**(1)**	**(1)**	**(1)**	**(1)**
MMS 25 µg/mL	A	1.03	47.36	48.58	49.15	6.87	32.58	19		610.30		6.29	318.65	232.57
	B	1.02	55.50	56.57	57.24	7.31	27.33	17		969.97		10.00	379.93	488.66
	Totals	**1.02**	**51.30**	**52.45**	**53.07**	**7.09**	**29.90**	**18**	**18**	**772.13**		**7.96**	**347.24**	**347.24**

LYM0193 **Second test in the absence of S9-mix (24-hour exposure)**

Compound		Day 0 factor	CE0 (%)	S (%)	RS (%)	SG	CE2 (%)	RTG (%)	Adj RTG (%)	MF ($x10^{-6}$)	Stat.	MI	MF Small colonies ($x10^{-6}$)	MF Large colonies ($x10^{-6}$)
solvent control	A	0.91	98.04	89.50	90.57	14.63	70.65	96		142.43		1.05	61.58	73.75
	B	1.09	99.62	108.30	109.58	13.49	82.85	104		129.18		0.95	69.90	52.51
	Totals	**1.00**	**98.82**	**98.82**	**100.00**	**14.06**	**76.45**	**100**	**100**	**135.79**		**1.00**	**66.26**	**62.50**
SR194090 0.5 µg/mL	A	0.82	92.08	75.55	76.45	12.54	89.30	104		149.53		1.10	91.68	48.72
	B	0.88	84.09	74.18	75.06	12.32	79.28	91		185.82		1.37	107.15	65.72
	Totals	**0.85**	**87.96**	**74.88**	**75.77**	**12.43**	**84.09**	**97**	**82**	**166.94**	**NS**	**1.23**	**99.19**	**56.83**
SR194090 1 µg/mL	A	0.74	73.75	54.87	55.52	11.82	84.09	92		158.79		1.17	108.41	41.69
	B	0.86	63.06	54.46	55.11	10.31	75.90	73		180.42		1.33	99.83	68.64
	Totals	**0.80**	**68.18**	**54.80**	**55.45**	**11.06**	**79.86**	**82**	**66**	**169.33**	**NS**	**1.25**	**104.44**	**54.48**
SR194090 2 µg/mL	A	0.57	52.42	29.88	30.24	7.17	72.70	49		151.69		1.12	100.08	44.39
	B	0.60	42.67	25.54	25.84	5.95	67.69	37		228.04		1.68	148.65	64.27
	Totals	**0.58**	**47.36**	**27.67**	**28.00**	**6.56**	**70.15**	**43**	**25**	**187.94**	**NS**	**1.38**	**123.31**	**53.97**
SR194090 2.5 µg/mL	A	0.36	27.33	9.81	9.93	4.01	81.64	30		234.13		1.72	139.06	74.53
	B	0.33	26.82	8.90	9.01	4.75	87.96	39		262.45		1.93	175.50	62.53
	Totals	**0.35**	**27.07**	**9.35**	**9.46**	**4.38**	**84.72**	**35**	**12**	**248.59**	*	**1.83**	**157.61**	**68.36**
SR194090 3 µg/mL	A	0.36	12.18	4.33	4.38	2.75	75.90	19						
	B	0.33	10.23	3.40	3.44	2.52	68.66	16						
	Totals	**0.34**	**11.20**	**3.85**	**3.90**	**2.63**	**72.18**	**18**	**6**	**(1)**	**(1)**	**(1)**	**(1)**	**(1)**
SR194090 4 µg/mL	A	0.19	0.98	0.18	0.18	0.95								
	B	0.27	0.33	0.09	0.09	0.76								
	Totals	**0.23**	**0.65**	**0.15**	**0.15**	**0.86**	**(2)**	**(2)**	**(2)**	**(2)**	**(2)**	**(2)**	**(2)**	**(2)**
MMS 5 µg/mL	A	0.89	65.80	58.70	59.40	14.46	60.44	81		703.82		5.18	335.43	226.58
	B	0.87	66.74	57.97	58.66	13.38	57.11	71		788.70		5.81	361.88	257.99
	Totals	**0.88**	**66.27**	**58.34**	**59.03**	**13.92**	**58.75**	**76**	**67**	**745.07**		**5.49**	**348.40**	**241.88**

LYM0193 Complementary assay to the first test in the absence of S9-mix (3-hour exposure)

Compound		Day 0 factor	CE0 (%)	S (%)	RS (%)	SG	CE2 (%)	RTG (%)	Adj RTG ($\times 10^{-6}$)	MF ($\times 10^{-6}$)	Stat.	MI	MF small colonies ($\times 10^{-6}$)	MF large colonies ($\times 10^{-6}$)
solvent control	A	0.96	77.01	73.94	93.94	9.23	87.96	98		86.15		0.67	46.24	36.69
	B	1.04	80.45	83.66	106.29	11.16	74.82	101		178.48		1.39	81.33	85.27
	Totals	**1.00**	**78.71**	**78.71**	**100.00**	**10.19**	**81.04**	**100**	**100**	**128.11**		**1.00**	**62.51**	**58.96**
SR194090 1 µg/mL	A	0.79	53.94	42.79	54.36	9.84	81.64	97		100.28		0.78	46.37	53.29
	B	1.08	58.75	63.27	80.38	10.21	94.99	117		92.69		0.72	45.80	45.80
	Totals	**0.94**	**56.30**	**52.64**	**66.88**	**10.03**	**87.96**	**107**	**101**	**96.58**	**NS**	**0.75**	**46.24**	**49.46**
SR194090 2.5 µg/mL	A	1.02	69.65	70.94	90.13	9.00	71.66	78		172.23		1.34	76.75	84.91
	B	0.91	71.66	64.88	82.43	9.54	72.70	84		134.05		1.05	75.66	52.07
	Totals	**0.96**	**70.65**	**67.96**	**86.34**	**9.27**	**72.18**	**81**	**78**	**152.78**	**NS**	**1.19**	**76.20**	**68.19**
SR194090 5 µg/mL	A	0.86	66.74	57.21	72.69	8.33	68.66	69		123.72		0.97	75.88	42.96
	B	1.00	44.64	44.80	56.92	7.89	68.66	66		155.88		1.22	84.35	67.51
	Totals	**0.93**	**54.72**	**50.91**	**64.68**	**8.11**	**68.66**	**67**	**62**	**139.62**	**NS**	**1.09**	**80.10**	**55.13**
SR194090 7.5 µg/mL	A	0.94	53.17	50.12	63.68	7.58	77.01	71		118.38		0.92	63.91	49.16
	B	0.86	49.47	42.73	54.29	7.91	68.66	66		170.12		1.33	105.96	55.13
	Totals	**0.90**	**51.30**	**46.33**	**58.86**	**7.75**	**72.70**	**68**	**61**	**142.81**	**NS**	**1.11**	**83.70**	**52.07**
SR194090 10 µg/mL	A	0.74	32.04	23.81	30.25	4.25	71.66	37		172.23		1.34	80.82	80.82
	B	0.81	30.43	24.73	31.42	3.78	71.66	33		153.87		1.20	101.52	48.92
	Totals	**0.78**	**31.23**	**24.29**	**30.87**	**4.01**	**71.66**	**35**	**27**	**162.99**	**NS**	**1.27**	**91.09**	**64.68**
SR194090 12.5 µg/mL	A	0.63	12.18	7.71	9.80	1.78	63.96	14						
	B	0.53	12.18	6.43	8.18	1.60	75.90	15						
	Totals	**0.58**	**12.18**	**7.07**	**8.99**	**1.69**	**69.65**	**14**	**8**	**(1)**	**(1)**	**(1)**	**(1)**	**(1)**
MMS 25 µg/mL	A	0.80	43.98	35.05	44.53	7.76	18.42	17		1122.16		8.76	743.63	314.49
	B	0.94	35.38	33.28	42.29	6.63	19.74	16		1107.39		8.64	591.71	461.79
	Totals	**0.87**	**39.53**	**34.34**	**43.64**	**7.19**	**19.07**	**17**	**15**	**1114.54**		**8.70**	**664.62**	**389.32**

Tissue Distribution of Total Radioactivity and Histopathology in Lymph Nodes Following Single and/or 28 days Repeated Oral Administration of[^{14}C]-SR33589B or SR33589B at 25 mg/kg/day and 100 mg/kg/day to Male Sprague Dawley rats. Amended Final Study Report

Study location: Sanofi-Aventis Recherche and Developpement, Longjumeau, France
Study number: FSRFU-RDI0020-EN-E02
Report number: RDI0020
Study dates: initiated May 29, 2006
GLP: no
QA: no
Test article:

[^{14}C]-SR33589B batches SYN1763 (25 mg/kg/day), 44.4 kBq/mg (1.2 µCi/mg)
And SYN1795 (100 mg/kg/day), 11.1 kBq/mg, (0.3 µCi/mg)
SR33589B batch CL-05754
Salt/base ratio : 1.07

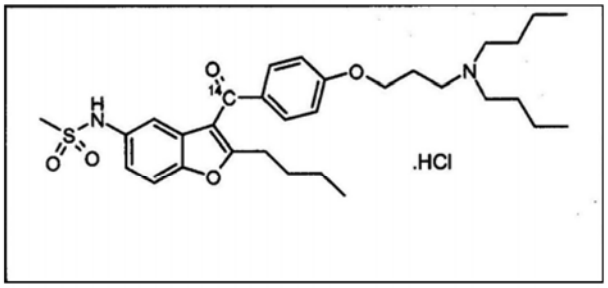

Figure (2.2.1) 1 - **Chemical structure of SSR33589B** and position of ^{14}C-labeling

Vehicle: 0.6% methylcellulose in distilled water
Animals: male Sprague-Dawley rats (OFA SD (IOPS caw))
Animals were fasted overnight prior to administration day 1 and day 28.
Treatment duration: single (once on day 1) or repeated doses (daily for 28 days)

The stated purpose of this study was to provide information on the tissue distribution and accumulation of total radioactivity in mesenteric and mandibular lymph nodes by autoradiography after single or repeated oral dosing of [^{14}C]-SR33589B (25 and 100 mg/kg/day).

Sponsor's summary of study design for tissue distribution

Substudy	1 (Tissue distribution)							
Sex	Male (M)							
Route	Oral							
Group	1				2			
Dose (mg/kg/day)	25				100			
(MBq/kg/day)	1.11 (30 µCi/kg/day)							
Volume (mL/kg/day)	5							
Sacrifice times after dosing (h)	Day 1		Day 28		Day 1		Day 28	
	4	24	4	24	4	24	4	24
Number of animals	3 rats/time/dose (24 rats)							
Animal numbers	1 2 3	4 5 6	7 8 9	10 11 12	111 112 113	114 115 116	117 116 119	120 121 122

At each time point 3 rats were euthanized.

- Blood samples were collected at time of euthanasia.
- 2 animals were used for quantitative image analysis.
- 1 animal was used for autohistoradiography
- Mesenteric and tracheobronchial lymph nodes were removed and fixed in 4% buffered formalin: these samples were sent to Sanofi-Aventis in Montpellier for autohistoradiography

Sponsor's summary of study design for microscopy

Substudy	2 (microscopic examination)		
Sex	Male (M)		
Route	Oral		
Group	3	4	5
Dose (mg/kg/day)	0 (vehicle)	25	100
Volume (mL/kg/day)	5		
Sacrifice	Day 29		
Number of animals	10 rats/dose (30 rats)		
Animal numbers	131 to 140	141 to 150	151 to 160

Rq: Day 1 is the first day of administration

At necropsy, mesenteric and tracheo-bronchial lymph nodes were collected for light microscopy and transmission electron microscopy (TEM).

Total radioactivity was determined by combustion and liquid scintillation counting (LSC). Other aliquots were analyzed by direct LSC. Liver samples also were collected but it is not clear which animals they were derived from. The methodology section is badly organized and I am not clear what procedures were performed on which animals. At the very least, total radioactivity was determined and used as a standards of calibration for quantification purposes.

The sponsor summarized the parameters analyzed:

2.9 Evaluation criteria

- Blood and plasma radioactivity concentrations after single or repeated doses
- Distribution and accumulation of TR in mesenteric and mandibular lymph nodes at day 1 and day 28
- Lymph nodes/blood concentration ratios
- Mesenteric/mandibular lymph nodes concentration ratios
- Accumulation index (Rac.) for blood, plasma, liver and lymph nodes
- Microscopic observations of mesenteric and tracheo-bronchial lymph nodes

2.10 Expression of results

- Total radioactivity concentrations in blood, plasma, liver, mesenteric and mandibular lymph nodes are expressed as ngEq./g.
- Qualitative tissue distribution data are presented as illustrations.
- Macroscopic and histomorphological observations are reported using PathData software, version 6.2b5 (PathData ® System). Results included incidence tables of macroscopic and microscopic examination and individual animal listing of observations.

It was not explained when the radiolabeled drug was administered or when the unlabeled drug was administered.

Results

Unscheduled mortality was reported for 5 animals. The sponsor decided that the deaths of the 2 HD animals might be related to treatment.

During animal experiment, 5 animals died without obvious explanation:
- Rat 7, Group 1, ^{14}C-SR35589B, 25 mg/kg/day (died on D17),
- Rat 142, Group 4, SR35589B, 25 mg/kg/day (died on D26),
- Rat 149, Group 4, SR35589B, 25 mg/kg/day (died on D25),
- Rat 156, Group 5, SR35589B, 100 mg/kg/day (died on D27),
- Rat 158, Group 5, SR35589B, 100 mg/kg/day (died on D16).

No rat was used for autohistoradiography.

Tissue concentration ratios

		Dose (mg/kg/day)			
		25		100	
Concentration ratio		4h	24h	4h	24h
Mesenteric ln / Blood	day 1	7.3	≥ 5.2	32.7	NC
	day 28	38.4	≥ 12.3	15.8	≥ 21.2
Mandibular ln / Blood	day 1	4.6	NC	4.2	NC
	day 28	6.2	NC	5.1	≥ 8.8
Mesenteric ln / Mandibular ln	day 1	1.6	≥ 1.2	7.7	NC
	day 28	6.2	≥ 3.0	3.1	2.4

(ln): lymph nodes - (≥): for concentration/BLQ ratio
(NC): not calculable

Accumulation index

	Rac. (D28/D1)			
	25 mg/kg/day		100 mg/kg/day	
Body fluids / tissues	4h	24h	4h	24h
Blood	0.6	NC	1.1	NC
Plasma	0.6	NC	1.2	≥ 1.6
Liver	0.7	4.0	1.4	≥ 3.5
Mesenteric ln	3.3	2.4	0.6	≥ 4.5
Mandibular ln	0.8	NC	1.4	≥ 1.9

(Rac.): accumulation index (conc. at day 28 / conc. at day 1)
(ln): lymph nodes - (≥): for concentration/BLQ ratio
(NC): not calculable

Dose-proportionality

	day 1		day 28	
	4h	24h	4h	24h
Body fluids / tissues	$Conc._{100mg}$ / $Conc._{25mg}$ ratio			
Blood	3.6	NC	6.6	NC
Plasma	3.1	NC	5.9	NC
Liver	3.1	NC	6.1	2.6
Mesenteric ln	16.3	NC	2.7	6.1
Mandibular ln	3.3	NC	5.4	NC

(ln): lymph nodes - (NC): not calculable

After single and repeated oral administration of [^{14}C]-SR33598B or repeated oral administration of SR33598B, it was noted that greater levels of radioactivity were located in the mesenteric lymph nodes than the mandibular lymph nodes. There was some accumulation of radioactivity in the mesenteric lymph nodes and little to no apparent accumulation in the mandibular lymph nodes.

Receptor Binding of Dronedarone and the Metabolites SR35021A and SR90154

I requested, by email, information regarding the receptor binding of the parent drug and 2 major metabolites. The sponsor referred me to the following studies, which I have assembled into a table along with the review status and content :

Study	status	content
685-4-001	Submitted in NDA 21913	Effect of dronedarone on enzymes of cellular function (adenylate cyclase, 5'-nucelotidase, several ATPases)
685-4-023	Submitted in NDA 21913	Effect of dronedarone on β and α adrenergic receptors, Ca channels, Na+/Ca++ and Na+/H+ exchangers.
685-4-043	Submitted and reviewed in NDA 21913	Dronedarone was tested against β-adrenergic receptors, and adenylate cyclase activity
685-4-052	Submitted and reviewed in NDA 21913	SR35021A, N-debutyl metabolite, inhibited binding to the L-type calcium channel and the cardiac Na+ channel with IC50 values from 1 to 7 μM. A very limited selection of receptors was examined.
685-4-067	Submitted and reviewed in NDA 21913	SR90154, the O-propionic acid metabolite had modest effects of 10% to 38% inhibition at 30 μM for the α1 adrenergic receptor, muscarinic cholinergic, A1 purinergic, L-type calcium channel (brain), Na+ channel and $K+_{ATP}$ channels. A very limited selection of receptors was examined.
CTT-0168	Submitted and reviewed in NDA 21913	Dronedarone showed binding to cardiac β adrenergic (only receptor type tested) receptors, IC50 =1755±360 nM
Van Beeren et al 2003	New material	Publication examining effects of dronedarone and SR35021A On T3 binding to TRα1 and TRβ1 in vitro. In vivo study examining TSH, rT3, T3 and T4 in male Wistar rats.

The Van Beeren publication showed that, *in vitro*, dronedarone produced a slight but statistically significant ($p<0.01$) 14±3% inhibition of of T3 binding to both TRα1 and TRβ1 receptors but no inhibition of binding of T3 to TRβ1. The debutylated dronedarone at 100 μM strongly inhibited binding of T3 to TRα1 by 77±3% ($p<0.01$) and inhibited binding to TRβ1 by 25±4%($P<0.01$) compared with control. The concentration required for an observable effect indicates low potency.

The *in vivo* studies used male Wistar rats given either water (controls), an aqueous suspension of 50 mg/kg or 100 mg/kg dronedarone given by oral gavage daily for 2 weeks. Amiodarone 100 mg/kg was used as a comparator. At the end of the dosing period, blood was collected for analysis of plasma cholesterol, triglycerides, T4, T3, rT3 and TSH. Livers were collected for analysis of LDL-cholesterol receptor (LDL-r) expression and type 1 deiodinase (D1) activity. The author's summary of these results is shown below.

556 Endocrinology, February 2003, 144(2):552–558 van Beeren *et al.* • Dron Is a TRα_1 Selective Antagonist

TABLE 3. Effect of Dron or AM treatment in rats on ΔBW, plasma thyroid hormones, and plasma lipids

	Controls (n = 8)	Dron50 (n = 8)	Dron100 (n = 6)	AM100 (n = 8)
Δ BW (g)	87 (63–93)	70 (50–90)[a]	65 (−25–75)[b]	62 (51–75)[b]
TSH (ng/ml)	1.02 ± 0.24	1.05 ± 0.54	0.87 ± 0.36[c]	1.87 ± 0.88[b]
T_4 (nmol/liter)	74 ± 9.6	62 ± 13	57 ± 12[d]	72 ± 15
FT_4 index	115 ± 15	97 ± 20	89 ± 18[d]	113 ± 23
FT_4 (pmol/liter)	39.5 ± 7.3	33.4 ± 7.1	33.7 ± 8.1	40.8 ± 9.0
T_3 (nmol/liter)	1.38 ± 0.10	1.17 ± 0.16[d]	1.09 ± 0.19[b]	1.03 ± 0.17[b]
FT_3 index	2.21 ± 0.16	1.84 ± 0.25[b]	1.71 ± 0.30[b]	1.61 ± 0.26[b]
FT_3 (nmol/liter)	0.10 ± 0.01	0.09 ± 0.02	0.10 ± 0.01	0.15 ± 0.02[b]
Total cholesterol (mmol/liter)	2.05 ± 0.18	1.86 ± 0.25	1.81 ± 0.50	2.27 ± 0.29[b]
LDL-chol (mmol/liter)	0.93 ± 0.05	0.95 ± 0.13	0.86 ± 0.37	1.15 ± 0.42[e]
HDL-chol (mmol/liter)	0.96 ± 0.10	0.85 ± 0.18	1.05 ± 0.11	1.20 ± 0.29[a]
Heart rate (beats/min)	382 ± 35	365 ± 26	390 ± 26	351 ± 23[a]
QTc interval (msec)	0.114 ± 0.013	0.125 ± 0.009[f]	0.142 ± 0.023[a]	0.141 ± 0.018[e]

Values are the mean ± SD. Δ BW, The difference between d 1 and d 15 body weights (median and range).
[a] $P < 0.05$ *vs.* controls.
[b] $P < 0.01$ *vs.* controls.
[c] $P = 0.1$ *vs.* controls.
[d] $P < 0.02$ *vs.* controls.
[e] $P = 0.07$ *vs.* controls.
[f] $P = 0.055$ *vs.* controls.

The author notes that:

> The heart has an abundance of TR[thyroid receptor]α1 relative to TRβ1, whereas tissues such as the liver express TRβ1 more abundantly than TRα1…One of the side-effects of amiodarone [AM] is an increase in plasma cholesterol caused by a down-regulation of the T3-dependent LDL-r [low density lipoprotein receptor] gene in the liver …
>
> Because of the higher affinity of DBDron [debutylated dronedarone] to TRα1, we hypothesized that the effect of Dron on heart rate and QTc interval would be similar to that of AM but that Dron, in contrast to Amiodarone, will not cause hypercholesterolemia and changes in liver LDL-r expression, as T3-induced changes in cholesterol metabolism are mainly mediated via TRβ1.

The above table of data supports the author's hypothesis. The author concludes the paper with the statement:

> In conclusion, the *in vitro* and *in vivo* data presented in this paper indicate that Dron, via its metabolite DBDron, is a TRα_1-selective inhibitor of T_3 binding to its receptor. This isoform selectivity can explain the effects of Dron on the heart (a mainly TRα_1 organ) and the lack of effect on the liver (a mainly TRβ_1 organ) and may also point the way to designing TR isoform-specific antagonists.

While this provides some insight into the receptor binding and thyroid effects, it still isn't the basic receptor binding screen that is typically a part of new drug characterization.

Overall Summary and Evaluation

Dronedarone is a benzofuran derivative structurally similar to amiodarone and demonstrating electrophysiologic characteristics of all 4 Vaughan-Williams classes of anti-arrhythmic compounds. Dronedarone was originally presented in NDA 21913 for treatment of atrial fibrillation (AF) or atrial flutter (AFL).

The Division issued a "non-approvable" letter for NDA 21913, for both clinical and non-clinical reasons. The clinical reasons for non-approval included an unfavorable risk: benefit relationship. The potential symptomatic improvement offered by the drug was also weighed against the nonclinical issues of carcinogenicity, teratogenicity, and endocrine effects (thyroid gland and female cyclicity). The complete response to these concerns was filed under NDA 22425 with a new indication of treating patients with AF/AFL or with a history of such events to reduce the risk of cardiovascular hospitalization or death.

Carcinogenicity

The sponsor provided measurement of circulating prolactin levels after a single dose and after 28 days repeated dosing of dronedarone. The reports do not provide details of what, if anything, was done to control the variability from diurnal and circadian factors. Accepting the data at face value, there were statistically significant increases in mean prolactin levels after 1 dose and after 28 days of repeated dosing. The duration of these elevations in mean prolactin levels has not been determined. Increased prolactin via dopamine 2 receptor antagonism is a generally accepted mechanism for mammary tumors in rodents.

In the Non-Clinical Summary, the following information was provided:

Table 14 - Binding assays carried out by MDS Panlabs (February 12 1999)

	Ligand	DRONEDARONE IC_{50}
Dopamine D_1	[^{3}H]SCH23390	>10 μM (30%)
Dopamine D_{2L}	[^{3}H]Spiperone	>10 μM (33%)
Dopamine D_3	[^{3}H]Spiperone	1.1 μM
Dopamine $D_{4.2}$	[^{3}H]Spiperone	4.2 μM

Material source: human recombinant, mammalian

There is weak binding to the dopaminergic receptors, in particular the D2 isoform. It is not known if the effects were agonistic or antagonistic. There was no comparison to the receptor binding affinities of drugs demonstrated to cause mammary tumors through prolactin increases.

As noted in the original NDA review, circulating prolactin levels as originally measured decreased or showed minimal changes that could have been within the realm of normal variability. The increases reported in the studies described in the current submission were relatively small compared to those reported for D2 receptor agonists such as haloperidol and clozapine (Xu et al., 2002). Increased prolactin levels are also correlated with irregularities of estrus cycles, something noted in other toxicology studies for this NDA and which the sponsor could have included in their case for a prolactin mechanism.

There are several points contrary to the sponsor's position that 1) the mammary tumors are due to increased prolactin and 2) the prolactin mechanism is irrelevant to humans:

1. It is not agreed that an increase in serum prolactin in rodents is irrelevant to humans.
2. It has not been demonstrated that increased serum prolactin does not occur in humans treated with this drug.
3. The sponsor has demonstrated minimal binding of the drug to the D2 receptor and has not demonstrated any binding of a metabolite to the relevant receptor.
4. The sponsor has not explored any other potential mechanism of carcinogenesis.

An alternative carcinogenic mechanism is an estrogenic effect, to which mice are believed to be more sensitive than rats. An estrogenic mechanism would also account for the hemangiomas and hemangiosarcomas due to the role that estrogen plays in vascular development in both species. No data was presented exploring this possible mechanism, including receptor binding profiles.

Below is a summary table of tumors listed for drugs demonstrated to increase circulating prolactin in rodents. All of these drugs were associated with an increased incidence of mammary tumors in mice and/or rats. Olanzapine and Quetiapine appear to be unusual in the list in that Olanzapine had no tumors reported in rats and neither drug appeared to cause pituitary tumors in mice. There were however, hemangiomas and hemangiosarcomas, similar to dronedarone. The remainder of the drugs accepted to cause rodent tumors by a prolactin mechanism show combinations of pituitary, mammary and pancreas tumors in one or both species. Dronedarone does not fall into that apparent pattern.

Summary of Tumors Reported in Package Inserts for Anti-Psychotics

drug	rats				mice			
	Pituitary	Mammary	Pancreas	other	Pituitary	Mammary	Pancreas	other
Aripiprazole(Abilify)		x		adrenal	x	x		
Paliperdone (Invega)	x	x	x		x	x	x	
Ziprasidone (Geodon)					x	x		
Quetiapine(Seroquel)		x						
Risperidone (Risperdal)		x(m+f)	x(m)		x	x		
Olanzapine(Zyprexa)						x		Hemangiomas and hemangiosarcomas*
Clozapine(clozaril)	No findings reported							
Zuclopenthixol(Clopixol)		x	x					

* did not occur in second study

The sponsor proposed that the increased incidence of histiocytic sarcoma, angiomatous hyperplasia, hemangioma and hemangiosarcoma may have been caused by changes in local blood flow, secondary to accumulation of foamy macrophages. The histologic changes of sinusal ectasia, sinusoidal erythrocytes, erythrophagocytosis and hilar angiectasis in the mesenteric lymph nodes in the rat carcinogenicity study with dronedarone were presented as indicative of chronic local vasodilation. At the time of the original report these findings plus angiomatous hyperplasia and the hemangiomas were described by the sponsor as part of a continuum of tumoral transformation. The sponsor presented a radiolabel distribution study and a study to demonstrate altered blood flow to the mesenteric lymph nodes. Whether or not chronic vasodilation is an accepted mechanism of carcinogenesis, neither study supported the hypothesis of altered blood flow. It was reported that the tumor incidences seen in the dronedarone studies were within the background range of the NTP studies reported in Haseman et al. However, the referenced publication is Haseman et al. "Use of dual control groups to estimate false positive rates in laboratory animal carcinogenicity studies." Fundamental and applied Toxicology: 573-584 (1986). There is a question of the relevance of the Charles River SD rats and CD-1 mice used in the historical studies to the SD(IOPS Caw) rats and the CD-1 mice used almost 20 years later.

Historical control data from in-house studies are limited to a single study:

Table 11 – Historical control rates of histiocytic sarcoma from in-house (same site) CD-1 female mice - 24-month oncogenicity study

	Male mice		Female mice	
Number of animals	**120**		**120**	
	No. of tumors	Incidence (%)	No. of tumors	Incidence (%)
Histiocytic sarcoma	4	3.3	9	7.5

Reading the reference provided by the sponsor, I could not locate the source of the numbers presented below:

Table 12 – Incidence of histiocytic sarcoma in untreated control CD-1 mice for 18 color studies - combined summary of all studies

	Male mice			Female mice		
Number of groups	**37**			**37**		
Number of animals	**2221**			**2212**		
	No. of tumors	Incidence (%)	Range (%)	No. of tumors	Incidence (%)	Range (%)
Histiocytic sarcoma	56	2.5	0-13.33	134	6.1	0-16.7

Going to the Charles River Website, the reference "Spontaneous Neoplastic Lesions in the Crl: CD-1(ICR) Mouse in Control Groups from 18 months to 2 year Studies" March, 2005, provided the following control data from studies conducted from 1987-2000:

Summary of selected neoplasias seen in control animals from the Charles River database

	Crl:CD1(ICR)		Crl:CD®(SD)	
	Male mice	Female mice	Male rats	Female rats
	Range %	Range %	Range %	Range %
Histiocytic sarcoma	1.11-8.00	1.67-18.33	0.77-6.00	1.11- 3.08
Mammary adenocarcinomas		0.78-8.33	0.56-4.29	8.57-58.33
hemangiomas	Not listed for whole body/mult. organ	1.43-2.67	0.56-3.33	Not listed for whole body/mult organ
hemangiosarcomas	1.67-12.00	1.67-12.00	0.56-2.67	1.43-1.67

The tumor incidences in CD1 mice used in the dronedarone carcinogenicity studies were within the historical ranges reported in the submission for histiocytic sarcomas and hemangiosarcomas and within the ranges that I found on the Charles River website. In the original reports, however, the sponsor listed historical control incidences of hemangiosarcoma from the published literature as 0-1.9%. There were no reports of hemangiosarcoma in 720 mice of the same strain used in another study in the sponsor's facilities.

Incidence of histiocytic sarcomas in mice: NDA 21913 carcinogenicity studies

	Males				females			
Dose mg/kg	0	75	150	300	0	75	150	300
# examined	120+	60	60	60	120+	60	60	60
Histiocytic sarcoma %	1 0.83	2 3.3	2 3.3	5** 8.3	7 5.8	4 6.7	2 3.3	7 11.7

+pooled samples **p=0.004

Incidence of hemangioma and hemangiosarcoma in mesenteric lymph nodes in mice: NDA 21913 carcinogenicity studies

	Males				females			
Dose mg/kg	0	75	150	300	0	75	150	300
# examined	116+	59	60	58	117+	58	59	60
hemangioma %	- -	1 1.7	- -	- -	- -	- -	- -	2* 3.3
Hemangiosarcoma %	-	-	-	-	-	-	-	2* 3.3

+pooled controls **p=0.032 (mortality adjusted incidences)

It is not clear why the sponsor chose to assess structural indicators of vascularity instead of a more dynamic measure of blood flow. The analysis of the tissue sections was very limited, raising a question as to how well the entire tissue was represented.

In the sponsor's textual discussion of the irrelevance of the carcinogenicity findings, they say that "Hemangiomas are not precancerous changes and do not transform into malignant hemangiosarcomas in either animals or man." Then why does the NTP recommend combining these two tumor types when doing statistical analysis (McConnell, et al.)?

There were three different tumor types found in the carcinogenicity studies. Hemangiomas appeared in both rodent species. Hemangioma and hemangiosarcoma, were seen in both sexes of mice. The sponsor postulates 3 different mechanisms of carcinogenicity occurring simultaneously to explain these tumors and the mammary tumors. Overall, the sponsor has not provided sufficient information to show that the carcinogenicity is not clinically relevant.

Endocrine Effects and Receptor Binding

The publication provided in response to my request for receptor binding data indicates some modulation of the thyroid axis by parent drug and one of the major metabolites (Van Beeren et al. 2003, Endocrinology 144(2):552-558 "Dronedarone acts as a selective inhibitor of 3,5,3'-triiodothyronine binding to thyroid hormone receptor-α1: in vitro and in vivo evidence."). However, the receptor profile that is usually a basic part of new drug characterization is still lacking.

The possible thyroid and cyclicity effects are reported to have been addressed clinically. As such, the material will be evaluated by the medical officer.

The non-clinical material presented by the sponsor does not completely address the Division's concerns.

References

PW Harvey, DJ Everett, CJ Springall. Journal of Psychopharmacology 22(2) Supplement 2008:20-27. "Adverse effects of prolactin in rodents and humans: breast and prostate cancer."

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AL Montejo. "Prolactin awareness: An essential consideration for physical health in schizophrenia." European Neuropsychopharmacology (2008) 18:S108-S114.

EE McConnell, HA Solleveld, JA Swenberg, GA Boorman. "Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. " JNCI 1986;76:283-289.

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/s/

Elizabeth Hausner
12/10/2008 08:28:10 AM
PHARMACOLOGIST
Elizabeth Hausner

Charles Resnick
12/10/2008 08:47:38 AM
PHARMACOLOGIST

Office Director Memorandum

NDA: NDA 21-913 (dronedarone) – Sanofi-Aventis

From: Robert Temple, MD

Date: August 28, 2006

I. Introduction:

Dronaderone, a relative of amiodarone but non-iodinated and with a much shorter half-life, about 24 hours at steady state (leading to b.i.d. dosing) has been studied for 1) the prevention/delay of recurrent AF in patients with AF within the last 3 months and in NSR when randomized and 2) for the reduction in ventricular rate in people with persistent AF. It is clearly "effective" for those uses, but not very, and a study in patients with NYHA Class II/III heart failure (ANDROMEDA) showed a significant increase in mortality, primarily due to CHF but also due to arrhythmias and "presumed CV death," (usually these are unobserved deaths, most likely to represent fatal arrhythmia or AMI but I could not find a description of them). The significance of this finding goes beyond suggesting avoidance of the drug in people with heart failure. As Dr. Stockbridge notes, the outcome studies asked for when considering anti-arrhythmics are not relevant solely to the population studied but to the safety of the drug in other populations, a concern raised by the CAST. Thus, the two drugs approved for maintenance of NSR in fibrillators each had reassuring outcome studies: the

Julian post-infarction study of sotalol, and the Diamond-HF and a second outcome study for dofetilide. Thus the implications of ANROMEDA apply to use of dronedarone in AF, not just in CHF, and a risk-management effort to avoid people with CHF does not resolve the problem. It is also true, of course, as Dr. Moreschi notes, that CHF is common in people with AF.

II. Effectiveness

As Drs. Stockbridge, Karkowsky and Moreschi-Friedlin (joint med-stat review) make clear, ADONIS and EURIDES, two 600+ patient (2:1 randomized) trials in patients with AF in the last 3 months and NSR for ≥ 1 hour at randomization, comparing 400 mg D bid to placebo clearly show a reduction in time to recurrent AF from D. The effect is quite small, however, HR's of 0.725 and 0.743 (or 73% recurrence on placebo vs 61% D in ADONIS and 77% placebo vs 66% D in EURIDES). While these are statistically significant, a roughly 25-30% risk reduction and 10% or so difference at one year is unimpressive [published data on amiodarone show reductions over 75%]. The endpoint studied was time to confirmed 2 measurements 10 minutes apart using TTEM (transtelephonic electrocardiogram monitoring) or ECG documented recurrence, an endpoint Dr. Moreschi considers a surrogate, not representing a clinical benefit. That seems debatable, but in any case both trials also showed significant effects on symptomatic recurrence, clearly not a surrogate endpoint. More important, however, it does not seem to be a clinical benefit one would accept a fatal risk to obtain.

HR at recurrence was lower in D patients by about 10 BPM, significant in one study and the ERATO study in 174 patients with AF not considered for cardioversion clearly showed rate reduction of about 12 b.p.m. at 2 weeks and 4 months as well as a decrease of about 25 b.p.m in exercise HR, again, a modest benefit available from drugs with well-established safety (beta-blockers, verapamil, digoxin, etc).

Both major studies used the 400 mg bid dose. A dose-finding study, DAFNE, compared placebo 800, 1200 and 1600 mg in a study with about 60 people per group, finding the best result in the 800 mg group. It was thus probably reasonable to abandon the higher doses, but FDA did urge studies at lower doses; no such study was undertaken.

III. Safety

There is some evidence, discussed by Drs. Stockbridge and Karkowsky, that D is genotoxic and carcinogenic, certainly an issue in a population without structural heart disease.

ANDROMEDA, a study in patients with predominately class II-III CHF randomized to 400 mg D bid or placebo, gave results that have convinced all reviewers that D cannot be approved at this time. The study randomized 627 patients with mean and median ages of about 70 years, about 30% in AF/Flutter at randomization, with a generally high rate of CAD and valvular disease and about 1/3 diabetic and hypertensive. About 58% were NYHA class III, about 40% class II, and just a few percent were class IV. About half had calculated CCr (Cockcroft-Gault) < 50 mL/min. Over 90% were on diuretics (40% spironolactone), over

80% on ACEI or ARB, about 60% on antiplatelet Rx and beta blocker, about 30% on statins and cardiac glycosides. The outcomes of the study (from DR. Karkowsky) were:

Endpoint	Pl n = 317	D n = 310	HR	Log-rank P
Death	12	25	2.13	0.03
D or Hosp, CHF	40	53	1.38	0.12
Hosp for CHF	31	39	__	0.27
Hosp for CV	50	71	__	0.02

The sponsor has suggested that D patients were more likely to stop ACEI/ARB because of increased creatinine and that this led to adverse outcomes. In fact (Moreschi, p38) almost twice as many D patients (49 vs 28) did not take these drugs. This did not explain the findings, however. For death plus CHF hospitalization this group did not show an adverse effect of D, while in patients on ACEI/ARB there was an adverse trend.

The causes of death are shown in the following table. Most prominent are CHF-related deaths, but arrhythmic causes and presumed CV death also tilted adversely.

	Deaths	
	Placebo N = 12	D 800 mg N = 25
CV Death	9	24
AMI	2	0
Worse CHF	2	10
Doc'd arrhythmia	2	6
Procedure	0	1
Other CV	0	2
Presumed CV	3	5

None of the reviews describe the "presumed CV" cases but they seem likely to be "found dead" cases, presumably arrhythmia, with or without new AMI.

The study was stopped early by the DMC because of the mortality finding.

IV. Conclusion

The sponsor must somehow overcome the ANDROMEDA finding to support approval. This will require an RCT of substantial size in a healthy AF population and would be difficult to do, now, in a sicker population. It does not seem likely that the very modest effect on NSR maintenance will encourage conduct of such a study.

As usual, the difference between an approvable and a NA action seems small but in this case, despite the well-documented small effects on NSR maintenance and HR, the benefit-risk calculus seems clearly adverse and I would not consider safety established under law. I believe D should be NA'd.

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/s/

Robert Temple
8/29/2006 07:07:19 PM
MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 21-913 (dronedarone)

Sponsor: Sanofi-Aventis

Review date: 15 May 2006

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 21-913

HFD-110/Fortney
HFD-110/Karkowsky/Moreschi
HFD-710/Friedlin

This application is ably summarized in Dr. Karkowsky's secondary review (27 April 2006). Medical (Moreschi) and statistical (Friedlin) reviewers both recommend Not Approvable action. Dr. Karkowsky recommends Approvable. In fact, any action one wants to take is supportable.

With this application, Sanofi-Aventis seeks two indications for dronedarone in the treatment (rate control) and prevention of recurrence of atrial fibrillation. For both of these, there is adequate evidence that dronedarone is effective.

Rate control is supported primarily by findings in ERATO, which was a randomized, double-blind, parallel, placebo controlled study of dronedarone 400 mg BID in 185 subjects with symptomatic AF and ventricular rate >80 bpm. Twenty-four-hour average heart rate was lower at 14 days on dronedarone, as was exercise heart rate. Both of these were highly statistically significant. If the effect on heart rate needs confirmation, the studies in prevention provide some. Among subjects with recurrence of AF in ADONIS and EURIDIS (see below), ventricular rate tended to be lower on dronedarone than on placebo (highly statistically significant in EURIDIS).

ADONIS and EURIDIS were two very similar randomized (2:1), double-blind, parallel, placebo-controlled studies of dronedarone 400 mg BID[1] in 625 and 612 subjects with AF within 3 months but normal sinus rhythm for >1 hour[2]. Subjects underwent scheduled transtelephonic monitoring and visit-based ECGs as well as transmitting ECGs when they experienced appropriate symptoms. The primary end point was time to any AF, and it was longer on dronedarone than placebo in both studies (p-values of 0.0017 and 0.014). Time to symptomatic AF was also longer on dronedarone in both studies (p-values of 0.021 in ADONIS and not stated for EURIDIS).

Here are the problems that would need to be resolved or dismissed with respect specifically to the rate control indication.

- The reduction in heart rate observed in ERATO was about 23 bpm from a baseline of 125 bpm. Among subjects with recurrent AF, the magnitude of effect was similar in ADONIS and EURIDIS. Thus, on average, subjects remained tachycardic. While the average responses do not rule out having some subjects

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[1] *Diarrhea renders doses higher than 800 mg intolerable.*

[2] *I see no further description of the actual distribution in times from AF to randomization.*

achieve symptomatic improvement because of a lower heart rate, symptomatic benefit has not been established.

- Only one dose was evaluated in rate control. As Dr. Karkowsky recommends, it may be possible to gain some insight into dose-response by analysis of 24-hour Holter data on heart rate in conjunction with the PK data[3].

Here are the problems that would need to be resolved or dismissed with respect specifically to the prevention of recurrence indication.

- The recurrence of AF in ADONIS and EURIDIS follows a biphasic time course. The recurrence rate in the first week or two is very high, about 30% on placebo and then is much lower thereafter, about 40% over the next year in the placebo group. The effect of dronedarone appears to be in the early phase. This phenomenon might be better characterized by taking into account subjects' time from last achieving normal sinus rhythm. Better still would be a trial in which dronedarone was discontinued after a few weeks. At the very least, support for long-term use is difficult to perceive.

Here are the problems that would need to be resolved or dismissed with respect to either indication.

- ANDROMEDA was a randomized, double-blind, parallel, placebo-controlled study of dronedarone 400 mg BID in subjects with stable (mostly NYHA class II-III) CHF and no AF. The study was stopped, so the mortality effect (relative risk 2.1 with upper 95% CI of 4.2) may be a bit of an overestimate. The excess is attributable in large part to more worsening heart failure (overall relative risk of death or hospitalization for heart failure of 1.4 with upper 95% CI of 2.1). In the lower risk ADONIS, EURIDIS and ERATIO studies, mortality rates were low and very similar on drug and placebo (with wide confidence limits and with no cause of death predominating), so one might conclude that a risk management strategy could be to discontinue dronedarone in patients who develop heart failure. However, this study was conducted, in analogy with DIAMOND-HF, to provide reassurance about risk based on a population with a high event rate; to decide that the findings are not germane to the lower risk setting completely contradicts the original premise.
- The Cmax and AUC for both dronedarone and its major (active) metabolite increase moderately more than proportionally to dose.
- Dronedarone prolongs QTc. The effect is, on average, around 10 ms at Cmax for the 400-mg dose[4]. The risk associated with increased QTc may be moderated (as it is with verapamil and diltiazem) by blocking effects on inward currents.
- Dronedarone was mostly negative in gene-toxicity assays[5] but positive in 2-year studies for histiocytic sarcomas in male rats, mammary adenocarcinomas in female mice, and hemangiomas in male rats, all at low multiples of human exposure. Of these, the mammary adenocarcinomas are thought perhaps to be hormonally mediated.

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[3] *The review of clinical pharmacology (Drs. Kumi and Garnett; 30 April 2006) attempts to analyze this from a dose-response study, but their analysis shows only a weak relationship between plasma levels and change in heart rate.*

[4] *Some data on plasma levels and change in QTc are shown in a figure on page 17 of the biopharmaceutics review. However, the drawn line is a poor fit to the data, as a residuals plot would have shown; the relationship is steeper than the line implies.*

[5] *Dr. Hausner points out that one assay in Chinese hamsters was positive, but the sponsor asserted the nominal incidence was within the range of historical controls.*

- Dronedarone was considered teratogenic in rats.
- Dronedarone has poor bioavailability and exposure can increase 3- to 4-fold with a fatty meal. Exposure can be increased 9- to 16-fold by CYP 3A4 inhibition.
- Dronedarone inhibits PGP and increased digoxin exposure by about 75%.

Since dronedarone has effects of decreasing the ventricular rate in patients with AF and in increasing the time to recurrence of AF in a population recently converted, one could choose to approve it and address its various shortcomings in labeling. No one on the review team seems to think that is a good idea, and I am inclined to agree. However, it is entirely a matter for the Office Director's discretion to decide whether any of these problems rise to the level of Not Approvable or Approvable action and whether some further study is appropriate (mortality in the target population, use for more than a few months, testing a risk management strategy for CHF, etc.).

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/s/

Norman Stockbridge
5/15/2006 10:24:07 AM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: April 26, 2006 (edited February 18, 2009)

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader, Division of Cardiovascular and Renal Products, HFD-110.

THROUGH: Dr. Norman Stockbridge, Division Director, Division of Cardiovascular and Renal Products, HFD-110.

TO: Dr. Robert Temple, Office Director, ODE-1

SUBJECT: Dronedarone Hydrochloride (Multaq®, SR33589B); Sanofi –aventis, U.S., Inc. as sponsor; NDA 21,913

This memo proposes that the two indications covered by the Sanofi aventis' submission dated 10 June 2005 are approvable but should not be approved at this time. The first indication is for the delay in recurrence of symptomatic atrial fibrillation in a population with previous events, who can be maintained in normal sinus rhythm for at least one hour. The second indication is for control of ventricular rate in patients who are not anticipated to be maintained in normal sinus rhythm.

The overwhelming impediment to drug approval is the results of the ANDROMEDA study. The ANDROMEDA study enrolled class II-IV (mostly II and III) NYHA patients with systolic dysfunction who had a recent hospitalization for CHF. That study was discontinued early because of an increase in mortality among those treated with dronedarone. The confidence interval for that study does not rule out a 4-fold increase in adverse mortality effect with dronedarone. Prior to any consideration for approval, the sponsor needs to define a population who can both benefit and also safely be treated with dronedarone. The sponsor also needs to propose an acceptable risk management program, which protect subjects with heart failure, prior to considering the marketing of dronedarone.

With respect to the indication, for the delay in recurrence of atrial fibrillation in patients who can sustain sinus rhythm for at least one hour, two studies demonstrate superiority of dronedarone at a dose of 400 mg BID to placebo. Dronedarone was superior to placebo in delaying the time to first recurrence of arrhythmia as well as the time to recurrence of the first symptomatic arrhythmia. The upper limit of dosing appears to be less than 800 mg BID based on the high dropout rate due to diarrhea as observed in the DAFNE study.

With respect to the indication, to control of ventricular rate in patients with chronic atrial fibrillation, a dose of 400 mg BID had a modest effect both on resting and exercise heart rate.

There was, however, no improvement in either exercise performance or symptom benefit among those treated with dronedarone.

The sponsor did not explore the entire usable dose range for this indication. A single regimen was studied that was equivalent to that studied for arrhythmia recurrence. There is no reason to believe that the dose for the two indications would be the same. It is unlikely, based on the modest effect on heart rate, that all subjects would be adequately controlled by this regimen. Furthermore, approximately 25% of those patients enrolled in this study discontinued within 4 months of starting therapy. It is unknown if lower doses would afford adequate benefit with an improved safety profile in the chronic atrial fibrillation population. Some additional analyses of the Holter-recordings performed to assess 24-hour heart rate in the ERATO study, particularly the heart rates at the end of the interdosing interval would be appropriate to assess whether the BID dose regimen is reasonable.

Dronedarone appears to be a carcinogen both in mice and rats. As assessed by the CAC, histiocytic sarcomas are increased in male mice and mammary carcinomas in females. In rats hemangiomas are increased. The mechanism for these tumors is unclear but may partly be a genotoxic effect, since S9 processed dronedarone produced a significant number of mutants in the Chinese hamster V79 fibroblast assay. The pattern of tumors seen with dronedarone differs from that of amiodarone where the only thyroid tumors were noted. Since dronedarone is meant for chronic use, the observed genotoxic effect for a long-term, symptom-based treatment, further nudges the risk-benefit calculation in a negative direction.

Since the drug is only approvable at this time, no attempts have been made to edit the label or make comments on the packaging. Comments to the sponsor, with the exception of those dealing with the label or packaging, by each of the disciplines are appended at the end of this review.

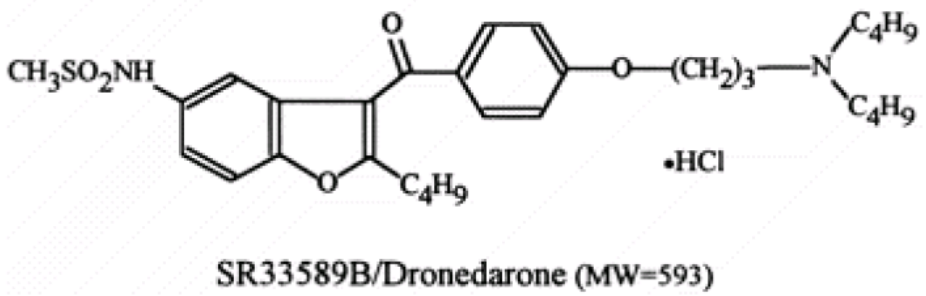
The sponsor's submissions as well as the following FDA reviews were consulted in the course of constructing this memo:

- Joint Medical Officer/Biostatistics review by Gail Moreschi, M.D., M.P.H., and Valeria Freidlin, Ph.D., dated 29 March 2006.
- Pharmacology Review by E. Hausner, D.V.M. (several), dated 3 March 2006. Memo by Kenneth Hastings, Dr.P.H., D.A.B.T., associate Director, OND, dated 4 April 2006.
- Biopharmaceutic review by R. Kumi, Ph.D., dated 30 March 2006.
- Chemistry Review by D.R. Lu, Ph.D. and W. Timmer, Ph.D., dated 7 April 2006 (2); Memo to file by R. Sood, dated 7 April 2006.
- DMETS Proprietary Trade name reviews by Laura Pincock, Pharm.D., dated 11 April, 2005; and Jinhee Jahng, Pharm.D., dated 4 October 2005 and 30 January 2006.
- Clinical Inspection by D. Tesch, Consumer Safety Officer, dated 15 March 2006.
- Environmental assessment (finding of no significant impact) by Bai Nguyen (based on contract review by Ruth Ganunis), dated 29 March 2006.
- Statistical review of carcinogenicity, by Jialu Zhang, Ph.D., dated 10 June 2005.

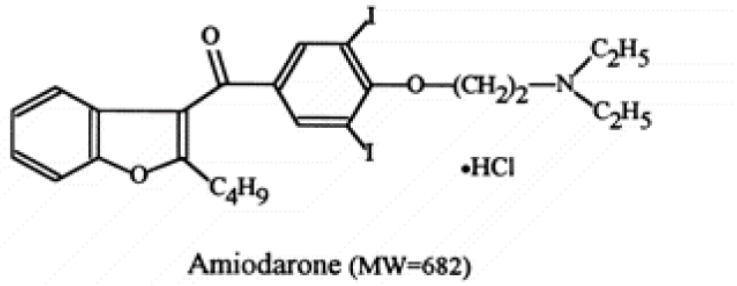
Chemistry:

The structures of dronedarone and amiodarone both are shown in Figure 1. Dronedarone is structurally similar to amiodarone but is a methanesulfonamide derivative, contains a longer side chain on the tertiary amine and does not contain iodine on the phenyl ring.

Figure 1: Structure of dronedarone and amiodarone:



Name (USAN): Dronedarone hydrochloride
Name (CAS): methanesulfonamide, N-(2-butyl-3-[43[(dibutylamino) propoxy]benzoyl]-5-benzofuranyl]-, monochloride
Molc. Formula: $C_{31}H_{45}ClN_2O_5S$
Molc Weight: 593.22 g/mol



Formulation: Tablet, single strength of 400 mg.

The final formulation for dronedarone has evolved. The proposed to-be-marketed formulation contains poloxamer 407, a solubilizing agent that constitutes 6.15% of the weight of the formulation. The solubilizer was added to decrease the effect of food on the bioavailability of drug.

Drs. Timmer and Lu considered the proposed formulation as approvable. The chemists recommend an expiration shelf-life data for drug product of 18 months.

The comments they wish to transmit to the sponsor are located at the end of this review.

Quality and reliability of data:

The financial disclosure statement indicates one investigator Dr. Ruskin, a sub-investigator in the ADONIS study, had a disclosable financial interest. In addition five sub-investigators and one primary-investigator had incomplete financial disclosure information. The small number of investigators and sub-investigators who did not submit adequate financial disclosure information, when compared to the several hundred who declared no conflict, supports our acceptance of the data as valid.

The central ECG core laboratory for the two pivotal studies ADONIS and EURIDES, MDS Pharma services, was inspected. The inspectors considered the data as analyzed by this core-lab reliable.

The EER report dated 14 March 2006 was considered ACCEPTABLE.

Other issues:

The Trade name Multac or Multaq was found acceptable by DMETS. The environmental assessment was found to be of no significant impact (FONSI).

Mechanism of action:

Dronedarone has many biological activities. Despite structural similarities to amiodarone, and despite overlap in the nature of the channels both block, the affinity of the drugs for the receptors may not be proportional in across all effects. Both drugs, moreover, have complex metabolic patterns, with the contributions by the metabolites to total activities of the drug remaining an unknown.

Based on a series of *in vivo*, *in vitro* and *ex vivo* studies encompassing receptor binding, cell culture, explanted organs and whole animals, dronedarone interacts with a variety of ion channels as well as having other effects. The context for assessing the importance of binding to any receptor is related to the C_{max} concentrations of 0.14 μM in conjunction with the large fraction of drug that is protein bound (>99%).

Channel effects:

Sodium channels:

Dronedarone inhibits sodium channels as observed in guinea pig papillary muscle. This inhibition, as assessed by an inhibition of dV/dT_{max} is use-dependent, with properties consistent with sodium channel blockers of the Ib type. In human cardio-myocytes, dronedarone as measured by patch clamp methodology, inhibited sodium currents, with 27% inhibition at doses of 0.3 μM and 97% inhibition at doses of 3 μM.

Potassium channels:

Dronedarone has affinity for a broad array of potassium channels in guinea pig heart. The specific IC_{50} concentrations for binding to the various receptors are show below in Table 1 and human potassium receptors (Table 2). The IC_{50} for inhibition of potassium channels would suggest that dronedarone would likely prolong ventricular repolarization and only at higher concentrations would it bind to atrial-selective potassium channels kv1.5

Table 1: Binding of dronedarone to potassium channels in guinea pig heart receptors (in μM):

I_{kf}	I_{ks}	I_{ki}	I_{kf}	I_{KACH}	I_{Ca-L}	I_{Ca-T}
≤ 3	10	≥ 30	> 30	~0.01	0.18	> 30

Table 2: Binding IC_{50}) of dronedarone to human potassium channels (in μM):

hERG (CHO cells expressed)	hERG expressed in HEK cells	Kv1.5
0.53	0.059	2.7

Calcium channels:

In a series of studies using cell homogenates, the binding constants for dronedarone to calcium channels was dependent on the origin of these channels. Based on the IC_{50} values, dronedarone likely will have effects on the L-type calcium channel as well as the sodium/calcium exchanger. The origin of the channel and the specific IC_{50} were: calcium L-channel (guinea pig brain) 0.14 μM; (rat heart) 0.5 μM; calcium N-channel (rat brain) inactive; calcium channel from sarcoplasmic reticulum (rabbit muscle) inactive; sodium/calcium exchanger (dog heart) 82% inhibition at 1 μM and sodium-proton pump (chick heart) inactive at 10 μM.

Adrenergic receptors:

After two weeks of treatment with dronedarone, ranging from 50-150 mg/kg to rats, cardiac membrane preparations showed a down-regulation of beta adrenergic receptors in a dose-related manner. In mongrel dogs intravenous dronedarone at a dose of 5 mg/kg and greater, the drug inhibited adrenaline induced blood pressure increase (α-adrenergic receptor blocker). It also inhibited isoprenaline induced tachycardia at similar doses (β_1-adrenergic receptor blocker). Origin of receptor and (binding constants) were β_1-adrenergic receptor-rat heart (2.2 μM), β_2-adrenergic receptors- rat lung (70% inhibition at 30 μM), α_1-adrenergic receptor-rat heart (30 μM); α_2-adrenergic receptor-guinea pig brain (28 μM). Based on these binding measurements dronedarone preferentially binds to β_1-adrenergic receptors.

Adenylate cyclase activity:

Dronedarone inhibits the stimulation of adenyl cyclase formation in rat myocyte-preparations when the preparations are stimulated by isoprenaline. The effect does not simply appear to be blockage of the adrenergic receptor, since dronedarone also inhibited adenyl cyclase generation when the membrane preparations were stimulated by glucagons or secretin, that do not act through the beta-adrenergic receptor. Dronedarone, however, did not inhibit adenyl cyclase generation when the stimulus was at the level of the regulatory or catalytic subunit. The inhibition of dronedarone on adenyl cyclase was non-competitive in nature.

Cardiac effects in intact animals:

Electrophysiology:

In anesthetized dogs (5 per gender/dose) two doses of intravenous dronedarone were administered 60 minutes apart at each of three dose levels. Surface ECGs were collected and intracardiac intervals were measured. Effects, limited to those that appear dose-related (as a

percentage change from baseline), are shown below. The greatest effects are in lengthening the atrio-ventricular node effective refractory period and the Wenckebach cycle length.

Table 3: ECG and intracardiac intervals (as % change from baseline) in anesthetized dogs:

Parameter	1 mg/kg	2.5 mg/kg	5 mg/kg
Heart rate	-15	-23	-36
Sinus cycle length	15	31	59
Atrial-His time	12	34	65
Wenckebach cycle length	31	75	112
Atrial effective refractory period	12	18	14
Atrio-ventricular nodal effective refractory period	15	99	125
Ventricular effective refractory period	7	8	23
PQ interval	9	23	51
QT interval	9	15	19

Hemodynamics:

The application contains both acute intravenous effects as well as longer term administration of dronedarone. The model systems include rats, dogs and pigs. The most consistent finding was that dronedarone decreases dP/dT_{max}, seen across species and across duration of treatments. These effects are consistent with the ability of dronedarone to block sodium channels

Bioactivity of metabolites:

Two major metabolites (see figure below) SR 35012A and SR90154 were screened for binding to an assortment of receptors. The screen assessed binding to the following receptors (and their origin): β_1-adrenergic (rat heart), β_2-adrenergic receptor (rat lung), α_1-adrenergic receptor (rat heart), α_2-adrenergic (guinea pig brain), cholinergic muscarinic (rat heart), Purinergic A_1 (rat brain), L-type calcium channel (guinea-pig brain, rat heart) , N-type calcium channel (rat brain), sodium channel (rat brain and heart), K-channel , ATP-dependent (rat heart). Of note, there was no screen for K-channel receptor binding, for IK_r, IK_s or IK_o channels.

Figure 2: Major metabolites of dronedarone:

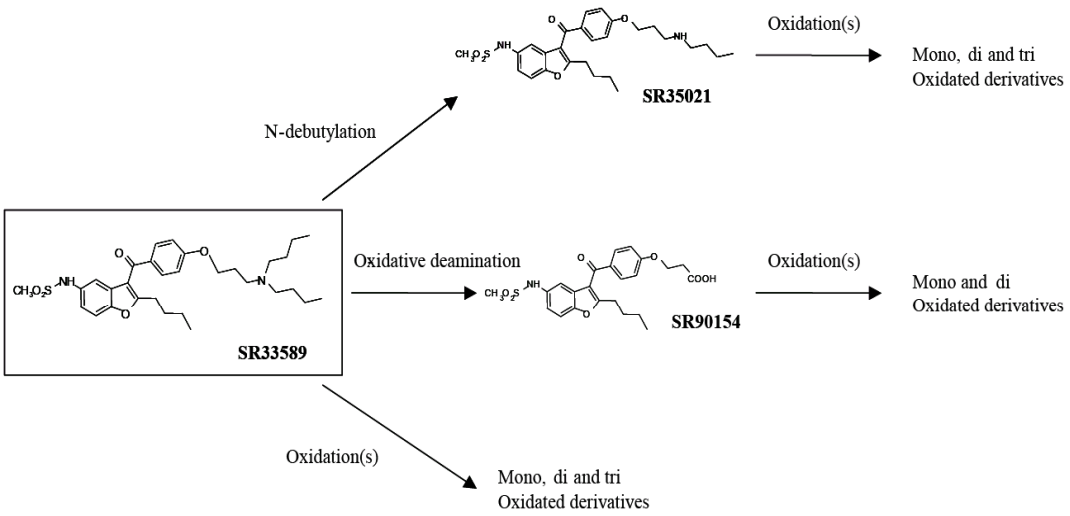


Figure (2.4.3.3) 1 - Major pathways of biotransformation of dronedarone

With respect to SR 35021A, the following receptors had EC_{50} of less than 10 µM: cholinergic muscarinic receptors (7.1 µM), L-type calcium channel (1.6 µM- brain and 3.5 µM- heart), sodium channel (1.4 µM) brain) and 7.2 µM (heart). The binding constants do not define whether the substrate is an agonist, antagonist or partial agonist nor does it define the magnitude of its effect at any receptor. For SR90154 all EC_{50} binding effects were at concentrations > 30 µM.

Carcinogenicity

In three repeat assays S9 processed dronedarone produced a significant increase in mutants in the Chinese hamster V79 fibroblasts.

The executive CAC met on 18 October 2005 to review the dronedarone mouse and rat carcinogenicity studies. The conclusions of the CAC were that the following findings were drug related: histocytic sarcomas in male mice, mammary adenocarcinoma in female mice and hemangiomas in male rats. The exposure to dronedarone, relative to the proposed human dose ranged from 4.6 in male rats to 8.2 in female mice. As suggested by Dr. Hausner, the mammary tumors as well as the alterations in cycling in female rats and dogs, may suggest changes mediated by an alteration in the hypothalamic-pituitary-endocrine axis.

Teratology

Dronedarone appears teratogenic in rats. Observations in the offspring include skeletal and external malformations in 17 out of 18 fetuses at a dose of 160 mg/kg (with some maternal toxicity) and 15 of 48 fetuses at a dose of at a dose of 80 mg/kg. Both these findings were observed in a preliminary dose-testing study. In the definitive study, at a dose of 100 mg/kg which was maternally toxic, approximately 90% (198/221) of the fetuses had external, organ-

system and/or skeletal abnormalities. No abnormalities were noted in the maternal group treated with 30 mg/kg. In the low dose group (10 mg/kg), there were reports of unilateral microopthalmia, and unilateral anopthalmia. In rabbit studies, two fetuses of different litters were profoundly deformed with craniofacial and laryngeal abnormalities.
.
Other effects: Thyroid hormones, phospholipidosis.

Doses of dronedarone of 50, 100 or 150 mg/kg were studied in rats. In male rats dronedarone at doses of 150 mg/kg but not doses of 100 mg/kg or 50 mg/kg decreased T4, T4/T3 ratio. In the three-month toxicology studies in rats there were small increases in TSH both in male and female rats at a dose of 60 mg/kg daily.

Foamy macrophages were reported in various organs in rats. At dose of > 5 mg/kg (3 month study) these macrophages were reported in lungs as well as in other tissues.

Pharmacokinetics:
Biopharmaceutics:

Dronedarone demonstrated non-linearity in exposure relative to dose. On the first day of dosing the proportionate increase in the AUC was 2.8 in increasing the dose from 200 mg BID to 400 mg BID, and 2.7 in increasing the dose from 400 to 800 mg BID. The proportionate increase in AUC by dose was 2.8 fold on day 1. The proportionate increase were slightly greater at day 14.

Table 4: Dose-related pharmacokinetic parameters of dronedarone and SR35021 (BID-dosing) mean ± SD:

Parameter		Dronedarone			SR35021		
		200 mg	400 mg	800 mg	200 mg	400 mg	800 mg
Cmax µg/ml	Day 1	23.1 ± 38	67.2 ± 36	162 ± 40	20.8 ± 21	49.5 ± 25	109 ± 29
	Day 14	40.3± 30	111 ± 17	298 ± 13	41.2 ±27	107 ± 22	282 ± 21
t_{max} median (h)	Day 1	3	3	3	5	5	5
	Day 14	5	5	5	5	5	5
AUC $_{0-12}$ ng h/ml	Day 1	111 ± 24	310 ± 28	846 ± 27	123 ± 19	275 ± 23	668 ± 24
	Day 14	276 ± 23	798 ± 19	2510 ± 12	325 ± 21	882 ± 17	2680 ± 20
$T_{1/2\alpha}$ (h)	Day 1	10 ± 33	18 ± 56	20 ± 33	16 ± 28	19 ± 24	22 ± 22
	Day 14	27 ± 32	30 ± 29	31 ± 32	24 ± 14	21 ± 16	20 ± 8

Absolute bioavailability

The absolute bioavailability of a dronedarone when administered orally while fasted was 4%. The absolute bioavailability orally while fed was approximately 15%. Comparing fasted to low fat and fat-rich meals shows a steady increase in AUC as the fat-content of the meal increases.

Distribution:

Dronedarone is approximately 99% bound to plasma protein, predominantly to albumin. Following administration of intravenous dronedarone, the volume of distribution associated with the terminal half-life was 2500-3400 Liters.

Distribution study in animals:

In male rats, oral administration of carbonyl-14C SR33598 (total dose of 30 mg/kg) produced a broad tissue distribution of radioactivity. Aside from the GI tract, high

concentrations were noted in lungs, liver, kidneys, spleen and thyroid at 1 to 8 hours post dose. In pigmented rats, dronedarone appears to be concentrated at sites containing melanin.

Metabolism:
In vitro CYP assay:

Dronedarone, when assayed in *in vitro* liver microsomal preparations showed only minimal inhibitory effect on the CYP family of enzymes. Of the enzymes inhibited, dronedarone inhibited CYP2D6 with K_i values of approximately 5 μM and CYP3A4 with a Ki of approximately 40 μM. One of the metabolites of dronedarone, RS-335021 inhibits several CYP 450 isoforms with K_i values of less than 40 μM. This metabolite inhibits the following isoforms (with the K_i values): CYP2D6 (4.4μM), CYP3A4 (8.1 μM), CYP2C19 (11.2μM), CYP2C9 (18.3 μM), CYP1A2 (30.6 μM), CYP2A6 (32.7 μM).

Drug-Drug interactions:

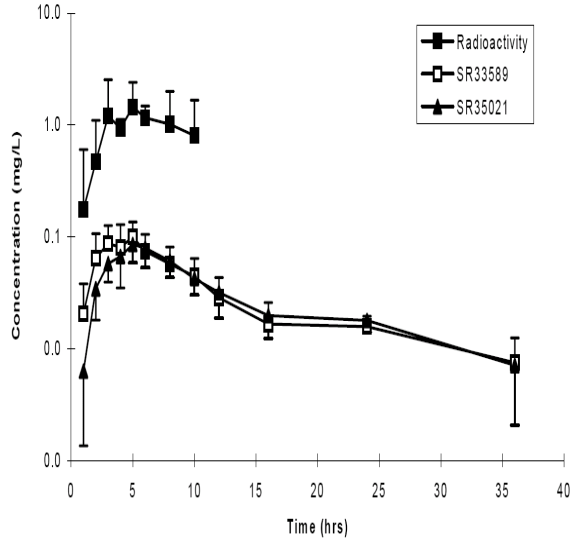
Several drug-drug interaction studies were performed with the results summarized in Table 24 of Dr. Kumi's review. Despite a lack of effect in the *in vitro* screen, dronedarone exposure is markedly increased in the presence of CYP3A4 inhibitors. Multiple dose ketoconazole (200 mg) increased Cmax and AUC of dronedarone at a 100 or 200 mg single dose, by 9 and 16 fold, respectively. It also seems that dronedarone acts a PGP inhibitor, increasing digoxin concentrations by 75% (C_{max}) and AUC by 150%.

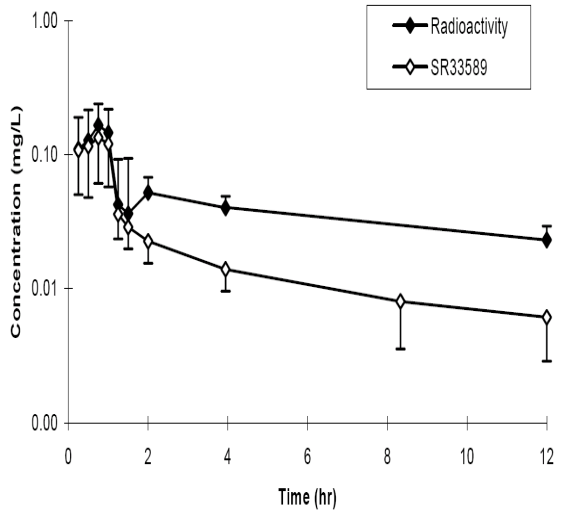
14C-tracer study in humans:

There were two 14C-labeled studies, one study with dronedarone administered orally and one intravenously. After oral administration, peak radioactivity occurs at approximately 4 hours. The concentration of the parent drug and one metabolite, SR 35021 accounts for only approximately 20% of the radioactivity (Figure 3). The specifics of the rest of the radioactivity remain unknown. The duration for which radioactivity was followed was only 10 hours and the terminal half-life of radioactivity after an oral dose cannot be determined with accuracy. After approximately 100 hours, nearly all the radioactivity was excreted in urine and feces, suggesting a functional half life of 25 hours for the metabolites of dronedarone (Figure 3).

After intravenous administration, the concentration of radioactivity and parent drug (SR33589) are equivalent shortly after drug administration (Figure 3). At about 2 hours, the concentrations appear to diverge, suggesting the generation of label-containing metabolites. The duration of observation (12 hours) does not allow an accurate assessment of the terminal radioactive half-life.

Figure 3: 14C-labeled dronedarone after oral (left) and intravenous (right) administration SR33589 is dronedarone:





Parameter (units)	Radioactivity[a,b]	SR33589[a]	SR35021[a]
C_{max} (mg/L)	1.75 (1.06)	0.10 (0.04)	0.09 (0.02)
t_{max} (h)	4.5 [c] (3 to 6) [d]	4.5 [c] (3 to 6) [d]	5.5 [c] (5 to 6) [d]
$t_{½}$ (h)	ND [e]	18.84 (4.01)	18.49 (2.57)
AUC_{0-t} (mg*h/L)	19.86 (29.85)	1.11 (0.41)	1.08 (0.34)
t (h)	11.0 (2.0)	36.0 (7.6)	40.8 (6.6)
AUC (mg*h/L)	ND	1.58 (0.39)	1.46 (0.34)
%(Extrapolated AUC /AUC)	ND	18.35 (6.54)	18.46 (4.43)

[a] Mean (±SD)
[b] Radioactivity is expressed as mg-equivalents where appropriate
[c] Median of all subjects
[d] Range for t_{max} from all subjects
[e] Not determined

Parameter (units)	Radioactivity[a,b]	SR33589[a]
C_{max} (mg/L)	0.17 (0.07)	0.14 (0.07)
t_{max} (h)	0.83 [c] (0.75 to 1.0) [d]	1.0 [c] (0.75 to 1.25) [d]
$t_{½}$ (h)	11.76 (5.78)	10.97 (5.21)
AUC_{0-t} (mg*h/L)	0.65 (0.32)	0.35 (0.15)
t (h)	17.33 (8.26)	17.33 (6.02)
AUC (mg*h/L)	0.95 (0.44)	0.49 (0.19)
%(Extrapolated AUC /AUC)	34.01 (8.56)	25.65 (11.48)

[a] Mean (±SD)
[b] Radioactivity is expressed as mg-equivalents where appropriate
[c] Median of all subjects
[d] Range for t_{max} from all subjects

Excretion:

Dronedarone label was excreted primarily in the feces. Of the tracer dose, 84% was eliminated in feces; 6% in urine. Full recovery of radioactivity required upward of 100 hours (Figure 4). There were more than of 30 metabolites detected in feces and urine. Approximately 20 of these metabolites each, reflect more than 1% of the tracer administered. A large fraction of these compounds were only partly characterized based ion mass spectroscopic fragmentation pattern. Only two of the metabolites SR35021 and SR90154 were screened through a series receptor binding assays (see above).

Figure 4: Time course of label excretion after oral dose of dronedarone:

Table (8.2.1.3) 1 - Mean recovery of radioactivity in urine, feces and expired air from six healthy male subjects following oral administration of 800 mg (6.63 MBq) of ^{14}C-SR33589B

Excretion (% of dose)			
Urine	Feces	Expired air	Total
5.8 ± 1.2	83.9 ± 5.1	0.0 ± 0.0	89.7 ± 4.7

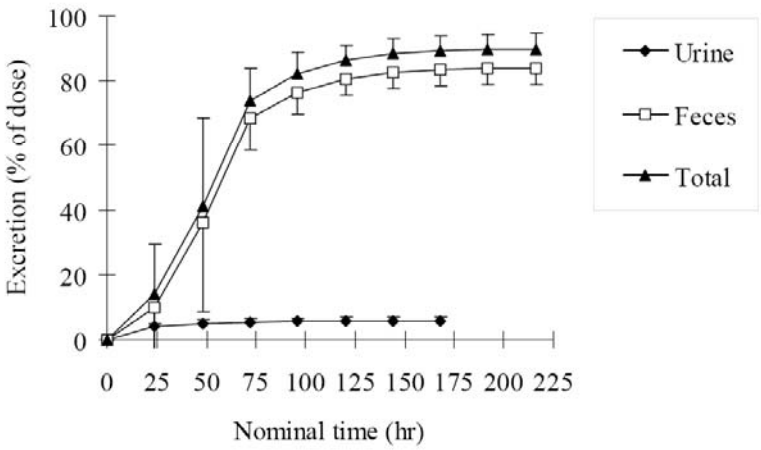


Figure (8.2.1.3) 1 - Mean cumulative excretion (±SD) of radioactivity in urine and feces from six healthy male subjects following oral administration of 800 mg (6.63 MBq) of ^{14}C-SR33589B

Specific populations:

After an 800 mg QD dose, the C_{max} for elderly (age 65-80 years, mean 70-72 years) was 15% higher on day 1 and 30% higher on day 17, than young males (age 25-40 years, mean 29 years). The C_{max} for elderly females was approximately 90% higher on day 1 and day 17 than young males. For AUC, elderly males had an increase of approximately 30% relative to young males. Elderly females had an increase of approximately 100% on days 1 and 17 compared to young males.

Japanese males appeared to have lower clearances than their Caucasian counterparts at a dose of 400 mg (cross-study comparisons). There was no information with respect to the kinetics in African-Americans.

There were no studies in patients with hepatic impairment that have been completed. One study POP5829 is ongoing.

Efficacy:

Dronedarone at a dose of 400 mg BID, administered with food, demonstrated a prolongation to the time of recurrence of atrial fibrillation in two placebo-controlled randomized studies, EURIDES[1] and ADONIS[2]. The studies were performed concurrently,

[1] European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone in patients for the Maintenance of Sinus Rhythm.-EFC3153

[2] American-Australian-African Trial with Dronedarone in patients for the maintenance of Sinus rhythm-EFC4788

under the same protocol. The core lab that performed the analyses of ECGs, TTEMs (transtelephonic electrocardiogram monitoring) and laboratory measurements was the same for both studies.

The differences in studies were the geographical areas from which populations were recruited. In the EURIDES study the population enrolled was derived from l2 countries: Netherlands, Germany, Poland, Hungary, Italy, France, Czech Republic, Belgium, Spain, Denmark, Finland and the United Kingdom; in the ADONIS study the populations were derived from: USA, Canada, Australia, Argentina and South Africa.

Patients were eligible for enrollment if, within the previous 3 months, they had an episode of atrial fibrillation or flutter and were in sinus rhythm for at least 1 hour at the time of randomization. Notable exclusion criteria included NYHA class III or greater heart failure and previous failure of amiodarone treatment. Proscribed medications included drugs with Vaughn-Williams Class I and/or III antiarrhythmic activity, drugs known to provoke torsades de pointes and potent CYP3A4 inhibitors. Anticoagulants were to be administered and monitored as per study site or published guidelines.

At baseline, each of the patients was given and instructed how to use TTEM device, as well as the best position to place that monitor for observing p-waves. The TTEM devices were to be used at specified times to capture the ongoing rhythm: days 2, 3, and 5, month 3, 5, 7 and 10, as well as when the subjects felt symptoms consistent with past fibrillation events. Standard 12-lead ECGs were recorded at the following specified times: day 1, 7, 14 and 21 as well as month 2, 4, 6, 9 and 12. Both TTEMs and 12-lead ECGs were to be repeated 10 minutes apart. The recurrence of an atrial fibrillation or flutter would be defined by the demonstration that the arrhythmia was present on the two measurements. If the arrhythmia was only present on the second of the measurements, even if subsequent ECGs failed to demonstrate an arrhythmia, the subject had met the endpoint.

At the time of an ECG or TTEM transmission[3] to the core lab, the lab queried the subject about the following five symptoms (palpitations, dizziness, fatigue, chest pain or dyspnea) as well as their intensity.

After baseline determinations, subjects were randomized in a 2:1 ratio to either dronedarone 400 mg BID or placebo. The dose was to be taken with or shortly after breakfast and dinner.

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[3] The timing of the recording and transmission of the TTEM was not necessarily closely linked. The ability to transmit the information was dependent on the working hours of the core lab as well the availability of a translator to query symptoms, if required by the patient's native language. The TTEM could have several ECGs in memory that would be transmitted concurrently. The maximum memory capacity of the TTEM was 6 recording. Consequently, only three episodes (with 10-minute replicates) could be captured before capacity was reached. Once down-loaded, the TTEM erased the tracing and additional recording space became available. At the time of transmission the patient was asked about the presence of six symptoms suggestive of recurrence of an arrhythmia. Since the patient did not fill out a diary, the recall of symptoms, perhaps several days after the event, relies on recall to an inordinate extent.

The primary study endpoint was time that normal sinus rhythm was lost, as judged by the initial time of recurrence of atrial fibrillation or flutter. This endpoint was assessed in the randomized and treated patient population with the comparison performed by a 2-sided Log-rank asymptotic test. The cumulative incidence functions for each treatment were calculated using the nonparametric Kaplan-Meier estimate. The relative risk, with 95% confidence interval was estimated using the Cox model with treatment group as the only factor. In addition to the primary analysis, per protocol and a covariate analyses were planned. The specific covariates were type of conversion of the last event (electrical, ibutalide use or overdrive pacing), chronic amiodarone use prior to enrollment and the presence of structural heart disease.

Secondary endpoints were:

- Time to recurrence in the presence of symptoms, assessed through a survival of competing risk analyses.
- Ventricular rate at the time of primary endpoint, analyzed by a 2-way ANOVA with treatment and ECG as covariates
- The time from attaining steady state of dronedarone to the time of the adjudicated first event. The statistical methodology was as used for the primary analysis.

Since the studies were carried out in a similar manner the disposition of patients, the characteristics of the patients, and outcomes for both studies will be tabulated together.

Patient disposition:

The disposition of the patients from both the ADONIS and EURIDIS study are shown in Table 5. In both studies the randomization was 2:1, dronedarone: placebo. There was a higher rate of discontinuation for adverse events among those treated with dronedarone compared to placebo-treated patients. Selected demographics, baseline conditions and concomitant medications are shown in Table 6.

Table 5: Disposition of subjects in ADONIS and EURIDIS:

	ADONIS		EURIDIS	
Screened	731		680	
Screening failures		102		65
Randomized	629		615	
Not treated		4		6
Randomized and treated	625		612	
	Placebo	Dronedarone	Placebo	Dronedarone
	208	417	201	411
Completed Therapy or end point	172 (83%)	336 (81%)	176 (88%)	344 (84%)
Discontinued	36 (17%)	81 (19%)	25 (12%)	67 (16%)
Endpoint of lack of efficacy	3 (1%)	1 (<1%)	0	0
AE	16 (8%)	45 (11%)	13 (6%)	36 (9%)
Compliance	4 (25)	3 (1%)	0	0
Patient's request	8 (4%)	21 (5%)	11 (5.5%)	27 (6.6%)
Other	5 (2%)	10 (2%)	1 (<1%)	4 (1%)

.

Table 6: Demographics, baseline cardiovascular disease and selected treatments for ADONIS and EURIDIS:

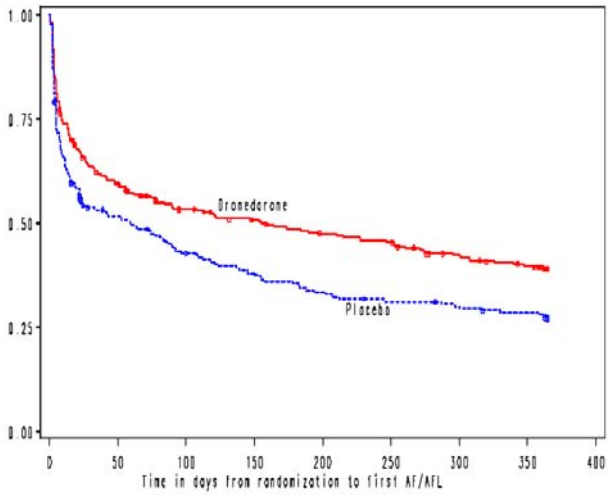
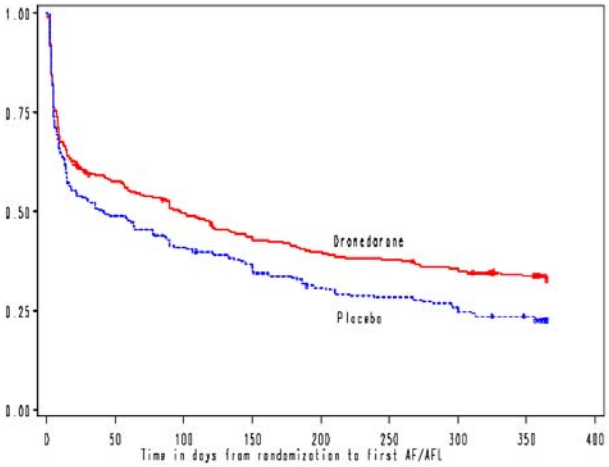
	ADONIS		EURIDIS	
	Placebo	Dronedarone	Placebo	Dronedarone
N=	208	417	201	411
Age in years (mean ±SD)	63 ± 11	65 ± 11	61 ± 11	62 ± 10
<65 N (%)	104 (50%)	186 (45%)	111 (55%)	338 (55%)
65-75 N (%)	80 (39%)	149 (36%)	76 (38%)	215 (35%)
≥ 75 N (%)	24 (12%)	82 (20%)	14 (7%)	59 (10%)
Weight in Kg (mean ± SD	88 ± 19	89 ± 20	86 ± 15	83 ± 14
Gender N- Male (%)	140 (67%)	293 (70%)	140 (70%)	285 (69%)
Race non-Caucasian N (%)	9 (4%)	26 (6%)	0	2 (<1%)
Concomitant cardiac disease, N (%)				
Hypertension	97 (47%)	242 (58%)	108 (54%)	255 (62%)
Structural heart disease	94 (46%)	199 (49%)	65 (33%)	149 (36%)
Coronary heart disease	44 (21%)	104 (25%)	31 (15%)	91 (22%)
Valvular heart disease (includes MVP)	42 (20%)	86 (21%)	19 (10%)	50 (12%)
Dilated cardiomyopathy	19 (9%)	34 (8%)	11 (6%)	16 (4%)
Functional pacemaker	13 (6%)	31 (8%)	7 (4%)	33 (8%)
Rheumatic heart disease	8 (4%)	18 (4%)	6 (3%)	7 (2%)
Hypertrophic cardiomyopathy	4 (2%)	13 (3%)	8 (4%)	10 (2%)
ICD,	2 (1%)	6 (1%)	3 (1%)	0
Congenital heart disease	1 (< 1%)	4 (1%)	2 (1%)	9 (2%)
LVEF (2-D Echo) mean ± SD	57 ± 12	58 ± 11	60 ± 9	60 ± 10
NYHA Class II	26 (13%)	50 (12%)	21 (10%)	46 (11%)
Baseline medications, N (%)				
Beta blockers excluding sotalol	114 (55%)	208 (50%)	124 (62%)	245 (60%)
ACEI and/or ARB	96 (46%)	194 (47%)	94 (47%)	215 (52%)
Digitalis	55 (26%)	94 (23%)	55 (27%)	79 (19%)
Diltiazem or verapamil	55 (25%)	103 (25%)	23 (11%)	36 (9%)
Diuretics	65 (31%)	150 (36%)	60 (30%)	121 (29%)
Spironolactone	4 (2%)	23 (6%)	14 (7%)	10 (2%)
Oral anticoagulants	149 (72%)	298 (72%)	142 (71%)	273 (66%)
Anti-platelet drugs	88 (42%)	191 (46%)	64 (32%)	135 (33%)
Statins	79 (38%)	168 (40%)	52 (26%)	95 (23%)

The two groups were reasonable well balanced. There were differences however, in the baseline demographics that include: the presence of hypertension, structural and coronary heart disease, which was more frequent in the dronedarone group. Approximately 90% of those enrolled were NYHA class I.

Primary efficacy outcome for time to first arrhythmic recurrence and the secondary outcome of time to first symptomatic arrhythmia recurrence, indicate a superiority of dronedarone to placebo in both studies.

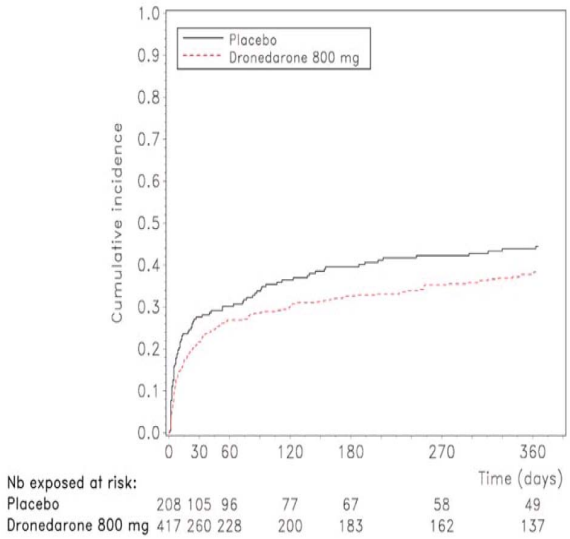
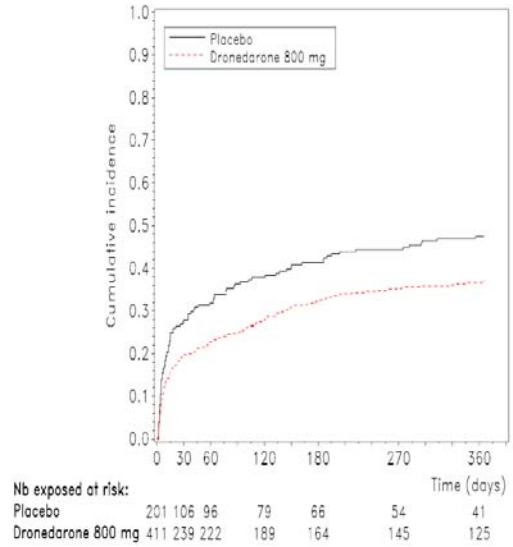
The Kaplan-Meier curve for the recurrence –free time for both ADONIS and EURIDIS is shown below. There was an approximately 27% decrease in risk of arrhythmia recurrence in the dronedarone relative to placebo patients.

Figure 5: Time course for recurrence of arrhythmia ADONIS (left) and EURIDIS (right), with corresponding p-values:

ADONIS	EURIDIS
 (figure provided by Dr. Valeria Freidlin) Figure 6- Primary efficacy endpoint, time to first AF/AFL	 (Figure provided by Dr. Valeria Freidlin) Figure 9- Primary efficacy endpoint, time to first AF/AFL
Relative risk (Cox Regression Model) [95%CI] 0.725 [0.59-0.89]	Relative risk (Cox Regression Model) [95%CI] 0.743 [0.57-0.96]

There was a statistically significant difference, comparing dronedarone to placebo, in the time to first symptomatic events (Figure 6). The sponsor also indicated a significant difference in time to recurrence after steady state for both ADONIS and EURIDIS (data not re-analyzed by FDA).

Figure 6: Time to first symptomatic recurrence in ADONIS (left) and EURIDIS (right), and p-values:

ADONIS	EURIDIS
	
Log rank test p=0.021	Log rank test p=0.0037

Ventricular rate at time of recurrence:

The heart rate at the time of first adjudicated recurrence is shown below. In both the ADONIS and EURIDIS study this heart rate was lower among those treated with dronedarone. Only in the EURIDIS study was effect significant. In neither study was the mean heart rate at the time of recurrence in what one would consider acceptable control (60-80 bpm).

Table 7; ventricular rate at time of recurrence in ADONIS (left) and ADONIS (right):

	ADONIS		EURIDIS	
	Placebo	Dronedarone	Placebo	Dronedarone
Heart rate	111 ± 32	103 ± 28	112 ± 29	100 ± 25
	P=0.078		P<0.001	

Choice of dose:

The only empirical data for the choice of both the dose of dronedarone (800 mg daily) with food is derived solely from the DAFNE[4] study. This study was a multinational, multicenter, double-blind, parallel-arm, placebo-controlled study comparing dronedarone versus placebo, in patients currently in atrial fibrillation who are planned for cardioversion. Patients were started on medication either placebo, or dronedarone at a dose of 400, 600 or 800 mg BID. The primary endpoint was time to recurrence of atrial fibrillation. The primary statistical analysis was the dose-response effect to the time recurrence of atrial fibrillation in those who could be cardioverted or who spontaneously reverted to normal sinus rhythm. The analytic plan assessed doses as evenly spaced parameters, using a Cox's model. The analytic plan included two baseline covariates in addition to dose; presence of structural heart disease and duration of current episode of atrial fibrillation.

Of the 270 subjects who were randomized and received blinded medication 205 were eventually cardioverted (electrical or pharmacologic) or spontaneously reverted to sinus rhythm and entered the intent to treat maintenance phase. Of these patients, there was no overall dose response in the time to recurrence of atrial fibrillation (p=0.7). Despite the overall lack of significant effect in the truncated population, the sponsor suggested that the 400 mg BID dose separated itself from the two higher doses. There was a substantially larger drop out rate that appeared dose-related, but was particularly evident at the 1600 mg dose.

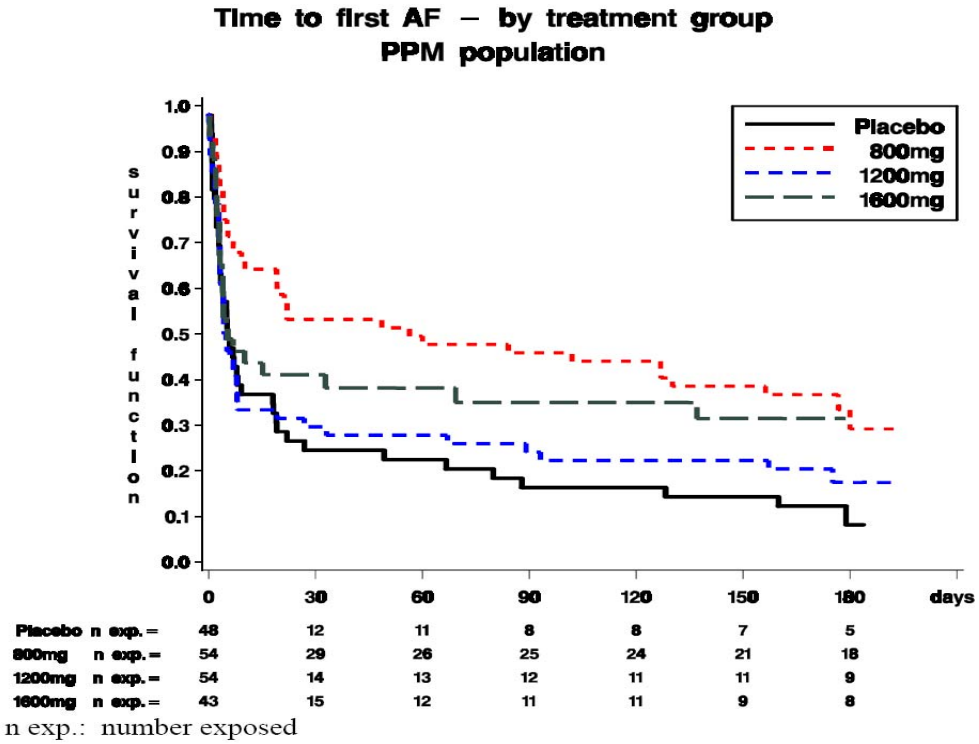
[4] Dronedarone Atrial Fibrillation study after Electrical cardioversion-DRI3550

Table 8: Disposition of patients in the DAFNE study:

Population	Placebo	Dronedarone (daily dose divided BID)			Total
		800 mg	1200 mg	1600 mg	
Randomized	66	76	66	62	270
In NSR at baseline	0	0	0	1	1
Randomized and treated	66	76	66	61	269
Adverse event	0	3	5	15	23
Patient request	1	0	1	0	2
Protocol Deviation	0	2	0	2	2
Other	0	0	0	1	1
Cardioversion failures	17	16	7	11	51
Entered Maintenance	49	56	56	44	205
Adverse event	0	1	3	10	14
Patient request	1	0	0	0	1
Protocol Deviation	0	0	0	0	0
Other	0	0	0	1	1
Completed	48	55	53	33	189

The time course to recurrence of first arrhythmia is shown below. The significance as tabulated by the sponsor is immediately following. Overall there was no dose effect (p=0.7).

Figure 7: Recurrence of arrhythmia in DAFNE for those in sinus rhythm by spontaneous conversion or pharmacologic/electrical methods when entering the maintenance phase:



n exp.: number exposed

The data as submitted do not rule out that higher of lower doses than 400 mg BID would be a reasonable anti-arrhythmic dose. The usable dose range for dronedarone is therefore, uncertain.

Indication of rate control:
The ERATO[5] study enrolled patients with symptomatic atrial fibrillation with a resting ventricular rate ≥ 80 BPM, for which cardioversion was not considered. Notable exclusion criteria included grade III or IV NYHA heart failure. Subjects had 24 hour Holters performed at baseline and day 14. Exercise testing, by graded cycle ergometry was also performed at baseline and day 14.

Primary endpoint:
The primary endpoint was the change in heart rate, averaged over 24 hours, as assessed by Holter. This rate was analyzed by an analysis of covariance taking into account as covariates, treatment and baseline medications that could alter heart rate, as well as demographic factors such as age and baseline heart rate.

Secondary end point included:

- The decrease in ventricular rate during sub-maximal and maximal symptom limited exercise test compared to baseline without decreasing exercise performance. Exercise performance was estimated by measurement of the maximum work load reached and the gas exchange variables.

- The decrease in mean ventricular rate measured by 24-hours at 4 months.

At each of the monthly visits, the subject filled out the Bubien and Kay patient symptom questionnaire. This questionnaire asked the patient about sixteen symptoms potentially related to the underlying atrial fibrillation. The questions attempted to capture the frequency and intensity of these symptoms over the previous thirty-day period. Frequency was assessed by summing the scores of the sixteen symptoms with 0= never to 4= always. Severity for each of the 16 symptoms was graded from 0= never to 3=extreme.

The study enrolled 185 patients. Those patients enrolled from one study site were excluded. Of the remaining 174 subjects, 89 received placebo and 85 dronedarone at a dose of 400 mg BID. There were 79 and 68 completers in the placebo and dronedarone groups, respectively. There were 10 and 17 discontinuations in the placebo and dronedarone group respectively, with 9 in placebo and 13 in the dronedarone attributed by the sponsor to adverse events.

Underlying cardiovascular disease was similar in the two treatments. The most common disease (and %) were: hypertension (48%), structural heart disease (38%), valvular disease (17%) and coronary artery disease (17%). Of those enrolled approximately 28% were NYHA class II. Approximately 87% were taking oral anticoagulants and 15% chronic anti-platelet therapy. Medications to control heart rate, with the exception of calcium antagonists, were similar in the two treatment groups and included beta-blockers (53%) and digitalis (43%).

[5] Efficacy and safety of dronedarone for the control of ventricular rate during atrial fibrillation. EFC 4508.

Calcium antagonists (verapamil or diltiazem) were used in 17% of placebo and 29% of dronedarone groups. It is unclear if patients were on maximal doses of those drugs which offer some rate control prior to the start of randomized treatment. Since there are pharmacokinetic effects of dronedarone with CYP2D6 (β-blockers), CYP3A4 (verapamil and diltiazem) and PGP (digoxin) substrates, the possibility that some of the heart rate effects may be a consequence of dronedarone's effect on these concomitant therapies cannot be dismissed.

Comparing dronedarone to placebo there was a -11.7 beat per minute difference on average heart rate throughout the 24-hour Holter on the day 14 assessments ($p < 0.0001$). There was also a decrease in maximal heart rate on exercise ergometry at day 14 of -25 bpm ($p < 0.001$). There was a change in heart rate at the final 4-month assessment -8.8 bpm ($p< 0.001$). There were however, no differences in duration of exercise performance (-0.12 minutes) p= NS, gas-exchange variables or Bubien and Kay frequency or severity scores.

Since only one dose regimen of dronedarone was studied for rate control, it is not possible to determine if better rate control would result from higher doses or a more benign safety profile with adequate rate control could be achieved by the use of lower doses.

Interdosing interval:

Based on pharmacokinetic considerations the BID dose interval appears appropriate. Below are some data from the ADONIS, EURIDIS, ANDROMEDA and ERATO studies from population PK sampling (adopted from Dr. Kumi's Table 8). For each study C_{min} was > 50% of C_{max}.

Table 9: C_{max} and C_{min} for dronedarone concentrations in the EURIDIS, ADONIS, ERATO and ANDROMEDA studies.

		EURIDIS	ADONIS	ANDROMEDA	ERATO
Dronedarone	C_{max} (ng/ml)	106 (50)	98 (64)	101 (54)	92 (107)
	C_{min} (ng/ml)	66 (56)	60 (58)	65 (66)	56 (56)
SR35021	C_{max} (ng/ml)	59 (45)	53 (51)	61 (500	50 (56)
	C_{min} (ng/ml)	40 (44)	38 (46)	36 (62)	38 (33)

With respect to the ERATO study any dynamic effect on heart rate at the interdosing interval that could be analyzed for an effect at the interdosing interval. This information was not supplied.

Safety:

Exposure:

The exposure among those enrolled into the atrial fibrillation/flutter or rate control studies are shown below. The studies include DAFNE, ERATO, EURIDIS and ADONIS. The ANDROMEDA study will be described separately.

Table 10: Exposure information atrial fibrillation studies:

	Placebo	Dronedarone		
		400 mg BID	600 mg BID	800 mg BID
N=	564	989	66	62
Mean days ± SD	205 ± 141	240 ± 142	64 ± 76	57 ± 71
Patient-years	316.7	650.3	11.6	9.7
Exposure at day				
30	446	833	23	23
180	316	661	12	9
360	100	283	0	0
Patients with TEAE (per patient year)	340 (1.1)	660 (1.0)	42 (3.6)	45 (5.9)
Serious TEAE (per patient year)	79 (0.25)	133 (0.20)	4 (0.34)	8 (0.82)
Deaths* (per patient year)	3 (0.009)	9 (0.014)	0	0
Patients discontinued (per patient year)	34 (0.10)	96 (0.15)	4 (0.34)	14 (1.4)
* Deaths from first dose till ten days after last dose.				

The numbers of patient-year exposure for dronedarone is approximately double that of placebo. There were a reasonable number of dronedarone subjects treated for approximately 1 year (360 days). There appears to be a dose response relationship, when correcting for patient exposure when considering TEAE and serious TEAE. Deaths within 10-days of completing treatment, when normalized to patient exposure, were greater in the dronedarone group.

Deaths-atrial fibrillation studies :

The following are the description of the deaths associated with the Afib studies. The numbers that I get differ from the numbers in the above table. Overall there were 7 (0.22 per patient year) deaths among those randomized to placebo and 15 among those treated with dronedarone 400 mg BID (0.23 per patient year). One placebo patient died from sudden death. There were four patients who were currently on dronedarone who died sudden deaths. The small number of events is neither alarming nor reassuring for the use of dronedarone in this population.

Table 11: Summary of death in the atrial fibrillation database (ADONIS, EURIDIS, ERATO and DAFNE):

Study	Pt ID/Age/gender	Description
Placebo		
xERATO	528005004/70 y-o Male	Infiltrate noted day 44, diagnosed as malignant neoplasm. Patient D/C'd drug on day 57 and died day 102.
xEURIDIS	528011008/77 y-o female	Never treated, died 11 months later.
ADONIS	124024042/72 y-o. male	Sudden death day 117.
ADONIS	124028001/84 y-o female	Had two non-Q-wave MIs, died day 254 of circulatory collapse
ADONIS	8400020008/72 y-o male	Day 73 had dyspnea and hemoptysis. Day 79 diagnosed with bacteremia. Died day 82.
xADONIS	840036006/63 y-o male	Day 140 heart failure worsened. Day 152 developed renal failure and became dialysis dependent. Medications D/C'd. Died 62 days later.
ADONIS	840040010/ 69 y-o Female	Hospitalized day 13 for chest pain (musculoskeletal). Day 15 had CVA. Died day 16.
Dronedarone		
xDAFNE	22050008/77 y-o male	Episode of trauma (ran over by tractor). Meds D/C'd. Died 4 weeks later.
ERATO	250004003/31 y-o female	Family history of early sudden death (father age 35, brother age 19). She was S/P surgery to correct ostium primum defect. Died day 8 from sudden death.
ERATO	528009007/75 y-o male	UTI day 163, medication D/C's day 169. Died day175.
xEURIDIS	528005001/85 y-o male	On day 282 had pacemaker implanted. Day 324 hospitalized for dyspnea. Died day 418 (94 days after drug D/C).
EURIDIS	528006007/77 y-o male	Died day 3 of sudden death.
EURIDIS	528011027/69 y-o male	Had MI day 310 (increased CPK and MB fraction). Lapsed into coma 2 days later and died.
ADONIS	32005005/ 79 y-o male	Hospitalized day 50 for fatigue and dyspnea (heart failure hx). V-fib on day 67 leading to death.
xADONIS	124011006/79 y-o male	History of CHF, CAD, HBP. Hospitalized day 3 for CHF. Hospitalized day 86 for AF. Med D/C and started on quinidine. Sudden death 8 weeks later.
ADONIS	124032005/77 y-o female	Had 2 episodes of pulmonary edema on days 60 and 89. On day 106 developed pulmonary edema and enterococcal septicemia. Died 12 days later.
ADONIS	710006002/83 y-o female	Sudden death on day 19. Baseline EF was 33%.
ADONIS	710006004/77 y-o female	Day 282 severe AF (associated with surgery to bunion). Day 299 chest pain with third degree A-V block. Developed cardiogenic shock and died.
xADONIS	84002004/86 y-o male	Day 132 diagnosed with metastatic liver and lung disease. Died day 224.
xADONIS	840004014/72 y-o female	Randomized but never received drug. Died from vertebral-basilar artery insufficiency (had events just prior to dosing).
xADONIS	84001006/64 y-o female	Had implantable defibrillator electively removed. Died 5 months post last dose of multiple myeloma.
ADONIS	840040011/48 y-o male	Obese, HBP, DM, had EF 27% at baseline. Died day 288 of sudden death.

X=unlikely to be related to study drug.

Deaths-ANDROMEDA:

The ANDROMEDA[6] study randomized 627 subjects (originally the study planned to enroll 1000 subjects) in a 1:1 ratio to either dronedarone 400 mg BID or placebo. The study was carried out in six Western European countries. It was prematurely discontinued seven months after randomization of the first patient due to an adverse mortality outcome in the dronedarone-treated patients.

The ANDROMEDA study enrolled subjects with symptomatic CHF (NYHA class II-IV), a wall motion index (WMI)[7] of $\leq$ 1.2 and requiring recent hospitalization and treatment with

[6] ANtiarrhythmic trial with DROnedarone in Moderate to severe CHF Evaluating morbidity DecreAse –EFC4966

[7] The wall motion index was determined by a central echocardiography laboratory after reading the baseline 2D-echocardiogram. The assessment averaged the segmental wall motion score over 16 segments. The individual scoring was as follows: Pronounced paradoxical motion (-1.0); slight paradoxical motion (-0.5); akinesia (0); pronounced hypokinesia (0.5); moderate hypokinesia (1.0); slight hypokinesia (1.5); normokinesis (2.0); slight hyperkinesia (2.5); pronounced hyperkinesia (3.0).

diuretics. The abnormal wall motion index reflects left ventricular dysfunction. According to the sponsor, multiplying the WMI by 30 approximates the EF. Notable exclusion criteria included recent myocardial infarction, recent decompensated heart failure (e.g., acute pulmonary edema, shock requiring pressors or acute MI), cardiomyopathy, or use of Vaughn-Williams Class I or III anti-arrhythmic agents.

There were 2402 patients screened, of which 650 were randomized and treated. The results of one center that enrolled 23 patients were excluded for poor quality control. Of the remaining 627 patients 317 were randomized to placebo and 310 to Dronedarone.

Selected baseline demographics are shown in Table 12.

Table 12: Demographics, cardiovascular history, cardiac status and selected concomitant medications in ANDORMEDA

Parameter	Placebo	Dronedarone
N=	317	310
Age, years (mean ± SD	69 ± 12	70 ± 12
Gender, Number male (%)	242 (76%)	230 (74%)
Race # non-Caucasian (%)	1 (<1%)	2 (1%)
Weight Mean ± SD, Kg	79 ± 19	78 ± 17
Cardiovascular history, selected, N=(%)		
Coronary heart disease	201 (63%)	266 (66%)
Valvular heart disease	175 (55%)	171 (55%)
Hypertension	107 (34%)	123 (40%)
Dilated cardiomyopathy	103 (33%)	79 (26%)
Diabetes mellitus	62 (20%)	73 (24%)
CABG	42 (13%)	57 (18%)
Severe ventricular arrhythmia	33 (10%)	33 (11%)
Stroke	31 (10%)	24 (8%)
Cardiac status		
Wall motion Index, mea ± SD	0.86 ± 0.23	0.90 ± 0.23
NYHA class (II/III/IV) (%/%/%)	118/186/13 (37%/59%/4%)	126/178/6 (41%/57%/3%)
Concomitant medications, selective, N (%)		
Diuretics	309 (98%)	297 (96%)
ACE-I/ARB	267 (84%)	274 (88%)
Chronic anti-platelet therapy	196 (62%)	203 (66%)
Oral anti-coagulants	102 (32%)	92 (28%)
Bet blockers (except sotalol)	191 (60%)	192 (62%)
Statins	97 (31%)	113 (57%)
Cardiac glycosides	101 (32%)	96 (31%)
Verapamil/diltiazem	12 (4%)	9 (3%)

In general, the two groups appear well matched at baseline. Those enrolled were largely male and nearly all Caucasian, most were NYHA class III failure. Given the underlying CHF, the fraction of patients using of diuretics and ACE-I/ARB are appropriate.

Although the primary endpoint of the study was composite of time to death or hospitalization for CHF, the DSMB recommended the discontinuation of the study because of an increase in the number of deaths in the placebo relative to the dronedarone-treated patients.

The relative risk for death and for the composite of death and hospitalization for adjudicated heart failure are shown below.

Figure 8 : Kaplan-Meier plots for death (left) and death or hospitalization for heart failure (right) in ANDROMEDA

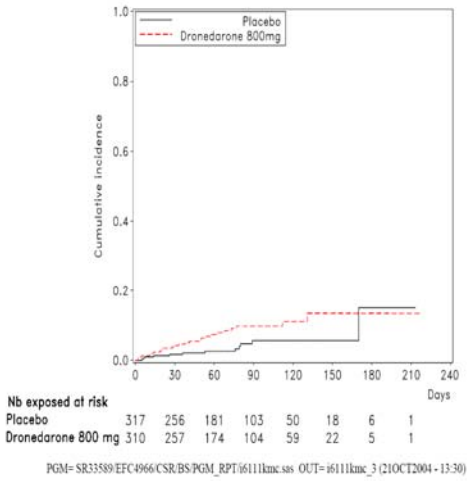


Figure (11.2.1) 1 - Kaplan-Meier cumulative incidence curves from randomization to death up to 16 January 2003- randomized and treated patients population excluding center 616004

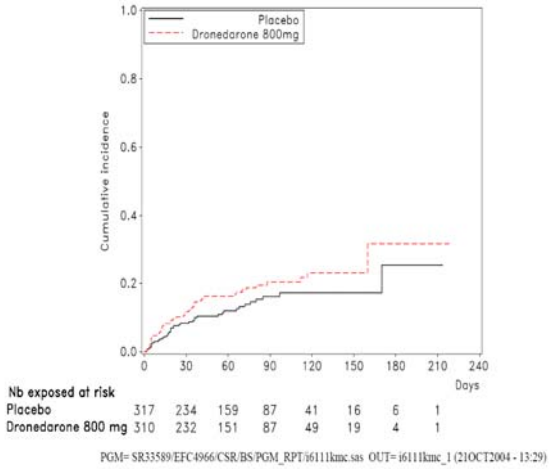


Figure (11.1.1) 1 - Kaplan-Meier cumulative incidence curves from randomization to death or hospitalization for worsening heart failure up to 16 January 2003- randomized and treated patients population excluding center 616004

Hazard ratios for several clinically meaningful measurements are shown Table 13. All Hazard ratios favor placebo. The upper CI for death extends beyond a factor of 4. The adjudicated cause of death is shown in Table14.

Table 13: Outcomes and statistical assessments for ANDROMEDA:

Parameter	Placebo N=317	Dronedarone N=310	Hazard ratio (95% CI	Log-rank p-value
Death	12	25	2.13 (1.1-4.2)	0.03
Died or hospitalized for worsening heart failure	40	53	1.38 (0.92-2.1)	0.12
Number hospitalized for worsening failure	31	39	Not calculated	0.27
Number hospitalized for cardiovascular reasons	50	71	Not calculated	0.02

Table 14: Adjudicated causes of death are shown below and (fraction of population) [fraction of deaths] ANDROMEDA:

	Placebo (N= 317)	Dronedarone (N=310)
Number of Events	12	25
Cardiovascular death	9 (3%) [75%]	24 (8%)[96%]
MI	2 (1%) [17%]	0
Worsening CHF	2 (1%)[17%]	10 (3%) [40%]
Documented arrhythmia	2 (1%) [17%]	6 (2%) [24%]
Procedure related	0	1 (<1%) [4%]
Other CV reason	0	2 (1%) [8%]
Presumed CV reason	3 (1%) [25%]	5 (2%) [20%]
Non-cardiovascular	2 (1%)[17%]	1 (< 1%) [4%]
Cancer	1 (< 15) [8%]	1 (< 1%) [4%]
Other	1 (<1%) [8%]	0
Non-adjudicated death	1 (<1%)[8%]	0

There was an increase in predominantly worsening heart failure deaths, but arrhythmia events were also increased.

The sponsor postulated that the increase in deaths in the dronedarone group in the ANDROMEDA study is a consequence of dronedarone's ability to inhibit creatinine secretion into the urine (see later). The sponsor further postulated that the patients with elevated creatinine would be more likely to have their ACE-I /ARB medication discontinued, losing the benefit of these treatments and predisposing to a negative mortality and hospitalization outcome.

The above postulated mechanism would suggest the following sequence of events. First, the subject would have an asymptomatic creatinine elevation, leading to the discontinuation of the ACE-I/ARB and only then would the patient be at risk for cardiac decompensation or death.

Although it is true that many dronedarone patients discontinued the ACE-I/ARB treatment than did placebo patients. Among those who died, there were few subjects whose creatinine increases was unrelated to either a cardiac or renal insult.

Discontinuations atrial fibrillation:

Table 15 contains a listing of Meddra terms applied to the discontinuations among those in the atrial fibrillation database. There did not appear to be substantial difference in comparing the placebo to dronedarone treatments. All 7 subjects who discontinued due to renal and urinary tract investigations were in the dronedarone treated group, consistent with the ability of dronedarone to alter creatinine measurements.

Table 15: Meddra terms for those discontinuing, limited to those > 5 events in the dronedarone 400 mg BID group in the atrial fibrillation database.

Meddra Term	Placebo	Dronedarone		
		400 mg BID	600mg BID	800 mg BID
Number exposed	564	989	66	62
Any event leading to discontinuation	34 (6%)	96 (10%)	4 (6%)	14 (23%)
Gastrointestinal (GI) Disorder	7 (1%)	16 (2%)	1 (1%)	7 (11%)
GI signs and symptoms	4 (1%)	7 (1%)	1 (1%)	3 (5%)
GI motility and defecation conditions	3 (1%)	4 (< 1%)	0	4 (7%)
Investigations	1 (<1%)	18 (2%)	0	2 (3%)
Renal and urinary tract investigations or urinalyses	0	7 (1%)	0	0
Hepatobiliary investigations	1 (< 1%)	5 (1%)	0	0
Cardiac disorders	10 (2%)	14 (1%)	2 (3%)	1 (2%)
Cardiac arrhythmias	4 (1%)	12 (1%)	1 (1%)	0
Nervous system disorders	6 (1%)	14 (1%)	0	1 (2%)
Neurological disorders	3 (1%)	9 (1%)	0	1(2%)
Skin and subcutaneous tissue disorders	3 (1%)	13 (1%)	0	1 (2%)
Epidermal and dermal conditions	2 (< 1%)	12 (1%)	0	1 (2%)
General disorders and administrative site conditions	2 (< 1%)	12 (1%)	1 (2%)	1 (2%)
General system disorders	1 (< 1%)	7 (1%)	1 (2%)	1 (2%)
Respiratory, thoracic and mediastinal disorders	2 (< 1%)	6 (1%)	0	0
Eye disorder	2 (< 1%)	5 (1%)	0	0

Overall adverse events atrial fibrillation:

Overall adverse events are shown below for any event limited to Meddra terms that contain more than 10 patients who were treated with the dronedarone 400 mg BID group. The bolded listings are those that appear more frequent in the dronedarone group and may be related to treatment.

Table 16: Meddra terms for overall adverse events in the atrial fibrillation database limited to major events:

Meddra Term	Placebo	Dronedarone		
		400 mg BID	600mg BID	800 mg BID
Number exposed	564	989	66	62
Any event leading to discontinuation	340 (60%)	660 (67%)	42 (64%)	45 (72%)
Gastrointestinal (GI) Disorder	**90 (16%)**	**188 (19%)**	**13 20%)**	**22 (36%)**
GI signs and symptoms	56 (10%)	112 (11%)	9 (14%)	9 (15%)
GI motility and defecation conditions	**37 (7%)**	**79 (8%)**	**5 (8%)**	**18 (29%)**
GI hemorrhage nec	2 (1%)	13 (1%)	1 (2%)	0
Infection and Infestations	**95 (17%)**	**194 (20%)**	**7 (11%)**	**7 (11%)**
Infections-pathogen class unspecified	**70 (12%)**	**155 (16%)**	**5 (8%)**	**5 (8%)**
Viral infectious disorder	24 (4%)	45 (5%)	1 (2%)	2 (3%)
Nervous system disorders	81 (14%)	144 (15%)	4 (6%)	6 (10%)
Neurological disorders	32 (6%)	77 (8%)	2 (3%)	4 (7%)
Headaches	40 (7%)	54 (6%)	2 (3%)	3 (5%)
Movement disorders (inc parkinsonism)	2 (< 1%)	10 (1%)	0	0
Investigations	**49 (9%)**	**133 (13%)**	**10 (15%)**	**8 (13%)**
Hepatobiliary investigations	13 (2%)	34 (3%)	3 (5%)	2 (3%)
Renal and urinary tract investigations or urinalyses	**3 (1%)**	**31 (3%)**	**2 (3%)**	**3 (5%)**
Enzyme investigations (nec)	5 (1%)	17 (2%)	0	0
Cardiac and vascular investigations (excl enzyme tests)	8 (1%)	11 (1%)	2 (3%)	2 (3%)
Physical examination topics	5 (1%)	12 (1%)	1 (2%)	1 (2%)
Hematology investigations	3 (1%)	13 (1%)	0	0
Endocrine investigations	5 (1%)	11 (1%)	1 (2%)	0
Cardiac disorders	**62 (11%)**	**123 (12%)**	**12 (18%)**	**13 (21%)**
Cardiac arrhythmias	26 (5%)	56 (6%)	3 (5%)	10 (16%)
Coronary artery disorders	21 (4%)	31 (3%)	0	1 (2%)
Heart failures	6 (1%)	24 (2%)	6 (9%)	2 (3%)
Cardiac disorders signs and symptoms	6 (1%)	11 (1%)	4 (6%)	3 (5%)
General disorders and administrative site conditions	60 (11%)	130 (12%)	6 (9%)	6 (10%)
General system disorders	**51 (9%)**	**115 (12%)**	**6 (9%)**	**5 (8%)**
Musculoskeletal and connective tissue disorders	61 (11%)	126 (13%)	2 (3%)	3 (5%)
Musculoskeletal and connective tissue disorders (nec)	**22 (4%)**	**61 (6%)**	**1 (2%)**	**1 (2%)**
Joint disorders	20 (4%)	52 (5%)	1 (2%)	2 (3%)
Muscle disorders	17 (3%)	28 (3%)	0	0
Respiratory, thoracic and mediastinal disorders	**58 (10%)**	**117 (12%)**	**2 (3%)**	**9 (15%)**
Respiratory disorders nec	37 (7%)	76 (8%)	1 (2%)	6 (10%)
Upper respiratory disorders (excl infections)	10 (2%)	21 (2%)	0	1 (2%)
Bronchial disorders (excl neoplasm)	7 (1%)	14 (1%)	1 (2%)	0
Lower respiratory tract disorders (excl obstruction and infect)	9 (2%)	13 (1%)	0	1 (2%)
Skin and subcutaneous tissue disorders	**36 (6%)**	**94 (10%)**	**4 (6%)**	**6 (10%)**
Epidermal and dermal conditions	**23 (4%)**	**73 (7%)**	**2 (3%)**	**3 (5%)**
Skin appendage conditions	10 (2%)	12 (1%)	1 (2%)	3 (5%)
Vascular disorders	35 (6%)	62 (6%)	1 (2%)	3 (5%)
Vascular hypertensive disorders	14 (3%)	25 (3%)	1 (2%)	1 (2%)
Increased and non-specific blood pressure	9 (2%)	14 (1%)	0	1 (2%)
Injury, poisoning and procedural complications	29 (5%)	57 (6%)	1 (2%)	2 (3%)
Injuries nec	23 (4%)	29 (3%)	1 (2%)	2 (3%)
Bone and joint injuries	4(1%)	10 (1%)	0	0
Psychiatric disorders	16 (3%)	52 (5%)	2 (3%)	1 (2%)

Sleep disorders and disturbances	9 (2%)	17 (2%)	1 (2%)	1 (2%)
Anxiety disorders and symptoms	4 (1%)	16 (2%)	1 (2%)	0
Depressed mood disorders and disturbances	2 (< 1%)	11 (1%)	0	0
Eye disorder	15 (3%)	29 (3%)	2 (3%)	2 (3%)
Vision disorders	6 (1%)	10 (1%)	1 (2%)	0
Metabolism and nutrition disorders	29 (5%)	28 (35)	3 (5%)	1 (2%)
Renal and urinary disorders	15 (3%)	26 (3%)	1 (2%)	0
Urinary tract signs and symptoms	13 (2%)	19 (2%)	0	0
Reproductive system and breast disorders	11 (2%)	24 (2%)	1 (2%)	1 (2%)
Ear and labyrinth disorders	5 (1%)	20 (2%)	3 (5%)	2 (3%)
Inner ear and 8th nerve cranial disorders	4 (1%)	16 (2%)	3 (5%)	2 (3%)
Neoplasms benign, malignant and unspecified	11 (2%)	22 (2%)	0	0
Endocrine disorders	9 (2%)	13 (1%)	0	1 (2%)
Thyroid gland disorders	9 (2%)	13 (1%)	0	1 (2%)
Blood and lymphatic system	**0**	**14 (1%)**	**0**	**0**

Thyroid:

Thyroid function measurements were measured frequently during the first month of treatment and every 1-3 months in the DAFNE, ADONIS and EURIDIS studies. Thyroid measurements were apparently not performed during the ERATO study.

There did not appear to be a strong signal in the shift-table that dronedarone provokes hypothyroidism (no increase in TSH) or hyperthyroidism (no increase in FT3).

Table 17: Thyroid measurements as shift table DAFNE, EURIDIS and ADONIS:

	FT3		FT4		TSH	
	increase	decreases	increase	decreases	increase	decreases
Dronedarone 400 mg BID	50/856 (5.8%)	15/856 (1.8%)	5/857 (0.6%)	7/857 (0.8%)	30/857 (3.5%)	28/857 (3.3%)
Placebo	38/439 (8.7%)	2/439 (0.5%)	9/439 (2.1%)	1/439 (0.2%)	16/439 (3.6%)	34/439 (7.7%)

Pulmonary toxicity

One subject # 348001007, a 72 year-old male enrolled in the EURIDIS study, had an adverse event of mild pulmonary fibrosis that led to discontinuation after 6 months of treatment. Baseline laboratory measurements including chest X-ray were listed as normal. Dr. C. Katalin head, radiology department Karolyi hospital, read side-by side, the baseline and end of treatment X-rays, and he concluded that the pulmonary fibrosis was present at the initial, baseline evaluation. The subject, however, did not have PFTs or a lung biopsy either at baseline or at the time of discontinuation, so that one can't definitively be sure that pulmonary fibrosis was present at baseline and if so, that it did not worsen during treatment.

There was an increase in events that might reflect early fibrosis. There were more adverse events listed as dyspnea and cough with dronedarone than with placebo. Whether these events are sentinel symptoms to early fibrosis or they reflect early heart failure (as an Ib sodium channel blocker, dronedarone is likely a negative inotrope) is unclear.

Mean duration of exposure to dronedarone is modest. Although there appears to be a reasonable numbers of subjects exposed for > 360 days, pulmonary fibrosis may take longer to become overt.

Renal clearance:

Dronedarone at a dose of 400 mg BID compared to placebo had a decrease in creatinine clearance of approximately 18%, with minimal differences in sinistrin (a non-cation substrate used to measure clearance). Dronedarone also inhibited clearance of N^1-methylnicotinamide (NMN) a substrate of the tubular organic cation transporter. Suggesting that the effect of dronedarone is on transport of cations and therefore could increase creatinine levels in the absence of a deleterious effect on renal function. There did not appear to any effect on renal blood flow (PAH clearance) or urinary 24-hour electrolyte excretion.

DMETS comments:

DMETS comments reflect concerns for labeling and the package insert. These issues will be revisited should an approval recommendation be made.

Biopharmaceutic comments:

Comments to Sponsor

- Please indicate when results from the hepatic impairment study, POP5820, will be submitted to the Agency. Without this information, the product labeling will be restrictive in this patient population
- You have not adequately addressed the issue of dose-response in the target population; therefore dosage adjustment is not feasible during dronedarone therapy.
- You have not provided sufficient permeability information to support dronedarone designation as BCS 2. Please provide all available information that demonstrate dronedarone is a high permeability compound.
- The dissolution methodology is acceptable, however, we do not agree with your dissolution specification. Based on the data provided the following specification is more appropriate: 1) Not less than 25 % and not more than 50 % is dissolved within 30 minutes 2) Q = 80 at 90 minutes
- In future submissions, any concentrations and/or subjects that have been excluded from the analysis should be maintained in the datasets. For this analysis, the sponsor identified 123 concentrations (from 10 subjects) as outliers and excluded these observations from the dataset.
- Please refer to the attached, revised label for detailed labeling recomendations

Chemistry comments:

IV. List Of Comments

A. Regarding the Drug Substance

1. Please add a particle size specification of D(0.9) and submit appropriate data.

B. Regarding the Drug Product

1. Please provide a labeled chromatogram from the ID / assay test via liquid chromatography (LC), which is actually a reverse-phase (RP) – HPLC based method.

2. Please restate the all assay specifications and test results as a percentage plus/minus a specific range.

3. Please remove the 'hydrochloride' from the label, package insert and carton(s). By convention, salts are not included in the established name.

   In addition Multaq® is expressed as the free base; that is, the drug contains 426 mg of dronedarone hydrochloride which corresponds to 400 mg dronedarone base. Hence inclusion of the term 'hydrochloride' is unnecessary.

4. The analytical method for uniformity of mass is Ph. Eur. 2.9.5. Please convert the test method to a USP/NF method.

5. Please submit the following information concerning the dissolution studies:

   a. All relevant dissolution data at 60 minutes for both the clinical and stability batches for the *film-coated tablet*.

   b. As in a) above, but for the *tablet core(s)*. (Note: The submission contains only disintegration data).

Medical officer comments:

1. The ongoing trial EFC5555 must show both efficacy and safety.
2. Other doses in the range of 50 mg to 800 mg should be investigated.

Additional comments:

1. Please submit an hour-by hour assessment of heart rate during the ERATO study to assess that the heart rate effects persist during the interdosing interval.
2. Please submit the CRFs for those who had asymptomatic elevated levels of creatinine during the ANDROMEDA study.

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/s/

Abraham Karkowsky
2/19/2009 01:09:07 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	N021913
Submission Code	N000
Letter Date	June 10, 2005
Stamp Date	June 10, 2005
PDUFA Goal Date	April 10, 2006
Reviewer Name	Gail Moreschi, M.D., M.P.H. Valeria Freidlin, Ph.D.
Review Completion Date	March 29, 2006
Established Name	Dronedarone hydrochloride
(Proposed) Trade Name	Multac
Therapeutic Class	Antiarrhythmic drug
Applicant	Sanofi-Aventis
Priority Designation	S
Formulation	Tablets
Dosing Regimen	400 mg twice a day
Indication	Rhythm and/or rate control
Intended Population	Atrial fibrillation/flutter

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1 EXECUTIVE SUMMARY

This NDA pertains to an important chronic medical problem, atrial fibrillation and/or flutter (AF/AFL). The incidence has been shown to increase with age and, therefore, as the population ages there will be an increase in the incidence of AF/AFL.

In the clinical submission of this NDA, the Sponsor has included five studies for efficacy. They are seeking two indications at this time: patients will remain longer in normal sinus rhythm on dronedarone compared to patients on placebo and if AF/AFL reoccurs while patients are on dronedarone their ventricular rate will be slower.

The DAFNE study was utilized by the Sponsor to determine the dose. Although the Agency as early as 1999 advised the Sponsor to provide a dosing range rather than a fixed dose, the Sponsor choose not to heed this advice. In the DAFNE study doses greater than 400 mg twice a day (BID) did not appear as efficacious as the 400 mg B.I.D. dose. Although the Sponsor was advised to study lower doses they failed to do this.

The ERATO trial evaluated ventricular rate control. In this study and in the Sponsor's two pivotal studies, the ADONIS and EURIDIS, the rate is not improved to the clinically acceptable range of 60 to 80 bpm at rest and 90 to 115 bpm with exercise. In the ERATO study, the patients on dronedarone showed no improvement over placebo in an exercise test.

In the pivotal ADONIS and ERUIDIS studies, the primary endpoint was surrogate markers for AF/AFL. The patients, when they had symptoms, used a transtelephonic device to transmit their ECG. The Sponsor did demonstrate in these two studies that patients taking dronedarone remain longer in normal sinus rhythm compared to placebo. However, their ventricular rate is not lowered in these studies to a clinically acceptable range should they revert to AF/AFL. The population chosen for these studies was relatively young and in good health.

In the reviewers' opinion, the critical study is the ANDROMEDA study which investigated patients with a previous episode of "severe" congestive heart failure (CHF). This study had clinical endpoints, death and hospitalizations, and not surrogate markers as in the other pivotal studies. The ANDROMEDA study revealed that dronedarone statistically significantly ($p = 0.027$) increased the risk of death from any cause (in fact, it more than doubled this risk, by 113%) and also increased ($p = 0.024$) the risk of hospitalizations for acute cardiovascular reasons as compared to placebo.

Although the Sponsor has another large ongoing trial in patients who are 70 or older with AF/AFL, these reviewers must recommend that this NDA is NOT APPROVABLE because of the increase in mortality. Finally, in evaluating the risk/benefit ratio, there is very little benefit to be gained from this drug which has been shown to statistically significantly increase the risk of death in older, sicker patients.

1.1 Recommendation on Regulatory Action

NOT APPROVABLE

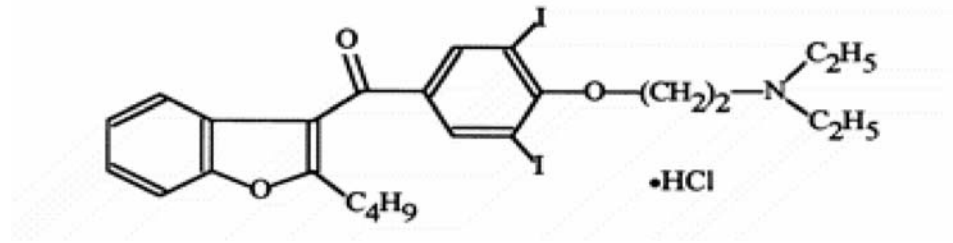
2 INTRODUCTION AND BACKGROUND

2.1 Product Information

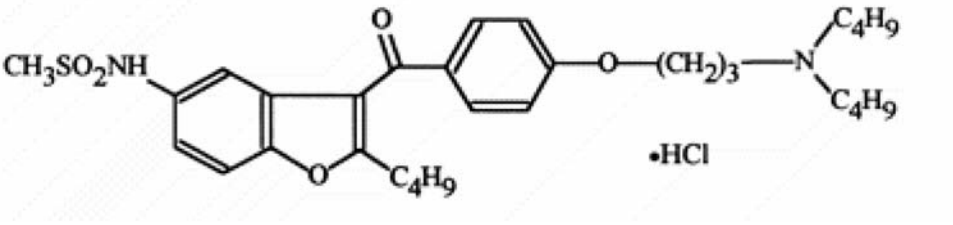
Dronedarone (SR33589B) is a new anti-arrhythmic agent belonging to the benzofurane class of anti-arrhythmic compounds that also includes amiodarone. Dronedarone has been developed by the Sponsor, Sanofi-Aventis, for the treatment of atrial fibrillation (AF) and atrial flutter (AFL).

There are 2 main physical-chemical differences that distinguish dronedarone from amiodarone: 1. the absence of iodine substituents on the benzofurane ring that was expected to eliminate thyroid side effects, and 2. the adjunction of a methane-sulfonamyl group that was expected to make the drug less lipophilic and therefore less subject to tissue accumulation (a probable mechanism of amiodarone organ toxicity).

The chemical structure of dronedarone in comparison to that of amiodarone is shown below.



Amiodarone (MW = 682)



SR33589B/Dronedarone (MW = 593)

(page 7 Module 2.5)

Figure 1 - Chemical structure of dronedarone compared to that of amiodarone

Like amiodarone, dronedarone demonstrates electrophysiological characteristics belonging to all 4 Vaughan-Williams classes of anti-arrhythmic compounds.

2.2 Currently Available Treatment for Indications

Atrial fibrillation (AF) is the most common tachyarrhythmia. AF maybe related to arterial hypertension, ischemic heart disease, heart failure, or mitral value disease. The incidence increases with age. Since more patients are living longer, the incidence is increasing. Treatment possibilities may include catheter ablation, cardiac surgery, an implantable pacemaker, or pharmacotherapy.

The main pharmacological therapeutic strategies include rate control, termination of the arrhythmia, and the prevention of thromboembolic events. In the choice of an antiarrhythmic drug both safety and efficacy are important considerations. There are two competing clinical strategies for atrial fibrillation: maintenance of sinus rhythm versus rate control. Both methods have advantages and disadvantages. Drugs that are currently used for the management of patients with AF/AFL are shown in the table below.

	Rhythm control	Rate control
Anti-arrhythmic		
Class Ia	Disopyramide Procainamide Quinidine	-- -- --
Class Ic	Flecainide Propafenone	-- --
Class II	--	betablockers (eg metoprolol, carvedilol)
Pure Class III	Dofetilide Ibutilide	-- --
Class IV	-- --	diltiazem verapamil
Multifactorial	Sotalol Amiodarone	sotalol amiodarone
Digitalis	-- --	digoxin digitoxin

(page 12 module 2.5)

Table 1 – Drugs currently used for patients with AF /AFL

2.3 Availability of Proposed Active Ingredient in the United States

Dronedarone is a new molecular entity and is not currently available in the United States. Currently it is not marketed in any country.

2.4 Important Issues With Pharmacologically Related Products

Amiodarone, originally marketed as an antianginal agent because of its coronary vasodilator properties, was observed to have potent antiarrhythmic effects. It was approved in 1985 for ventricular arrhythmias. Although not FDA approved for AF/AFL, it is clinically utilized for this indication and appears safe for patients with CHF. However, in some patients amiodarone has significant adverse reactions which include pulmonary toxicity, thyroid dysfunction and phototoxicity.

2.5 Presubmission Regulatory Activity

Several meetings were held between the original Sponsor, Sanofi Pharmaceuticals, Inc, and the FDA's Division of Cardio-Renal Drug Products.

May 27, 1999, an End of Phase I Meeting was held to discuss the development program. The Sponsor stated that in the initial phase they would focus on an indication for atrial arrhythmias. Later they plan to conduct trials for ventricular arrhythmias. At this meeting the Division recommended that a dosing regimen based on a titration scheme rather than a selection of "the dose" should be considered. Additionally, the Sponsor was to provide any effect on QT prolongation, pulmonary toxicity, thyroid dysfunction, and phototoxicity. Also, the endpoint, pharmacokinetics, drug interactions, and the enrollment of paroxysmal and/or chronic AF patients were discussed.

April 9, 2001, an End-of-Phase 2 Meeting was held with the Division. The Sponsor was seeking feedback on the design of three proposed Phase 3 studies. At this meeting the Agency noted that the risk/benefit ratio of dronedarone was an issue since the desired indication was not an improvement in morbidity or mortality. Since the dose response was not completely characterized, the Agency suggested that the Sponsor study doses below and above 800 mg to find the optimal dose. The Division Director encouraged them to study patients with chronic AF. The Sponsor was informed that for approval the Agency would require either a mortality trial in high-risk patients including AF/AFL patients with no restrictions on concomitant medications, or a DIAMOND-type of study. This meeting was clarified further by phone and mail.

July 13, 2004, a Pre-NDA meeting was held with the Division to discuss the ANDROMEDA results. This was a long term morbidity/mortality trial in CHF patients which was stopped early due to an adverse mortality effect in the dronedarone treated patients. The Sponsor described the positive findings of the ERUIDIS and ADONIS studies. Dr. Temple stated that the overall effectiveness of dronedarone is lower than three other treatments. The Sponsor theorized that in the ANDROMEDA trial more dronedarone patients had their ACE inhibitors discontinued. Dr. Temple noted that an alternative hypothesis is that dronedarone has an adverse effect in CHF patients that is potentially corrected with ACE inhibitors. Dr. Temple advised the Sponsor that the Agency must be assured that dronedarone will not lead to adverse mortality in CHF patients. The Sponsor requested that this trial be done post-marketing. Dr. Temple stated that as there was no obvious survival benefit to rhythm control, the Agency would probably not agree to the

additional trial as a post-marketing commitment. The Sponsor asked if the application could be filed with no additional trials and Dr. Temple said this would be likely.

An additional Pre-NDA meeting was held January 3, 2005, between the Sponsor and the Division to discuss a new protocol evaluating the efficacy of dronedarone for the prevention of cardiovascular hospitalization or death in patients with AF/AFL. Dr. Temple asked the Sponsor if they were sure they have selected the correct dose. The Sponsor stated that the 400 mg BID was the only effective dose in their dose-ranging trial. Dr. Temple stated that the sample size in the new study should be based on the total number of events to be sure that the trial is adequately powered. Also, he stated that because dronedarone is not intended as a life-saving treatment, the Agency must be assured that it does not lead to increased mortality. The Sponsor asked if there was any chance of approval prior to the completion of the trial. Dr Temple said that approval without the final results was very improbable.

2.6 Other Relevant Background Information

The Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) in France and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom are awaiting the results of EFC5555 before granting approval.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

3.2 Animal Pharmacology/Toxicology

The following is from Dr. Elizabeth Hausner's Review.

"A. Brief overview of nonclinical findings: Proposed for atrial arrhythmia, dronedarone is an amiodarone analogue lacking the iodine substituents. In in vitro systems, isolated organ culture and whole animal studies have been used to compare this agent to amiodarone. There are many similarities between the effects of the two agents on the ion channels of the heart and the behavior in various non-clinical models of cardiac function that are intended to show anti-arrhythmic potential.

The drug has relatively low oral bioavailability of in the dog 14 % and rat 22%. The volume of distribution is large, from 12 to 66 l/kg with a moderately high systemic clearance of 2-4 l/h/kg. In all species studied, including human, dronedarone was highly protein bound (>99%). Dronedarone is also highly metabolized with one known active metabolite (SR35021).

In addition to the usual toxicological characterization, dronedarone has also been assessed for immunotoxicologic potential (no significant issues apparent at this time), effect upon thyroid function (incompletely described) and dyslipidosis (occurs to a lesser extent than seen with amiodarone). Mild respiratory effects (decreased respiratory rate and tidal volume) were seen in the single dose respiratory safety pharmacology study. Phototoxicity (mild to moderate at the equivalent of 2X MRHD) has been demonstrated in albino animals. Dronedarone has been demonstrated to bind to melanin. How this will affect phototoxicity is unknown. The sponsor has provided no characterization of the mechanism of the carcinogenic findings or the endocrine effects.

Some aspects of the non-clinical toxicology are puzzling. There are a number of instances where effects do not seem to follow a dose-response. It also appears that there is a lessening or abrogation of effects with extended dosing. That is, effects apparent after 1 month or 3 months of dosing are not evident after 6 months. Yet, plasma levels are no less at 6 months than they were at 3 months.

The sponsor is to be commended on the thoroughness of some aspects of the nonclinical characterization. That is, because of the similarity to amiodarone, immunotoxicity and phototoxicity studies were conducted and comparator compounds (positive controls) appear frequently. An outside review panel was assembled to provide a second opinion on the carcinogenicity studies. Yet the reporting does not do justice to these efforts. For example:
1) There were inconsistencies between the CTD non-clinical summary and the actual study reports.
2) There were inconsistencies within reports where textual numbers were not precisely the same numbers from the summary tables or single animal data
3) There were instances where findings were mentioned within the text of a report for which I could not find tables of numerical summaries.
4) The quality of the Carcinogenicity report by the outside review panel was disappointing at best."

"B. Pharmacologic activity: Dronedarone has been shown to have properties of beta adrenergic blockade, and cardiac Na, K and Ca channel modulation. However, there is inadequate characterization of the receptor binding properties of both dronedarone and the two major metabolites SR35021 and SR90154. In particular, the possibility of interaction with the thyroid receptor, hormonal receptors and steroidal receptors should be investigated.

C. Nonclinical safety issues relevant to clinical use: Dronedarone has been shown to be teratogenic, genotoxic, carcinogenic and to disrupt female cyclicity. The target organs of toxicity appear to be the kidney, liver, and gastrointestinal tract. Renal changes were usually without histological correlates and manifested primarily as changes in serum creatinine and serum electrolytes, excreted creatinine and electrolytes. Mild to moderate phototoxicity has been shown non-clinically in rats at a dose of 200 mg/kg (1200 mg/m2 or 2.5x MRHD based on a surface area comparison). Dronedarone does affect thyroid metabolism but this is incompletely defined. Hepatic effects range from elevations in ALT and AST to necrotic foci, possibly too small to cause perceptible changes in liver status tests. Safety pharmacology showed that dronedarone

caused decreases in respiratory rate and tidal volume. Dyslipidosis manifested as foamy macrophages occurs but apparently to a lesser extent than seen with amiodarone.

A radiolabel distribution/excretion study showed that the mean concentration of total radioactivity in the heart, liver and lungs was approximately 13, 5 and 20 times higher respectively at 4 hours post-dose on day 14 compared to 24 hours post dose on day 1. This is indicative of tissue accumulation. Comparing 4-hours post-dose at the earliest steady state vs. 4-hour post-dose several weeks later would more clearly address this potential issue.

Cardiac effects are also noted in rats, dogs and macaques. These include such things as decreased heart rate, increased PR interval and increased QT interval. QTc was as decreased heart rate, increased PR interval and increased QT interval. QTc was inconsistently increased, possibly due to the fact that Bazett's formula was uniformly used no matter what the heart rate of the animals. First degree block was reported in rats, dogs and monkeys. Second degree block was also reported in macaques. Increased T wave amplitude was also noted in some studies. Many of the changes can be viewed as extensions of the expected pharmacology. Both dronedarone and the active metabolite SR35021 inhibit the hERG channel with almost the same potency as cisapride, the positive control for the studies."

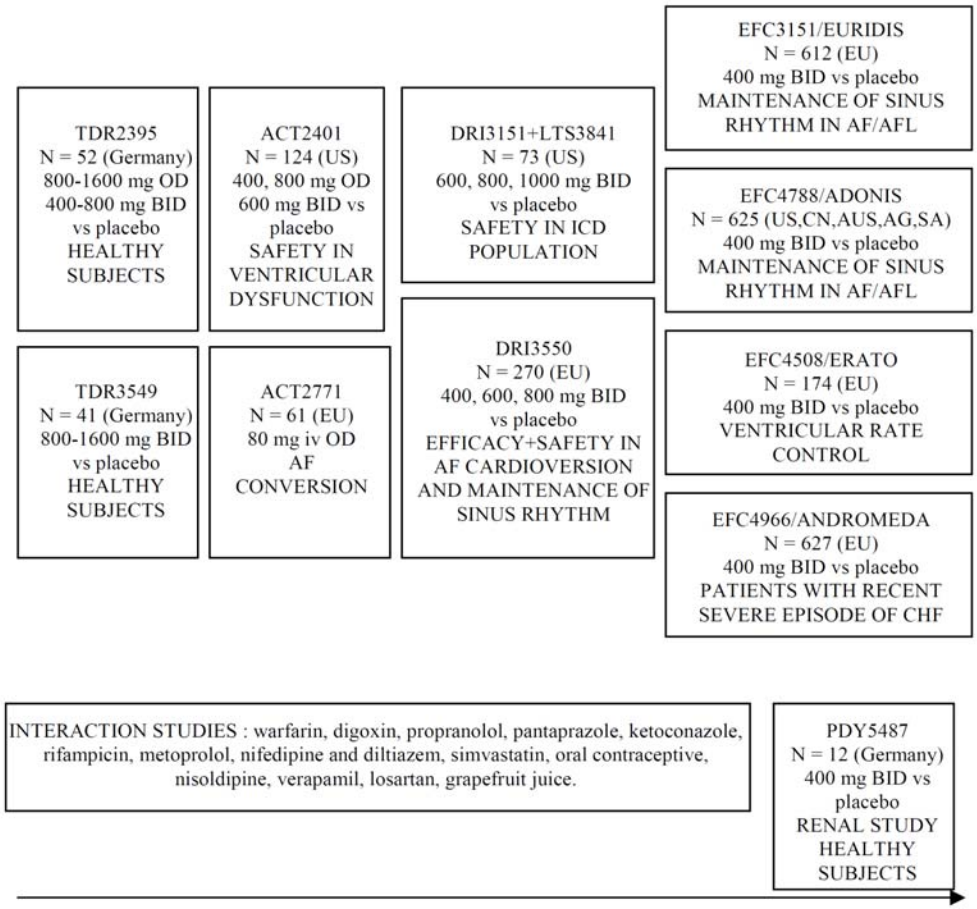
4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical studies were all submitted electronically and reviewed.

4.2 Tables of Clinical Studies

An overview of the clinical program is shown in the following figure.



EU: Europe, US: United States, CN: Canada, AUS: Australia, AG: Argentina, SA: South Africa.
(page 15 module 2.5)

Figure 2 - Clinical development program of dronedarone

4.3 Review Strategy

Drs. Moreschi and Freidlin completed the Efficacy Review together. Dr. Freidlin advised Dr. Moreschi on the Safety Review.

4.4 Data Quality and Integrity

DSI visited Corelab, France. No irregularities were found.

4.5 Compliance with Good Clinical Practices

It appears that all studies were done in compliance with Good Clinical Practices.

4.6 Financial Disclosures

Dr. Jeremy N. Ruskin, a subinvestigator who participated in Study EFC4788, has received honoraria for consultation for another Sanofi-Synthelabo compound. Sanofi-Synthelabo does not believe any bias, intentional or unintentional, was introduced by this significant payment of other sorts.

5 CLINICAL PHARMACOLOGY

This section is from Dr. Robert O. Kumi's Review

5.1 Pharmacokinetics

"1. Dronedarone Pharmacokinetics (ADME)
Absorption/absolute bioavailability and general pharmacokinetics (PK)
• Dronedarone ***absolute oral bioavailability*** (BA) following administration of a capsule formulation (800 mg) is approximately 15 %, but this value may not be reflective of the absolute oral BA of the to be marketed tablet formulation (proposed 400 mg dose) due to differing food effect (formulation dependent) and dose-dependent pharmacokinetics oral administration
• Administration of ***food*** increases mean dronedarone absorption from approximately 2- (low fat meal) to 5-fold (high fat meal)
• Dronedarone exposure increased in a ***greater than dose proportional manner*** following single and multiple dose administration. For a two-fold increase in dose, the exposure increased by 2.5 to 3.5-fold over the 200 to 1600 dose range
• ***Steady state*** is achieved approximately seven days after repeated administration of 400 mg dronedarone twice daily
• The mean accumulation ratio is ~ 2.6 at the proposed dosage
• Dronedarone exhibits dose- and time-dependent PK
• Dronedarone has limited properties associated with PGP substrate status

Distribution
• Dronedarone is approximately 99 % bound to plasma proteins at therapeutic drug concentrations; the main binding component is albumin
• Following single dose administration of IV dronedarone (40 – 80 mg), the volume of distribution associated with the terminal elimination phase was 2500 – 3400 L

Metabolism and P-glycoprotein
In vitro information
• Dronedarone metabolism was mainly mediated by CYP3A, yielding the major metabolite, SR35021
• Dronedarone has a low inhibitory potential towards major CYPs), including on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. The most inhibitory potential was towards CYP3A4 (I/Ki ~ 0.01) and CYP2D6 (I/Ki ~0.06)

• Dronedarone exhibited similar PGP inhibitory potential as cyclosporine A by preventing the efflux of two PGP substrates, digoxin and vincristine

In vivo information
Dronedarone is extensively metabolized following dronedarone administration and negligible amounts of intact dronedarone are present in the feces. N-debutylation appears to be the main metabolic pathway of dronedarone, leading to the formation of SR35021; however additional processes occur including oxidation of SR35021, oxidative deamination, and direct oxidation. Ultimately, several metabolites (> 30) are formed and excreted in the urine and feces. SR35021 is not detected following IV administration, suggesting that it is formed mainly presystemically during first pass.

Properties of metabolites
The activities of all the identified metabolites (n > 30) were not tested; however, the major metabolite, SR35021 is 3 to 10 times less potent than dronedarone. SR35021 plasma levels are approximately half that of dronedarone; other individual metabolites account for < 3 % of the administered dronedarone dose. Based on the low exposure of the metabolites, they are unlikely to impact overall activity associated with dronedarone administration, unless they are individually or collectively more potent than dronedarone.

Overall, SR35021 exhibited PK properties (accumulation, half-life, volume of distribution) that were similar to that of dronedarone.

<u>Excretion (Elimination)</u>
• Mass balance indicates that orally administered dronedarone is ultimately excreted in the urine (6 %) and feces (84 %) primarily as metabolites. No unchanged dronedarone was excreted in the urine. Similar findings were obtained following IV administration. Radioactivity was undetectable after two weeks.
• The systemic plasma clearance (IV administration) ranged from 130 to 150 L/h and the apparent oral clearance (CL/F) was ~ 500 L/h for the 400 mg dose.
• Dronedarone half-life following IV administration was between 13 and 19 hours; following oral administration half-life appeared to be dose- and time- dependent ranging from 27 to 32 hours."

5.2 Pharmacodynamics

"Pharmacodynamic effects of dronedarone
• Alters electrophysiological measures: generally increases QT-, PR- and RR- and QRS-intervals and decreases T-wave amplitude
• Decreases heart rate (bradycardic effect)
• Tends to decrease blood pressure (systolic and diastolic)
• Causes an increase in serum creatinine levels by inhibiting renal tubular secretion of creatinine; which leads to apparent decrease in renal function (CLcr decreased). However, this effect is reversible upon discontinuation of dronedarone therapy."

5.3 Exposure-Response Relationships

"QT/QTc Information
A clear dose-response relationship was shown for QT prolongation in healthy subjects.

Special Populations
• ***Renal Insufficiency:*** The effect of impaired renal function was not evaluated in the dronedarone program
• ***Hepatic insufficiency:*** The effect of impaired hepatic function has not been evaluated, but there is an ongoing study to evaluate this patient population.
• ***Gender:*** Relative to elderly males, elderly females have exposures that are approximately 30 % higher.
• ***Age:*** Relative to healthy young males, healthy elderly males have exposures that are about 40 % higher
• ***Race:*** Relative to healthy male Caucasians, healthy Asian (Japanese) males have exposures that are about 100 % higher."

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The primary indication sought by the Sponsor is the efficacy of dronedarone for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of AF/AFL.

The secondary objectives are:

- assessment of the efficacy of dronedarone versus placebo on AF/AFL- related symptoms;
- assessment of the efficacy of dronedarone versus placebo on ventricular rate control in case of AF/ AFL recurrence;
- assessment of the efficacy of dronedarone versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of AF/ AFL after the drug plasma level steady state is reached;
- assessment of the tolerability of dronedarone versus placebo in the target population.

The pharmacokinetic (PK) objective was to document dronedarone and SR35021, the main metabolite, trough plasma levels at steady state and to describe the PK of the selected dose in the target population.

6.1.1 Methods

The Sponsor has submitted five trials pertaining to their efficacy claim: DAFNE (DRI3550), ADONIS (EFC4788), EURIDIS (EFC3153), ERATO (EFC4508), and ANDROMEDA (EFC4966). The DAFNE study determined the dose to be utilized and has previously been reviewed by Dr. Williams. His review is attached in the appendix and only a few comments will be included here. Also, this study was reviewed in detail by Dr. Christine Garnett. Her review is included with Dr. Robert Kumi's review.

The two pertinent trials to support the sponsor's claim are the ADONIS and EURIDIS studies which are essentially similar in design and will be discussed here. The ERATO study was a supportive study of their claim for ventricular rate control. These reviewers, however, consider the most important study to be the ANDROMEDA. This study has clinical outcomes as the primary endpoints whereas the other pivotal studies have surrogate primary endpoints. According to the sponsor this study consisted of patients with a recent severe episode of congestive heart failure (CHF). However, it is noted by the reviewers that when the patients were randomized into the study they were in Class II (39 %) or III (58 %) which is only mild to moderate CHF as shown in table 6 on page 26. Only 3% of the randomized patients were in Class IV. These reviewers consider this the most important trial based on the statistically significant ($p = 0.027$) increased number of deaths (more than doubled) in the patients treated with dronedarone.

6.1.2 General Discussion of Endpoints

Clinically atrial fibrillation (AF) is defined as temporary, persistent (intermittent), or chronic. There are two general approaches to the treatment of persistent and chronic AF: rhythm or rate control. Several clinical trials including the AFFIRM, RACE, PIAF, and STAF have attempted to document which approach is superior. However, this decision probably should be individualized for each patient depending on their age, underlying illness, personal choice, and their response to drugs. The Sponsor has attempted to show efficacy for both the rhythm and rate control approaches. Additionally, atrial fibrillation is common in patients with congestive heart failure (CHF). AF increases the risk of cardiovascular morbidity among these patients. Therefore, another efficacy goal of the Sponsor was to show a decrease in the number of deaths and/or hospitalizations in patients with CHF. The endpoints in the pivotal trials, ADONIS and EURIDIS, were surrogate markers whereas the ANDROMEDA study has clinical outcomes, death or hospitalizations, as the primary endpoint.

6.1.3 Study Design

A brief synopsis of the studies submitted for efficacy will follow. Additional information regarding these studies is included in the appendix. Since these reviewers believe the ANDROMEDA to be the most important study, it will be described here first briefly and in more detail in the appendix. The ADONIS and EURIDIS are the two pivotal trials. They have essentially the same design and will be described after the ANDROMEDA. The DAFNE was a phase IIB trial to determine the dose. It was previously reviewed by Dr. Williams and will be

briefly mentioned here. Dr. Williams' review is included in the appendix. The ERATO, designed to be a supportive study for ventricular rate control, will be briefly cited here.

6.1.3.1 The ANDROMEDA Study (EFC4966)

Title: Antiarrhythmic trial with dronedarone in moderate to severe CHF evaluating morbidity decrease

Study dates: June 12, 2002 to August 19, 2003. There was a premature end to both the study drug treatment and randomizations on January 16, 2003, which is discussed later.

Study Population: patients with moderate to severe congestive heart failure with left ventricular dysfunction.

Design: Multicenter, multinational, double-blind, parallel-group, placebo-controlled study of efficacy of dronedarone 800 mg daily, for reducing death or hospitalizations for worsening heart failure.

Study centers: 72 active centers in 6 European countries: Denmark, Hungary, the Netherlands, Norway, Poland, and Sweden

Study objectives:
Primary**:** To evaluate whether dronedarone reduces death from any cause or hospitalizations for worsening heart failure in patients, according to the sponsor, with moderate to severe congestive heart failure (CHF) and left ventricular dysfunction (LVD), when added to usual evidence-based treatments for CHF, over a minimum period of 12 months as compared to placebo.

Secondary objectives were to evaluate whether dronedarone:
• reduces death from any cause;
• reduces hospitalization for worsening heart failure;
• reduces hospitalization for acute cardiovascular reasons;
• reduces arrhythmic/sudden death;
• is effective in maintaining sinus rhythm in the target population.

Safety and tolerability of dronedarone versus placebo were evaluated. Dronedarone and SR35021 plasma levels at steady state were documented.

Methodology**:** Multicenter, multinational, double-blind, parallel-group, placebo-controlled study of dronedarone 800 mg daily (400 mg BID) for reducing death or hospitalizations for worsening heart failure. In addition to the blinded Steering Committee (SC) responsible for the conduct of the trial, a central, independent data safety monitoring board (DSMB) monitored the safety of patients in the study, and an independent, blinded Critical Events Committee (CEC) adjudicated the causes of deaths and hospitalizations.

Number of patients evaluated**:**
Planned: 1,000: Main analysis population: Randomized: 627; Treated: 627;
Evaluated: Efficacy: 627; Safety: 627

On January 16, 2003, 7 months after the randomization of the first patient, the inclusions in the study and ongoing study drug treatment were discontinued following a recommendation of the DSMB, because of a higher number of deaths observed in patients randomized to the active treatment compared to placebo. The DSMB, following a second safety analysis February 17, 2003, recommended follow-up of mortality, major clinical events and renal function for all patients, up to July 17, 2003 (6 months after end of inclusions).

All patients randomized in center 616004 (n = 23) were excluded from the main analysis population by the Sponsor due to a major violation in good clinical practice (GCP) documented in this center, raising doubts about the integrity of the data provided by this center. In Supplement No. 015, the sponsor states there were 23 patients in this center. Eleven patients were randomized to receive dronedarone and 12 were in the placebo group. Among these patients none of them experienced hospitalization for worsening of heart failure or death up to January 16, 2003. Therefore, there was no primary efficacy event at this center.

Inclusion criteria:
Patients $\geq$18 years hospitalized with symptomatic CHF, current New York Heart Association (NYHA) class II-IV, requiring treatment with a diuretic, with at least 1 episode of dyspnea or fatigue at rest or on slight exertion (corresponding to NYHA class III or IV) within the previous month. Wall motion index (WMI) $\leq$1.2 [corresponding to a left ventricular ejection fraction (LVEF) of approximately $\leq$ 0.35], determined by a blinded central evaluation of a recorded standard echocardiography, was required.

Duration of treatment**:** Planned treatment duration for the last randomized patient was 12 months (event driven trial).

Pharmacokinetics: Dronedarone and SR35021 plasma levels were planned to be assessed at Month 1 (M1) and M6 in about 50% of patients. As well, several blood samples (pre-dose, 2h, 4h, 6h, 8h, 10h and 12h post-dose) were to be taken in a subgroup of about 30 patients at M1.

Safety included: Adverse events (AEs), clinical laboratory evaluations [liver function, renal function, electrolytes, metabolism, white blood cells, hemoglobin (Hb) and platelets], vital signs, 12-lead electrocardiogram (ECG).

Statistical methods**:** For all efficacy and safety evaluations, patients were analyzed according to the treatment actually received.

Analysis periods: 3 analysis periods were defined: “Up to January 16, 2003”; “Up to February 17, 2003”; and “Up to July 17, 2003”. These periods were considered for efficacy and safety analyses. In addition, the treatment emergent period (or “on-treatment period”), i.e.,

between first and last study drug administration plus 10 days, was also evaluated for safety, as planned in protocol.

Efficacy: The primary analysis of the primary endpoint, carried out up to January 16, 2003, was the comparison of the 2 treatment groups using a 2-sided Log-rank test (level of significance 0.05). Cumulative incidence functions in each treatment group were calculated using Kaplan-Meier estimate as well as the corresponding 95% confidence interval (CI) at specified time points. Cox's proportional hazard model was used to estimate the hazard ratio (labeled in tables "Relative risk" with 95% CI). The original protocol states the primary and the secondary analyses will not include covariates (Appendix 16.1.1, Sections 10.7.1.2.3 and 10.7.2.2).

Secondary analyses
The primary analysis was also performed up to February 17, 2003.

Sensitivity analysis and per-protocol analysis
A sensitivity analysis including patients randomized in the Polish center 616004 was done on the periods "Up to January 16, 2003" and "Up to February 17, 2003". On treatment analysis was performed on the per protocol population.

The Sponsor's post hoc covariate analyses
The Sponsor submitted post hoc covariant analyses that were not prespecified in the original protocol. The Sponsor's covariate analyses were as follows:
The primary efficacy endpoint was analyzed by the Sponsor using the following covariates: baseline weight, creatinine clearance, WMI, NYHA status, and concomitant intake (up to date of endpoint or censoring) of beta-blocker, digitalis, spironolactone, ACE inhibitors or AII receptor antagonists. First, a Cox proportional hazard model was used with all covariates (intake of concomitant medication was included as time dependent covariates) in order to adjust the treatment effect to variables with possible influence on the endpoint. Then, a Cox proportional hazard model was performed for each subcategory defined by these covariates; in these univariate analyses, intake of co-medication is intake up to the endpoint or censoring date whenever the co-medication started. Kaplan-Meier cumulative incidence curves have been done for each subcategory of the more significant covariates among those defined above. This analysis was performed on the periods "Up to January 16, 2003" and "Up to February 17, 2003".

Analyses of secondary endpoints:

- for death from any cause, the analysis consisted in the comparison of the 2 treatment groups using a 2-sided Log-rank test. Cox's proportional hazard model was used to estimate the hazard ratio with 95% CIs;
- for hospitalization for worsening heart failure and for hospitalization for acute cardiovascular reasons, the cumulative incidence of first hospitalization considering death from any cause as a competing risk was estimated by treatment group and compared by the Log-rank test. The number of days to first hospitalization was summarized as a quantitative variable and compared using a Wilcoxon test;
- for arrhythmic/sudden deaths the same method was used as for death from any cause.

Pharmacokinetics: Descriptive statistics for C_{max}, AUC_{0-12}, C trough, and for $C_{max,av}$ or C_{trough}, were calculated for dronedarone treatment.
There were 2 analyses: 1 compartmental analysis for patients having a full pharmacokinetics (PK) profile at M1, for C_{max}, t_{max}, AUC_{0-12}, and C_{trough}; and 1 descriptive analysis according to time windows.

Safety: The frequency of patients with treatment emergent AEs (TEAEs), deaths, treatment emergent serious AEs (SAEs) and TEAEs leading to discontinuation of study drug were summarized by treatment group, by primary system organ class and preferred term. The TEAEs were also summarized by relationship to study drug and intensity.

Clinical laboratory data, vital signs and ECG parameters (only when in normal sinus rhythm), and their changes from baseline were summarized at each protocol time point. Repeated evaluations of change from baseline were analyzed using a mixed model with the baseline assessment as covariate, for creatinine, potassium and heart rate (HR). The number and percentage of patients presenting at least 1 post baseline potentially clinically significant abnormality (PCSA) in laboratory tests, vital signs and ECG parameters were summarized; comparisons between the 2 treatment groups by Fisher's exact test were restricted to creatinine and potassium.

6.1.3.2 The ADONIS Study (ECF4988)

Title: American-Australian-African trial with Dronedarone in atrial fibrillation or flutter patients for the maintenance of Sinus rhythm (ADONIS)

Study dates: November 29, 2001 to September 25, 2003

Study Population: patients with a recent episode of atrial fibrillation or atrial flutter

Design: Multicenter, multinational, double-blind, parallel-group study, comparing efficacy of dronedarone versus placebo for maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of atrial fibrillation/atrial flutter.

Study centers: 101 active centers in 5 countries: USA, Canada, Australia, South Africa and Argentina.

Objectives:
Primary: To assess the efficacy of dronedarone versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of atrial fibrillation/atrial flutter (AF/AFL).

Secondary:

- to assess the efficacy of dronedarone versus placebo on AF/AFL-related symptoms;
- to assess the efficacy of dronedarone versus placebo on ventricular rate control in case of AF/AFL recurrence;
- to assess the efficacy of dronedarone versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of AF/AFL after drug plasma level steady state is reached;
- to assess the tolerability of dronedarone versus placebo in the target population;
- to document dronedarone and SR35021, the main metabolite, trough plasma levels at steady state and describe the pharmacokinetics (PK) of the selected dose in the target population.

Methodology:
Multicenter, multinational, double-blind, parallel-group, placebo-controlled study of the efficacy of dronedarone 800 mg daily (400 mg BID) in AF/AFL patients. In addition to the blinded Steering Committee (SC) responsible for the good conduct of the trial, an independent Data Safety Monitoring Board (DSMB) monitored periodically patient safety. The detection of AF/AFL recurrences was based on a centralized review of transtelephonic electrocardiogram monitoring (TTEM) and 12-lead electrocardiogram (ECG) with adjudication of the first AF/AFL recurrence by a group of 4 senior cardiologists of ECG Corelab.

Number of patients planned: 552; Randomized: 629; Treated: 625
Evaluated**:** Efficacy: 625; Safety: 625

Diagnosis and criteria for inclusion: Patients of either sex, aged 21 years or greater, in sinus rhythm for at least 1 hour at the time of randomization and with at least 1 ECG-documented AF/AFL episode in the last 3 months.

Criteria for evaluation:
Efficacy:
Primary endpoint**:** time in days between randomization and the first AF/AFL recurrence, defined as an episode lasting 10 minutes or more, as indicated by 2 consecutive, 12-lead ECGs or TTEM tracings recorded 10 minutes apart, and both showing AF/AFL confirmed by the ECG Corelab.

Secondary endpoints**:**
- symptomatic AF/AFL among the adjudicated first AF/AFL recurrence;
- ventricular rate assessed at the time of the adjudicated first AF/AFL recurrence;
- time elapsed in days between Day 5 midnight (steady state) and the adjudicated first AF/AFL recurrence within 12 months from randomization.

Pharmacokinetics: Plasma concentrations of dronedarone (SR33589) and SR35021 were planned to be assessed at trough, i.e., just before dosing (C_{trough}), in all patients, at visits Day 7, Day 21, Month 4 (M4), M9 and M12.

Safety: Adverse events (AEs), clinical laboratory evaluations (liver function, renal function, electrolytes, metabolism, white and red blood cells and platelets, and endocrinology), vital signs, 12-lead ECG, chest X-ray.

Statistical methods**:** For all efficacy and safety, patients were analyzed according to the allocated treatment by interactive voice response system (IVRS) at time of randomization.

Efficacy:
The primary analysis of the primary endpoint, in the randomized and treated patients population, was the comparison of the 2 treatment groups using a 2-sided Log-rank asymptotic test. Cumulative incidence functions in each treatment group were calculated using the nonparametric Kaplan-Meier estimate. The relative risk with 95% confidence interval (CI) was estimated using a Cox model with treatment group as the only factor.

The primary endpoint was supplemented by:

- a PP approach, considering the time of primary endpoint and the time of last study drug administration plus 10 days as competing risks;
- a baseline covariate analysis (binary prognostic factors: electrical cardioversion, ibutilide infusion or overdrive pacing for the last AF/AFL episode in the 5 days prior to randomization, chronic treatment with amiodarone, structural heart disease) using a Cox model.

The analyses of the secondary endpoints comprised the following:

- the primary endpoint was analyzed according to the presence/absence of symptoms through a survival competing risks analysis;
- ventricular rate assessed at the time of primary endpoint was analyzed using a 2-way analysis of variance (ANOVA), with treatment and ECG recording methods as covariates;
- time between steady state and adjudicated first AF/AFL recurrence was analyzed in the modified randomized and treated patients population, using the same analytical techniques as those used for the primary efficacy endpoint (the PP approach as defined above, was also applied).

Pharmacokinetics: Concentration data were log-transformed for analyses. In the dronedarone group, repeated measures were analyzed using a mixed model including age category, gender, and treatment as between factors in order to determine day of steady state. Average trough plasma concentration ($C_{trough,av}$) and average maximum plasma concentration ($C_{max,av}$) were calculated individually as the average of all values determined to be at steady state for each patient. Comparisons among groups [females / males, <65 years / >65 years, and moderate cytochrome P450 (CYP) 3A4 inhibitor / no CYP3A4 inhibitor] were performed using a 3-way ANOVA (age, gender, moderate CYP3A4 inhibitor categories). Contrasts with 95% CIs were computed and were converted to ratios of means with 95% CIs using the antilog transformation.

Safety: All safety analyses were carried out in the randomized and treated patients population, considering all assessments which occurred from first study drug intake to last study drug intake plus 10 days, i.e., treatment emergent. The frequency of patients with treatment emergent AEs (TEAEs), deaths, treatment emergent serious AEs (SAEs) and TEAEs leading to discontinuation of study drug were summarized by treatment group, by primary system organ class and preferred term. The TEAEs were also summarized by relationship to study drug and intensity.

Clinical laboratory data, vital signs and ECG parameters (only when in normal sinus rhythm), and their changes from baseline were summarized at each protocol time point. Repeated evaluations of change from baseline were analyzed using a mixed model with the baseline assessment as covariate, for creatinine, potassium and heart rate (HR). The number and percentage of patients presenting at least 1 post-baseline potentially clinically significant abnormality (PCSA) in laboratory tests, vital signs and ECG parameters were summarized; comparisons between the 2 treatment groups by Fisher's exact test were restricted to creatinine and potassium.

6.1.3.3. The EURIDIS Study (EFC3153)

Title: European trial in atrial fibrillation or flutter patients receiving dronedarone for the maintenance of Sinus rhythm

Study dates: November 19, 2001 to August 14, 2003

Study Population: patients with a recent episode of atrial fibrillation or atrial flutter

Design: Multicenter, multinational, double-blind, parallel-group study, comparing efficacy of dronedarone versus placebo for maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of atrial fibrillation/atrial flutter

Study centers:
65 active centers in 12 countries: Netherlands, Germany, Poland, Hungary, Italy, France, Czech Republic, Belgium, Spain, Denmark, Finland and United Kingdom.

Objectives:
Primary: To assess the efficacy of dronedarone versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of atrial fibrillation/atrial flutter (AF/AFL).

Secondary:
- to assess the efficacy of dronedarone versus placebo on AF/AFL-related symptoms;
- to assess the efficacy of dronedarone versus placebo on ventricular rate control in case of AF/AFL recurrence;

- to assess the efficacy of dronedarone versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of AF/AFL after drug plasma level steady state is reached;
- to assess the tolerability of dronedarone versus placebo in the target population;
- to document dronedarone and SR35021, the main metabolite, trough plasma levels at steady state and describe pharmacokinetics (PK) of the selected dose in the target population.

Methodology: Identical to ADONIS reviewed above.

Number of patients**:** Planned: 552; Randomized: 615; Treated: 612
Evaluated**:** Efficacy: 612; Safety: 612

Diagnosis and criteria for inclusion:
Patients of either sex, aged 21 years or greater, in sinus rhythm for at least 1 hour at the time of randomization and with at least 1 ECG-documented AF/AFL episode in the last 3 months.

Duration of treatment**:** 12 months and observed approximately 13 months

Criteria for evaluation: efficacy, pharmacokinetics, and safety were identical to the ADONIS study cited above.

6.1.3.4. The ERATO Study (EFC4508)

Title: Efficacy and safety of dronedarone for the control of ventricular rate during atrial fibrillation (ERATO)

Study dates: August 8, 2002 to June 9, 2004

Study Population: Patients with symptomatic permanent atrial fibrillation

Design: Multicenter, multinational, double-blind, parallel-group study comparing efficacy of dronedarone versus placebo for control of ventricular rate during atrial fibrillation

Study centers: 35 active centers in 9 countries: Belgium, Czech Republic, France, Italy, Netherlands, Poland, Spain, Sweden and Switzerland.

Objectives:
Primary: To assess the efficacy of dronedarone for the control of ventricular rate in patients with atrial fibrillation (AF) at rest.

Secondary objectives:

- To assess the efficacy of dronedarone in reducing ventricular rate in patients with AF during exercise without decreasing exercise tolerance;
- To assess the tolerability of dronedarone in the selected population;
- To document dronedarone and SR35021 plasma levels.

Methodology: Multicenter, multinational, double-blind, randomized, parallel-group, placebo controlled study of the efficacy of dronedarone 800 mg daily (400 mg BID), in AF patients. An independent Data Safety Monitoring Board (DSMB) monitored periodically patient safety.

Number of patients: Planned: 160; Randomized: 174; Treated: 174
Evaluated: Efficacy: 174; Safety: 174

Diagnosis and criteria for inclusion:
Patients of either sex, aged 21 years or greater, with symptomatic (symptomatic refers to any AF-related symptoms including palpitations) permanent AF (AF > 6 months) for which cardioversion was not considered; and with resting ventricular rate $\geq$ 80 bpm at screening measured on a 6-second rhythm strip.

Duration of treatment**:** 6 months and observed for approximately 7 months

Criteria for evaluation**:**
Efficacy:
Primary endpoint**:** Change in mean ventricular rate (HR) measured by 24-hour Holter recording at rest on Day 14 (steady state) compared to baseline.

Secondary endpoints**:**
- Exercise tolerance on Day 14 compared to baseline (maximal exercise duration defined as time elapsed between the start of the exercise test and its stop).
- evaluation of exercise performance: difference in heart rate (HR) at sub-maximal and maximal exercise between baseline and Day 14;
- difference in HR evaluated by the 24-hour Holter recording between baseline and Month 4.

Pharmacokinetics: Plasma concentrations of dronedarone (SR33589) and its metabolite SR35021 were planned to be assessed at trough, i.e., just before dosing (C_{trough}), on Day 14 (steady state), M2 and M4.

Safety: Adverse events (AEs), clinical laboratory evaluations (liver function, renal function, electrolytes, metabolism, white and red blood cells and platelets), vital signs, and ECG.

Statistical methods:
Efficacy: The primary analysis of the primary endpoint was performed using an analysis of covariance (ANCOVA) taking into account treatment group and baseline intake of medications [beta-blockers, calcium antagonists (diltiazem, verapamil), digitalis considered separately] as factors, as well as age and baseline Holter HR value as covariables. Missing data were imputed

using multiple imputation technique to provide treatment effect assessment based on all randomized patients.

Secondary endpoints:
Maximal exercise duration: Considering a sequential approach, main analysis of maximal exercise duration was performed only if the primary analysis of the primary endpoint was significant, without adjustment, at a significance level of 5%. Missing data were imputed using the same multiple imputation technique as that used for the primary analysis of the primary endpoint.
Other secondary variables: The same ANCOVA, on changes from baseline, was performed without multiple imputation for missing data.

Safety: All safety analyses were carried out, considering all assessments which occurred from first study drug intake to last study drug intake plus 10 days, i.e., treatment emergent. The frequency of patients with treatment emergent AEs (TEAEs), deaths, treatment emergent serious AEs (SAEs) and TEAEs leading to permanent discontinuation of study drug were summarized by treatment group, by primary system organ class and preferred term. The TEAEs were also summarized by relationship to study drug and intensity.

Clinical laboratory data, vital signs and ECG parameters, and their changes from baseline were summarized at each protocol time-point. Repeated evaluations of change from baseline were analyzed using a mixed ANCOVA model for creatinine, potassium, CPK and HR. The number and percentage of patients presenting at least 1 post baseline potentially clinically significant abnormality (PCSA) in laboratory tests, vital signs and ECG parameters were summarized; comparisons between the 2 treatment groups by Fisher's exact test were restricted to creatinine, potassium, creatine phosphokinase and digoxin. The same ANCOVAs on changes from baseline in digoxin and International Normalized Ratio (INR) for patients with concomitant intake of digitalis and oral anticoagulants (OAC), respectively, were performed.

6.1.3.5 The DAFNE Study (DRI3550)

Title: Dose-ranging study of the efficacy and safety of Dronedarone for the maintenance of sinus rhythm in patients undergoing cardioversion for atrial fibrillation

Study dates: February 2, 1999 to July 5, 2000

Indication: Atrial fibrillation

Design: Multinational, multicenter, double-blind, parallel arm, placebo-controlled study of 400, 600, and 800 mg b.i.d. oral dronedarone treatment for six months; Phase IIB

Study centers: There were 50 active centers in 11 countries: 11 in Netherlands, 8 in Spain, 7 in Poland, 6 in France, 5 in Germany, 4 in Belgium, 3 in Sweden, 2 in Switzerland, 2 in Israel 1, in Finland, 1 in Italy.

Objectives:
The primary objective was to determine the most effective dose of dronedarone for the maintenance of sinus rhythm in patients undergoing cardioversion for AF.

Secondary objectives were to assess versus placebo:

- the characteristics of the AF episode in the 3 dronedarone groups in case of AF recurrence;
- the incidences of spontaneous conversion to sinus rhythm occurring in the 3 dronedarone groups during the period of study drug administrations preceding the DC-shock;
- the success rate of cardioversion in the 3 dronedarone groups following the first period of study drug administration;
- SR33589 and SR35021 plasma trough levels during the study;
- the tolerability of 3 dose regimens of dronedarone in the selected population.

Methodology: Multinational, multicenter, double-blind, placebo-controlled, dose-ranging study testing in parallel 3 dronedarone dose levels in comparison with placebo for the maintenance of sinus rhythm. An oral anti-coagulant was started 3 weeks before Day 1 and was continued at least 4 weeks following cardioversion. Two blinded study committees were involved: an independent Safety committee monitored and analyzed study safety through evaluations of data (only the Chairman had access to the unblended treatment list); a Steering committee monitored study conduct and, based on recommendations of the Safety Committee, assessed risk-benefit ratios.

Number of patients:
Planned: a sufficient number of patients randomized in order to have 192 patients in sinus rhythm after cardioversion (cf. Amendment No. 2, October 8,1999).:

Diagnosis and criteria for inclusion:

- patients of either sex aged 21 to 85 years, with persistent AF (>72 hours and <12 months duration of the present episode at the screening visit) for whom cardioversion and anti-arrhythmic treatment was warranted;
- written, informed consent

Duration of treatment**:** 6 months

Criteria for evaluation**:**
Efficacy: The primary efficacy endpoint was the time to first recurrence of AF (duration >10 minutes) in patients converted to sinus rhythm, based on 12-lead Electrocardiogram (ECG) and Trans-telephonic ECG monitoring (TTEM) measurements (Amendment No. 2, October 8, 1999).

Pharmacokinetics: SR33589 and SR35021 plasma concentrations were measured on Days 5-8 (conversion), 14, 30, 90 and 150 and were classified C_{trough}, $C_{max.}$

Safety: Extent of exposure, adverse events (AEs), physical examination, concomitant medications, laboratory measurements, vital signs, ECG, congestive heart failure (CHF, using New York Heart Association [NYHA] functional class), chest x-ray, ophthalmological examination

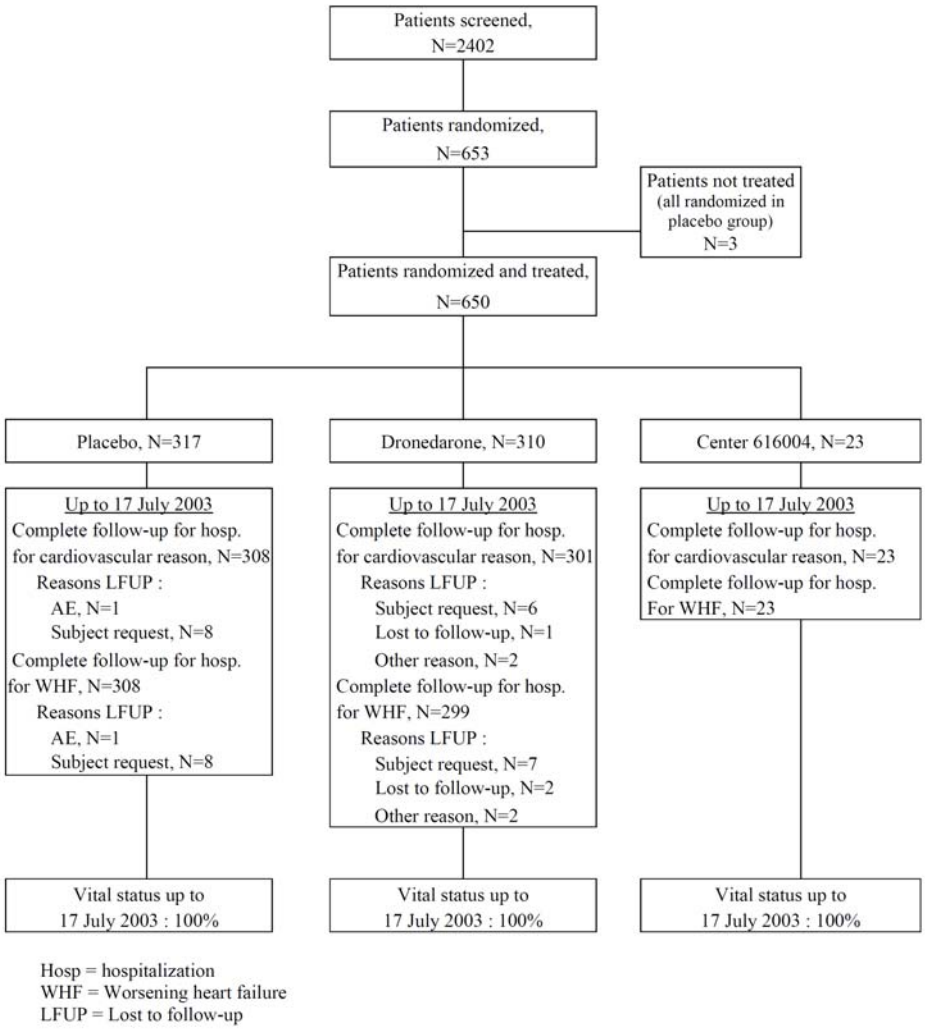
For complete review please refer to Dr. Williams' review in DFS dated 10/23/02.

6.1.4 Efficacy Findings

6.1.4.1 The ANDROMEDA Study

These reviewers consider the ANDROMEDA study to be the most important study because this study was the only study with clinical outcomes as the primary endpoints. Therefore, the Efficacy Findings from this study will be presented first. Below is a diagram showing the disposition of patients for the primary analysis and vital status.

6.1.4.1.1. Overview



(page 55 ECF 4966)

Figure 3- Disposition of patients for primary analysis and vital status

Center 616004 with 23 patients was excluded by the sponsor from the main analysis population due to major violations in Good Clinical Practice (GCP) which were identified by monitoring and confirmed in another ongoing dronedarone study. Therefore, the Steering Committee (SC) decided to exclude this center from the main analysis population. In Supplement No. 015, the sponsor states there were 23 patients in this center. Eleven patients were randomized to receive dronedarone and 12 were in the placebo group. Among these patients, none of them experienced hospitalization for worsening of heart failure or death up to January 16, 2003. Therefore, there was no primary efficacy event at this center.

Prior to January 16, 2003, in the main analysis population, which is the randomized and treated patients excluding center 616004, 23.0% of patients had permanently discontinued the dronedarone treatment. More patients discontinued dronedarone than the placebo, mainly due to AEs as shown in the table below. The AEs will be addressed in the Safety Section.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Patients who prematurely discontinued the study drug	57 (18.0 %)	87 (28.1 %)	144 (23.0 %)
Main reason for premature discontinuation			
Adverse event	28 (8.8 %)	57 (18.4 %)	85 (13.6 %)
Subject's request	24 (7.6 %)	22 (7.1 %)	46 (7.3 %)
Subject lost to follow-up	0 (0.0 %)	1 (0.3 %)	1 (0.2 %)
Other reason	5 (1.6 %)	7 (2.3 %)	12 (1.9 %)

(page 56 EFC4966)

Table 2- Number (%) of patients who prematurely withdrew from treatment prior to January 16, 2003, randomized and treated excluding center 616004

Demographic characteristics in the main analysis population between the dronedarone and placebo groups excluding center 616004 were similar as shown in the following table.

Parameter		Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Age (years)	n	317	310	627
	Median	72	71	71
	Mean	68.8	69.5	69.1
	SD	12.1	11.5	11.8
	Min - Max	27 - 96	33 - 90	27 - 96
Age (years) [n (%)]	<65	102 (32.2 %)	101 (32.6 %)	203 (32.4 %)
	[65;75[	93 (29.3 %)	92 (29.7 %)	185 (29.5 %)
	>=75	122 (38.5 %)	117 (37.7 %)	239 (38.1 %)
Height (cm)	n	314	308	622
	Median	172	172	172
	Mean	171.6	171.9	171.8
	SD	8.8	9.3	9.0
	Min - Max	147 - 195	147 - 198	147 - 198
Weight (Kg)	n	314	308	622
	Median	77.5	78.0	77.9
	Mean	79.13	77.72	78.43
	SD	18.70	17.00	17.88
	Min - Max	36.8 - 188.7	37.5 - 147.0	36.8 - 188.7
Gender [n (%)]	Male	242 (76.3 %)	230 (74.2 %)	472 (75.3 %)
	Female	75 (23.7 %)	80 (25.8 %)	155 (24.7 %)
Race [n (%)]	Caucasian	316 (99.7 %)	308 (99.4 %)	624 (99.5 %)
	Black	1 (0.3 %)	0 (0.0 %)	1 (0.2 %)
	Asian / oriental	0 (0.0 %)	1 (0.3 %)	1 (0.2 %)
	Other [a]	0 (0.0 %)	1 (0.3 %)	1 (0.2 %)

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Table 3- Summary of demographic parameters (excluding center 616004)

The above table shows an older population in the ANDROMEDA Study compared to the ADONIS and EURIDIS Studies. There are more males than females who are primarily Caucasian.

6.1.4.1.2. Cardiovascular History

The cardiovascular history of the main analysis population is displayed in the table below. Looking carefully at this table, in the placebo group there is a higher number of patients with an ICD and also with a history of AF/AFL. Among the patients in the placebo group with AF/AFL, there in an increase in the number of patients with their first episode, and there is a higher number of patients with persistent and permanent AF/AFL. At randomization there are a higher number of patients in AF/AFL in the placebo group which gives the study some imbalance in favor of dronedarone.

	Placebo (N=317)	**Dronedarone 800 mg (N=310)**	**Total (N=627)**
Patients with an ICD	6 (1.9 %)	4 (1.3 %)	10 (1.6 %)
Patients with an history of AF/AFL	126 (39.7 %)	114 (36.8 %)	240 (38.3 %)
Type of AF history			
First episode	58 (48.3 %)	45 (42.9 %)	103 (45.8 %)
Paroxysmal	13 (10.8 %)	20 (19.0 %)	33 (14.7 %)
Persistent	14 (11.7 %)	11 (10.5 %)	25 (11.1 %)
Permanent	35 (29.2 %)	29 (27.6 %)	64 (28.4 %)
Patients in AF/AFL at the randomization stage [a, b]	85 (28.0 %)	72 (24.1 %)	157 (26.0 %)

[a] According to the 12-lead ECG done at the randomization stage
[b] Patients with a pacemaker atrial drive have been considered as being in sinus rhythm

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Table 4- Number (%) of patients according to their arrhythmic history (exclude c. 616004)

The cardiovascular history was similar in both treatment groups, although the table below shows some variation between the placebo and dronedarone groups. Most patients suffered from coronary artery disease and/or cardiac valve disease.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Coronary heart disease	201 (63.4 %)	206 (66.5 %)	407 (64.9 %)
Valvular heart disease	175 (55.2 %)	171 (55.2 %)	346 (55.2 %)
Hypertension	107 (33.8 %)	123 (39.7 %)	230 (36.7 %)
Dilated cardiomyopathy	103 (32.5 %)	79 (25.5 %)	182 (29.0 %)
Diabetes mellitus	62 (19.6 %)	73 (23.5 %)	135 (21.5 %)
Coronary artery bypass grafting	42 (13.2 %)	57 (18.4 %)	99 (15.8 %)
Documented severe ventricular arrhythmia	33 (10.4 %)	33 (10.6 %)	66 (10.5 %)
Stroke	31 (9.8 %)	24 (7.7 %)	55 (8.8 %)
Percutaneous coronary revascularisation	26 (8.2 %)	27 (8.7 %)	53 (8.5 %)
Pacemaker	17 (5.4 %)	21 (6.8 %)	38 (6.1 %)
Alcohol induced cardiomyopathy	6 (1.9 %)	13 (4.2 %)	19 (3.0 %)
Hypertrophic cardiomyopathy	7 (2.2 %)	11 (3.5 %)	18 (2.9 %)
Congenital heart disease	0 (0.0 %)	2 (0.6 %)	2 (0.3 %)

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Table 5- Number (%) according to cardiovascular history (excluding c. 616004)

The primary causes for CHF were similar in the 2 treatment groups. The most frequent primary causes were myocardial infarction, coronary heart disease, and dilated cardiomyopathy as shown in the table below.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Myocardial infarction	99 (31.2 %)	106 (34.2 %)	205 (32.7 %)
Coronary heart disease [a]	76 (24.0 %)	73 (23.5 %)	149 (23.8 %)
Dilated cardiomyopathy	77 (24.3 %)	58 (18.7 %)	135 (21.5 %)
Hypertension	30 (9.5 %)	31 (10.0 %)	61 (9.7 %)
Atrial fibrillation	19 (6.0 %)	16 (5.2 %)	35 (5.6 %)
Alcohol induced cardiomyopathy	6 (1.9 %)	6 (1.9 %)	12 (1.9 %)
Hypertrophic cardiomyopathy	2 (0.6 %)	3 (1.0 %)	5 (0.8 %)
Mitral regurgitation	1 (0.3 %)	3 (1.0 %)	4 (0.6 %)
Aortic stenosis	1 (0.3 %)	2 (0.6 %)	3 (0.5 %)
Aortic regurgitation	1 (0.3 %)	1 (0.3 %)	2 (0.3 %)
Diabetes mellitus	0 (0.0 %)	2 (0.6 %)	2 (0.3 %)
Mitral stenosis	0 (0.0 %)	1 (0.3 %)	1 (0.2 %)
Other valvular heart disease	1 (0.3 %)	0 (0.0 %)	1 (0.2 %)

Note: 4 patients under Placebo, 8 patients under Dronedarone have not reported primary cause.
[a] Except Myocardial infarction
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Table 6- Number (%) of patients according to primary cause of CHF (excluding c. 616004)

The range of Wall Motion Index (WMI) determined by echocardiography, always ≤1.2, was in line with the inclusion criteria. The majority of patients in both groups were class II or III of the NYHA classification. Patients in class II were to have had an episode of class III or IV in the month preceding inclusion. This is summarized in the table below showing the WMI and cardiovascular clinical examination (NYHA class) at baseline. The table shows an increase in the number of patients in the placebo group who are in Class III and IV CHF; therefore revealing another slight imbalance in favor of dronedarone.

	Placebo (N=317)	**Dronedarone 800 mg (N=310)**	**Total (N=627)**
Echocardiography - Wall motion index			
n	316	309	625
Median	0.9	1.0	0.9
Mean	0.86	0.90	0.88
SD	0.23	0.23	0.23
Min - Max	0.3 - 1.2	0.3 - 1.2	0.3 - 1.2
Cardiovascular clinical examination - NYHA classification [n (%)]			
CLASS I (Asymptomatic)	0	0	0
CLASS II (Mild)	118 (37.2 %)	126 (40.6 %)	244 (38.9 %)
CLASS III (Moderate)	186 (58.7 %)	178 (57.4 %)	364 (58.1 %)
CLASS IV (Severe)	13 (4.1 %)	6 (1.9 %)	19 (3.0 %)

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Table 7- Summary of echocardiography and cardiovascular clinical examination (NYHA class) at baseline (excluding center 616004)

6.1.4.1.3. Other important baseline characteristics

The following table summarizes the baseline calculated creatinine clearance (mL/minute) using the Cockroft formula. As seen in this table, at baseline, almost half of the patients in both groups had a calculated creatinine clearance levels <50 mL/minute, indicating some degree of renal insufficiency in the study populations. It should be noted that in the placebo group there was a slightly larger percent of patients with limited creatinine clearance compared to dronedarone therefore giving a slight imbalance in favor of dronedarone regarding kidney function at baseline.

	Placebo (N=317)	Dronedarone 800 mg (N=310)
Missing	10	9
<50	128 (41.7%)	133 (44.2%)
<30	31 (10.1%)	41 (13.6%)
[30 ; 50[	97 (31.6%)	92 (30.6%)
>=50	179 (58.3%)	168 (55.8%)
[50 ; 80]	115 (37.5%)	114 (37.9%)
>80	64 (20.8%)	54 (17.9%)

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Table 8- Summary of baseline calculated creatinine clearance (mL/minute) (excluding center 616004)

The baseline vital signs are summarized in the table below which shows that the baseline mean systolic and diastolic blood pressures show a slight imbalance in favor of dronedarone.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Systolic blood pressure (mmHg)			
n	314	308	622
Median	120	120	120
Mean	122.2	119.8	121.0
SD	19.7	18.6	19.2
Min - Max	80 - 200	80 - 190	80 - 200
Diastolic blood pressure (mmHg)			
n	314	308	622
Median	75	70	70
Mean	74.4	72.5	73.4
SD	12.8	11.7	12.3
Min - Max	45 - 118	44 - 115	44 – 118

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Table 9- Summary of the baseline vital signs (excluding c. 616004)

In the following table the baseline ECG parameters (heart rate and QTc-Bazett interval) are summarized. The median and mean heart rates are slightly higher in the placebo group therefore showing a slight imbalance in favor of dronedarone.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Heart rate (bpm)			
n	219	227	446
Median	80	77	78
Mean	80.7	78.0	79.3
S.D.	16.8	15.7	16.3
Min - Max	48 - 126	44 - 128	44 - 128
QTc Bazett interval (ms)			
n	219	227	446
Median	444	451	450
Mean	442.3	445.7	444.0
S.D.	40.8	35.8	38.3
Min - Max	292 - 632	328 - 551	292 - 632

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Table 10- Summary of 12-lead ECG at baseline (excluding c. 616004)

6.1.4.1.4 Concomitant medication

The following table summarizes the number (%) of patients who received not permitted concomitant medications. This table shows that the dronedarone patients had a higher rate of not permitted medications including amiodarone.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Total forbidden concomitant medications	17 (5.4%)	22 (7.1%)	39 (6.2%)
Drugs which can cause Torsades de Pointes	16 (5.0%)	21 (6.8%)	37 (5.9%)
Amiodarone	4 (1.3%)	8 (2.6%)	12 (1.9%)
Potent inhibitors of CYP3A4	3 (0.9%)	7 (2.3%)	10 (1.6%)
Vaughan-Williams class I or III antiarrhythmic drugs [a]	3 (0.9%)	1 (0.3%)	4 (0.6%)

[a] Including Sotalol and excluding Amiodarone
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Table 11- Number (%) of patients who received not permitted concomitant medications (excluding center 616004)

In the table below, the number (%) of patients who received specific permitted medications at baseline is summarized. Although the Sponsor states "The number of patients who received evidence-based medicine treatment, such as ACE inhibitors, AII receptor antagonists, beta blocking agents, or statins, was high and not different between treatment groups at baseline," these reviewers note that there is a slight increase in the patients on dronedarone who were on ACE inhibitors or Angiotensin II receptor antagonists at baseline.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Total specific medications	317 (100.0%)	309 (99.7%)	626 (99.8%)
Diuretics	309 (97.5%)	297 (95.8%)	606 (96.7%)
Diuretics (other than spironolactone)	302 (95.3%)	288 (92.9%)	590 (94.1%)
Spironolactone	124 (39.1%)	131 (42.3%)	255 (40.7%)
ACE inhibitors or Angiotensin II receptor antagonists	267 (84.2%)	274 (88.4%)	541 (86.3%)
ACE inhibitors	241 (76.0%)	242 (78.1%)	483 (77.0%)
Angiotensin II receptor antagonists	28 (8.8%)	36 (11.6%)	64 (10.2%)
Chronic antiplatelet therapy	196 (61.8%)	203 (65.5%)	399 (63.6%)
Oral anticoagulant	102 (32.2%)	92 (29.7%)	194 (30.9%)
Beta blocking agents	192 (60.6%)	192 (61.9%)	384 (61.2%)
Beta blocking agents (except Sotalol)	191 (60.3%)	192 (61.9%)	383 (61.1%)
Statins	97 (30.6%)	113 (36.5%)	210 (33.5%)
Metabolized by CYP3A4	73 (23.0%)	94 (30.3%)	167 (26.6%)
Not metabolized by CYP3A4	24 (7.6%)	20 (6.5%)	44 (7.0%)
Digitalis	101 (31.9%)	96 (31.0%)	197 (31.4%)
Digoxin	92 (29.0%)	84 (27.1%)	176 (28.1%)
Digitalin	5 (1.6%)	7 (2.3%)	12 (1.9%)
Digitalis other than Digoxin or Digitalin	6 (1.9%)	5 (1.6%)	11 (1.8%)
Moderate inhibitors of CYP3A4	14 (4.4%)	10 (3.2%)	24 (3.8%)
Calcium antagonists with heart rate lowering effects [a]	12 (3.8%)	9 (2.9%)	21 (3.3%)
NSAID	12 (3.8%)	8 (2.6%)	20 (3.2%)

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Table 12- Number (%) of patients who received specific permitted medications at baseline (excluding center 616004)

In the table below is the number (%) of patients (after baseline) who received specific permitted concomitant medications. Tables 12 and 13 show the use of ACE inhibitors or Angiotensin II receptor antagonists increased from the baseline by 10.1% in the placebo group and by 5.1 % in the dronedarone group. Note that there is only a 0.8% difference between the dronedarone group and the placebo group relative to taking ACE inhibitors or Angiotensin II receptor antagonists during this study.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Total other specific concomitant medications	317 (100.0%)	310 (100.0%)	627 (100.0%)
Diuretics	315 (99.4%)	305 (98.4%)	620 (98.9%)
Diuretics (other than spironolactone)	309 (97.5%)	299 (96.5%)	608 (97.0%)
Spironolactone	168 (53.0%)	172 (55.5%)	340 (54.2%)
ACE inhibitors or Angiotensin II receptor antagonists	299 (94.3%)	290 (93.5%)	589 (93.9%)
ACE inhibitors	271 (85.5%)	260 (83.9%)	531 (84.7%)
Angiotensin II receptor antagonists	41 (12.9%)	47 (15.2%)	88 (14.0%)
Chronic antiplatelet therapy	211 (66.6%)	212 (68.4%)	423 (67.5%)
Oral anticoagulant	118 (37.2%)	109 (35.2%)	227 (36.2%)
Beta blocking agents (except Sotalol)	235 (74.1%)	241 (77.7%)	476 (75.9%)
Statins	116 (36.6%)	127 (41.0%)	243 (38.8%)
Metabolized by CYP3A4	88 (27.8%)	103 (33.2%)	191 (30.5%)
Not metabolized by CYP3A4	32 (10.1%)	28 (9.0%)	60 (9.6%)
Digitalis	112 (35.3%)	109 (35.2%)	221 (35.2%)
Digoxin	101 (31.9%)	97 (31.3%)	198 (31.6%)
Digitalin	6 (1.9%)	7 (2.3%)	13 (2.1%)
Digitalis other than Digoxin or Digitalin	7 (2.2%)	5 (1.6%)	12 (1.9%)
NSAID	26 (8.2%)	18 (5.8%)	44 (7.0%)
Moderate inhibitors of CYP3A4	19 (6.0%)	13 (4.2%)	32 (5.1%)
Calcium antagonists with heart rate lowering effects [a]	17 (5.4%)	11 (3.5%)	28 (4.5%)

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Table 13- After baseline, the number (%) of patients who received specific permitted concomitant medications (excluding center 616004)

6.1.4.1.5 Analysis of primary endpoint: death or hospitalization for worsening of heart failure

The results of the primary analysis which was death or hospitalization for worsening of heart failure up to January 16, 2003 are summarized in the following table. This is a troublesome table showing that dronedarone increased by 38% the risk of death or hospitalization for heart failure as compared to placebo.

	Placebo (N=317)	Dronedarone 800 mg (N=310)
Number of patients who died or who have been hospitalized for worsening heart failure	40	53
Relative risk[a]	1.38	
95% CI[a]	[0.918 ; 2.088]	
Log-rank's test result (p-value)	0.118	

a Determined from unadjusted Cox regression model
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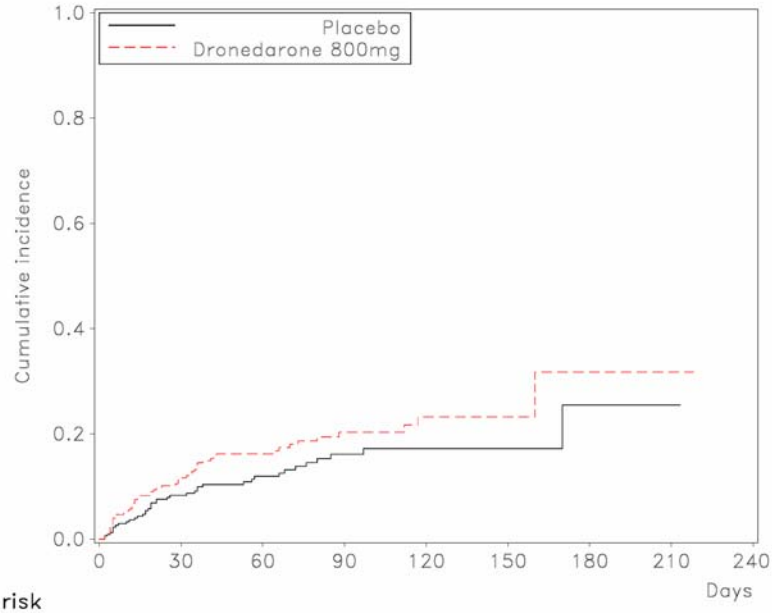
Table 14- Analysis of time from randomization to death or hospitalization for worsening of heart failure up to January 16, 2003 (excluding center 616004)

This analysis of death or hospitalization for worsening of heart failure is also shown in the Kaplan-Meier cumulative incidence curve below.



Nb exposed at risk								
Placebo	317	234	159	87	41	16	6	1
Dronedarone 800 mg	310	232	151	87	49	19	4	1

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Figure 4- Kaplan-Meier incidence curves to January 16, 2003 (excluding c. 616004)

6.1.4.1.5.1. The Sponsor's post hoc secondary supportive analyses of primary endpoint

The post hoc adjusted relative risks based on prognostic factors for the primary endpoint are summarized in the following table. This analysis was not pre-specified in the original protocol.

Prognostic factor	Risk	Adjusted relative risk[a]		
		Relative risk	95% CI	p-value
ACE inhibitor or A II receptor antagonist	Intake / No intake	0.32	[0.192 ; 0.520]	579E-8
Baseline creatinine clearance[b]	>= 50 ml/min / < 50 ml/min	0.46	[0.271 ; 0.793]	0.00499
Baseline NYHA	> II / II	1.75	[1.061 ; 2.881]	0.02823
Digitalis	Intake / No intake	1.58	[1.024 ; 2.423]	0.03876
Weight (Kg)	Continuous parameter	1.01	[0.996 ; 1.025]	0.150
Treatment	Dronedarone / Placebo	1.29	[0.841 ; 1.989]	0.241
Beta-blocker[c]	Intake / No intake	1.28	[0.799 ; 2.038]	0.308
Baseline WMI[d]	Continuous parameter	1.01	[0.388 ; 2.636]	0.983
Spironolactone	Intake / No intake	1.00	[0.649 ; 1.544]	0.996

Note: intake of medications has been analyzed as time dependent variable
a Determined from Cox regression model
b Creatinine clearance estimate using Cockroft formula
c Excluding Sotalol
d WMI is used to estimate LVEF, with LVEF = WMIx30 (5)
(page 68 EFC4966)

Table 15- Post hoc adjusted relative risk of death or hospitalization for worsening heart failure by prognostic factors up to January 16, 2003 (excluding center 616004)

The following table shows the unadjusted relative risk of death or hospitalization for worsening of heart failure by prognostic factor subcategories up to January 16, 2003. In this table the patients with a higher baseline creatinine clearance have a greater risk with dronedarone than with placebo.

Prognostic factor	Category	Number of patients: Placebo N	Placebo Nb of events	Dronedarone 800 mg N	Dronedarone 800 mg Nb of events	Unadjusted relative risk[a] Dronedarone/Placebo: Relative risk	95% CI	p-value
ACE inhibitor or A II receptor antagonist	Intake	289	31	261	36	1.33	[0.821 ; 2.149]	0.247
	No intake [b]	28	9	49	17	0.99	[0.440 ; 2.226]	0.980
Baseline creatinine clearance	<50 ml/min	128	25	133	29	1.12	[0.658 ; 1.918]	0.671
	>=50 ml/min	179	13	168	21	1.85	[0.924 ; 3.714]	0.08244
Baseline NYHA	II	121	9	131	15	1.58	[0.689 ; 3.600]	0.281
	>II	196	31	179	38	1.34	[0.835 ; 2.156]	0.225
Digitalis	Intake	107	18	90	23	1.43	[0.770 ; 2.646]	0.258
	No intake [b]	210	22	220	30	1.37	[0.789 ; 2.372]	0.265
Weight	<78 kg	162	24	154	25	1.10	[0.629 ; 1.930]	0.735
	>=78 kg	155	16	156	28	1.85	[0.997 ; 3.421]	0.05114
Beta-blocker [c]	Intake	227	29	222	36	1.33	[0.813 ; 2.162]	0.259
	No intake [b]	90	11	88	17	1.52	[0.710 ; 3.256]	0.281
Baseline WMI	<1	181	18	145	29	2.05	[1.137 ; 3.687]	0.01698
	>=1	136	22	165	24	0.92	[0.513 ; 1.638]	0.770
Spironolactone	Intake	154	21	132	18	1.07	[0.570 ; 2.020]	0.827
	No intake [b]	163	19	178	35	1.66	[0.952 ; 2.909]	0.07413

a Determined from Cox regression
b No intake is co-medication either never taken or prematurely stopped (i.e. prior to endpoint or censoring date)
c Excluding Sotalol
(page 70 EFC4966)

Table 16- Unadjusted relative risk of death or hospitalization for worsening heart failure by prognostic factors up to January 16, 2003 (excluding center 616004)

A sensitivity analysis performed on all randomized and treated patients (including center 616004) is shown in the following table. This analysis supported the primary efficacy analysis which excluded center 616004. No deaths in the dronedarone treatment group were recorded in center 616004.

	Placebo (N=329)	Dronedarone 800 mg (N=321)
Number of patients who died or who have been hospitalized for worsening heart failure	40	53
Relative risk[a]	1.38	
95% CI[a]	[0.918 ; 2.088]	
Log-rank's test result (p-value)	0.119	

a Determined from unadjusted Cox regression model
(page 125 EFC4966)

Table 17- Analysis of time from randomization to death or hospitalization for worsening heart failure up to 16 January 2003, including center 616004

6.1.4.1.6 Secondary efficacy endpoints

6.1.4.1.6.1. Death from any cause

In the following table are the results of the analysis of death from any cause up to January 16, 2003. This is a very troublesome table showing that dronedarone significantly (p = 0.027) increased, by 113%, (more than doubled) the risk of death from any cause as compared to placebo.

	Placebo (N=317)	**Dronedarone 800 mg (N=310)**
Number of patients who died	12	25
Relative risk[a]	2.13	
95% CI[a]	[1.071 ; 4.247]	
Log-rank's test result (p-value)	0.02717	

(page 71 EFC4966) (This analysis was confirmed by Dr. Valeria Freidlin)

Table 18- Analysis of death up to January 16, 2006, (excluding center 616004)

This analysis was confirmed by the statistical reviewer. In this reviewer's analysis, p=0.025 in Log-rank test and relative risk (hazard ratio) = 2.15 with the 95%CI of (1.081, 4.28) was in favor of placebo.

The primary causes of death up to January 16, 2003, as adjudicated by the Critical Events Committee (CEC) are summarized in the following table. The majority of deaths in both treatment groups were of cardiovascular origin. This table shows among the dronedarone patients there is a worsening of congestive heart failure and an increase in documented arrhythmias.

	Placebo (N=12)	**Dronedarone 800 mg (N=25)**
Cardiovascular death	9 (75%)	24 (96%)
Myocardial infarction	2 (16.7%)	0 (0.0%)
Worsening CHF	2 (16.7%)	10 (40%)
Documented arrhythmia	2 (16.7%)	6 (24%)
Procedure related	0 (0.0%)	1 (4%)
Other cardiovascular reason	0 (0.0%)	2 (8%)
Presumed cardiovascular reason	3 (25%)	5 (20%)
Non cardiovascular death	2 (16.7%)	1 (4%)
Cancer	1 (8.3%)	1 (4%)
Other non cardiovascular reason [a]	1 (8.3%)	0 (0.0%)
Non adjudicated death [b]	1 (8.3%)	0 (0.0%)

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Table 19- Number (%) of patients according to adjudicated primary cause of death up to January 16, 2003 (excluding center 616004)

In both treatment groups the majority of deaths were of cardiovascular origin. Within the dronedarone group, non-sudden deaths accounted for the majority of deaths as shown in the table below.

	Placebo (N=9)	**Dronedarone 800 mg (N=24)**
Sudden death unwitnessed	3 (33.3%)	3 (12.5%)
Sudden death witnessed	3 (33.3%)	7 (29.2%)
Non-sudden death	3 (33.3%)	14 (58.3%)

(page 73) EFC4966)

Table 20- Number (%) of patients according to adjudicated timing of cardiovascular deaths up to January 16, 2003 (excluding center 616004)

The Sponsor submitted the following post hoc covariate analyes which were not prespecified in the protocol. The table below summarizes the post hoc adjusted relative risk of death by prognostic factors up to January 16, 2003. According to the Sponsor, the most important risk factor for death was the absence of treatment with ACE inhibitor or Angiotensin II receptor antagonist in the dronedarone group. However, the reviewers believe these covariate analyses are difficult to interpret because: 1. the analyses were not prespecified and therefore are data driven; 2. ACE inhibitor and A II receptor antagonist intake were not baseline characteristics and therefore, this relationship cannot be determined; and 3.the Table 6 on page 26 shows that there was a very small (0.8 %) difference between the groups relative to treatment with ACE inhibitors or Angiotensin II receptor antagonists.

Prognostic factor	Risk	Adjusted relative risk[a]		
		Relative risk	95% CI	p-value
ACE inhibitor or A II receptor antagonist	Intake / No intake	0.21	[0.097 ; 0.432]	0.00003
Treatment	Dronedarone / Placebo	1.83	[0.887 ; 3.782]	0.102
Baseline creatinine clearance[b]	>= 50 ml/min / < 50 ml/min	0.65	[0.267 ; 1.604]	0.353
Beta-blocker[c]	Intake / No intake	0.79	[0.386 ; 1.624]	0.525
Weight (Kg)	Continuous parameter	0.99	[0.967 ; 1.018]	0.557
Baseline NYHA	> II / II	1.18	[0.555 ; 2.501]	0.669
Digitalis	Intake / No intake	1.10	[0.536 ; 2.268]	0.792
Baseline WMI[d]	Continuous parameter	1.18	[0.247 ; 5.666]	0.834
Spironolactone	Intake / No intake	1.05	[0.511 ; 2.170]	0.888

Note: intake of medications has been analyzed as time dependent variable
a Determined from Cox regression model
b Creatinine clearance estimate using Cockroft formula
c Excluding Sotalol
d WMI is used to estimate LVEF, with LVEF = WMIx30 (5)
(page 74 EFC4966)

Table 21- Post hoc adjusted relative risk of death by prognostic factors up to January 16, 2003 (excluding center 616004)

In the following table is the unadjusted relative risk by prognostic factor subcategories from randomization to death up to January 16, 2003. This table shows that in the unadjusted analysis, dronedarone treatment significantly increased the risk of death in patients with moderate to severe renal insufficiency (baseline creatinine clearance <50 mL/minute). Also, in the dronedarone group there was significantly increased death with more severe heart failure (NYHA class >II), in the patients with no intake of ACE inhibitor/AII receptor antagonist, or with spironolactone, and with baseline WMI <1.

In the main analysis population up to February 17, 2003, 34 dronedarone patients and 18 placebo patients died. This analysis was consistent with the analysis up to January 16, 2003; dronedarone significantly (p = 0.019) increased, by 96%, the risk of death.

Prognostic factor	Category	Number of patients: Placebo N	Placebo Nb of events	Dronedarone 800 mg N	Dronedarone 800 mg Nb of events	Unadjusted relative risk[a] Dronedarone/Placebo: Relative risk	95% CI	p-value
ACE inhibitor or A II receptor antagonist	Intake	281	10	249	10	1.14	[0.472 ; 2.737]	0.774
	No intake [b]	36	2	61	15	5.06	[1.157 ; 22.177]	0.03131
Baseline creatinine clearance	<50 ml/min	128	6	133	17	2.70	[1.065 ; 6.867]	0.03644
	>=50 ml/min	179	5	168	6	1.36	[0.412 ; 4.492]	0.614
Beta-blocker [c]	Intake	221	7	209	12	1.85	[0.728 ; 4.699]	0.196
	No intake [b]	96	5	101	13	2.34	[0.834 ; 6.587]	0.106
Weight	<78 kg	162	9	154	14	1.63	[0.705 ; 3.768]	0.253
	>=78 kg	155	3	156	11	3.72	[1.035 ; 13.345]	0.04409
Baseline NYHA	II	121	5	131	7	1.28	[0.405 ; 4.029]	0.676
	>II	196	7	179	18	2.77	[1.156 ; 6.625]	0.02234
Digitalis	Intake	101	2	89	12	6.45	[1.443 ; 28.802]	0.01470
	No intake [b]	216	10	221	13	1.27	[0.555 ; 2.892]	0.574
Baseline WMI	<1	181	4	145	15	4.60	[1.526 ; 13.868]	0.00671
	>=1	136	8	165	10	1.05	[0.415 ; 2.674]	0.912
Spironolactone	Intake	150	6	134	8	1.58	[0.547 ; 4.552]	0.399
	No intake [b]	167	6	176	17	2.55	[1.007 ; 6.480]	0.04840

a Determined from Cox regression
b No intake is co-medication either never taken or prematurely stopped (i.e. prior to endpoint or censoring date)
c Excluding Sotalol
(page 75 EFC4966)

Table 22- Unadjusted relative risk by prognostic factor subcategories for death up to January 16, 2003, (excluding center 616004)

The analysis performed 6 months after discontinuation of inclusions and the ongoing study drug treatment, July 17, 2003, showed a similar number of deaths in both treatment groups: 42 patients in the dronedarone group, and 39 in the placebo group. The number of deaths due to worsening heart failure was similar in both treatment groups: 15 patients in the dronedarone group, and 13 in the placebo group. To these reviewers the significance of this is unknown. Among the arrhythmic/sudden death there were no reported cases of torsades de pointes. The deaths will be reviewed in the safety section.

Analysis of the per protocol population supported the results of the main population analysis. In the table below is the efficacy response data of the secondary efficacy parameters per-protocol population up to January 16, 2003, regarding death from any cause.

Primary cause of death	Placebo (N=294)	Dronedarone 800 mg (N=278)
Total (a)	11	21
Missing cause	1 (9.1 %)	0 (0.0 %)
Cardiac death		
Sudden death - Witnessed	2 (18.2 %)	5 (23.8 %)
Sudden death - Alive within 24 H prior death	1 (9.1 %)	0 (0.0 %)
Sudden death - Arrhythmic death	1 (9.1 %)	0 (0.0 %)
Sudden death - Other	0 (0.0 %)	1 (4.8 %)
Worsening CHF	1 (9.1 %)	8 (38.1 %)
Cardiac procedure	0 (0.0 %)	1 (4.8 %)
Myocardial infarction	2 (18.2 %)	1 (4.8 %)
Other cardiac death	0 (0.0 %)	1 (4.8 %)
Vascular death		
Other vascular death	0 (0.0 %)	1 (4.8 %)
Non-cardiovascular death	2 (18.2 %)	2 (9.5 %)
Unknown cause	1 (9.1 %)	1 (4.8 %)

(page 3202, Appendix 16.2.6.2.2.1.1.7 EFC4966)

Table 23- Summary of local primary cause of death January 16, 2003, per protocol population

The above table shows the dronedarone patients had an increase in sudden death (probably an arrhythmia). This table also shows a worsening of congestive heart failure in the dronedarone treated patients.

The following table shows the efficacy response data of the secondary efficacy parameters of the per-protocol population a month later regarding death from any cause. This table reveals an increase in death from worsening of CHF.

Primary cause of death	Placebo (N=294)	Dronedarone 800 mg (N=278)
Total (a)	16	28
Missing cause	2 (12.5 %)	0 (0.0 %)
Cardiac death		
Sudden death - Witnessed	2 (12.5 %)	5 (17.9 %)
Sudden death - Alive within 24 H prior death	1 (6.3 %)	0 (0.0 %)
Sudden death - Arrhythmic death	2 (12.5 %)	0 (0.0 %)
Sudden death - Other	0 (0.0 %)	2 (7.1 %)
Worsening CHF	4 (25.0 %)	11 (39.3 %)
Cardiac procedure	0 (0.0 %)	1 (3.6 %)
Myocardial infarction	2 (12.5 %)	2 (7.1 %)
Other cardiac death	0 (0.0 %)	1 (3.6 %)
Vascular death		
Hemorrhagic stroke	0 (0.0 %)	1 (3.6 %)
Other vascular death	0 (0.0 %)	1 (3.6 %)
Non-cardiovascular death	2 (12.5 %)	3 (10.7 %)
Unknown cause	1 (6.3 %)	1 (3.6 %)

(page 3224 Appendix 16.2.6.2.2.2.1.7. EFC4966)

Table 24- Summary of local primary cause of death February 16, 2003 in the per protocol population

6.1.4.1.6.2 Hospitalization for worsening of heart failure

An analysis of the time to first hospitalization for worsening heart failure up to January 16, 2003, is summarized in the following table. Although the Sponsor states that "There was no statistically significant difference between groups in first hospitalization for worsening heart failure," it is apparent from this table that more patients on dronedarone were hospitalized (39 = 13%) as compared to placebo (31 = 10%).

	Placebo (N=317)	**Dronedarone 800 mg (N=310)**
Number of patients hospitalized for worsening heart failure	31	39
Log-Rank	0.271	

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Table 25- Analysis of time to first hospitalization for worsening of heart failure up to January 16, 2003 (excluding center 616004)

The following table provides an analysis of acute cardiovascular reasons from randomization to the first hospitalization up to January 16, 2003. This table shows that statistically significantly (p = 0.024) more dronedarone patients (71 = 23%) were hospitalized for cardiovascular reasons as compared to placebo (50 = 16%).

	Placebo (N=50)	**Dronedarone 800 mg (N=71)**
Worsening CHF	30 (60%)	35 (49.3%)
Myocardial ischemia	8 (16%)	13 (18.3%)
Ventricular arrhythmia	2 (4%)	3 (4.2%)
Supraventricular arrhythmia	1 (2%)	4 (5.6%)
Stroke	3 (6%)	4 (5.6%)
Other cardiovascular reason	4 (8%)	9 (12.7%)
Presumed cardiovascular reason	2 (4%)	3 (4.2%)

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Table 26- Number (%) of patients according to adjudicated primary cause of the first hospitalization for acute cardiovascular reasons up to January 16, 2003 (excluding c.616004)

6.1.4.1.7 The Andromeda Study Conclusions

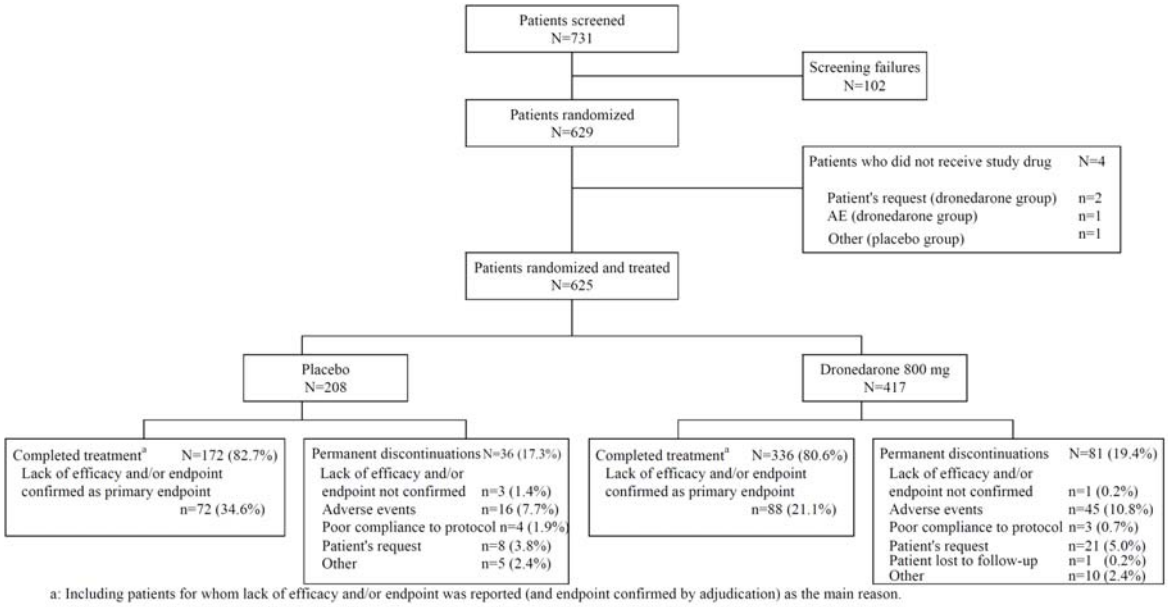
Among the patients on dronedarone there were statistically significantly ($p \leq 0.027$) more deaths from any cause and more hospitalizations for acute cardiovascular reasons as compared to placebo._ Although the Sponsor attributes this increase in mortality and morbidity to the lack of ACE inhibitors or Angiotensin II receptor antagonists in the dronedarone patients, these reviewers do not concur with the sponsor's conclusions. The reviewers believe that the covariate analyses including ACE inhibitors or Angiotensin II receptor antagonists intake are difficult to interpret because: 1. the analyses were not prespecified and therefore are data driven; 2. ACE inhibitor and A II receptor antagonist intake were not baseline characteristics and therefore, this relationship cannot be determined; and 3. the Table 6 on page 26 shows that there was a very small ((0.8 %) difference between the groups relative to treatment with ACE inhibitors or Angiotensin II receptor antagonists.

The percentage for both groups receiving ACE inhibitors or Angiotensin II receptor antagonists was similar, dronedarone 93.5% and placebo 94.3%, during the study. This study is the most important study as the clinical outcomes were the primary endpoints whereas the other pivotal studies have surrogate primary endpoints.

6.1.4.2. The ADONIS Study (EFC4788)

6.1.4.2.1 Overview

The following figure summarizes the patients who have completed the drug study treatment and those who prematurely permanently discontinued.



(page 53 ECF4788)

Figure 5- Disposition of patients

The following table lists the deviations leading to exclusion from analysis.

Category/reason[a]	Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
Deviation related to inclusion criteria	10 (4.8 %)	14 (3.4 %)	24 (3.8 %)
No qualifying AF/AFL episode[b]	9 (4.3 %)	8 (1.9 %)	17 (2.7 %)
No ECG documenting SR before randomization[c]	2 (1.0 %)	6 (1.4 %)	8 (1.3 %)
Deviations related to study drug administration	5 (2.4 %)	11 (2.6 %)	16 (2.6 %)
Treatment received not equal at least once to the randomized treatment	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Compliance to study drug < 75% [d]	5 (2.4 %)	11 (2.6 %)	16 (2.6 %)
Deviations related to previous or concomitant medications	12 (5.8 %)	32 (7.7 %)	44 (7.0 %)
Previous medications not correctly discontinued[e]	2 (1.0 %)	3 (0.7 %)	5 (0.8 %)
Forbidden concomitant medications[f], [g]	12 (5.8 %)	32 (7.7 %)	44 (7.0 %)
Adjudicated first AF/AFL recurrence prior to first study drug intake	2 (1.0 %)	0 (0.0 %)	2 (0.3 %)
Total of patient excluded from the per-protocol population	28 (13.5 %)	52 (12.5 %)	80 (12.8 %)

a A patient could be counted in more than one category/reason
b No 12-lead ECG within 100 days before randomization indicating 'atrial tachycardia' or 'atrial fibrillation' or 'atrial flutter' or 'paroxysmal atrial fibrillation'
c Last ECG within 7 days before randomization not indicating SR; patients with first ECG between randomization and first study drug intake documenting SR were not excluded (SR: 'sinus rhythm' or 'coronary sinus pace-maker' or 'junctional rhythm' or 'junctional tachycardia' or 'atrial drive' or 'atrio-ventricular drive')
d Compliance is assessed by the ratio of the number of tablets actually taken from first study drug intake to last study drug intake over the theoretic number of one tablet BID from day of first study drug intake to day of last study drug intake
e Includes Vaughan-Williams-Singh class I or III antiarrhythmics drugs, amiodarone, Sotalol
f Not permitted (i.e., forbidden) concomitant medications include Vaughan-Williams-Singh class I or III antiarrhythmics drugs, amiodarone, Sotalol, drugs which can cause torsades de pointes, potent inhibitors of CYP3A4, substrates of CYP3A4 with a narrow therapeutic margin
g Between day of first study drug intake (included) and day of last study drug intake or adjudicated first AF/AFL recurrence whichever occurred first (excluded). Patients who stopped amiodarone the day of first study drug intake are not excluded, as per-protocol this treatment might be stopped the day of randomization.
(page 54 EFC4788)

Table 27- Number (%) patients excluded by reason

6.1.4.2.2. Patients' characteristics

The demographic data for randomized and treated patients is summarized in the following table.

Parameter		Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
Age (years)	n	208	417	625
	Median	65	66	66
	Mean	63.0	64.6	64.1
	SD	11.4	11.3	11.4
	Min - Max	30 - 87	20 - 88	20 - 88
Age (years)[n(%)]	<65	104 (50.0 %)	186 (44.6 %)	290 (46.4 %)
	[65-75[	80 (38.5 %)	149 (35.7 %)	229 (36.6 %)
	>=75	24 (11.5 %)	82 (19.7 %)	106 (17.0 %)
Height (cm)	n	204	410	614
	Median	173	175	175
	Mean	172.7	173.1	173.0
	SD	10.6	10.9	10.8
	Min - Max	142 - 200	138 - 198	138 - 200
Weight (Kg)	n	208	417	625
	Median	85.7	86.8	86.4
	Mean	87.81	88.61	88.34
	SD	19.27	19.88	19.67
	Min - Max	51.0 - 167.7	35.0 - 185.9	35.0 - 185.9
Gender [n(%)]	Male	140 (67.3 %)	293 (70.3 %)	433 (69.3 %)
	Female	68 (32.7 %)	124 (29.7 %)	192 (30.7 %)
Race [n(%)]	Caucasian	199 (95.7 %)	391 (93.8 %)	590 (94.4 %)
	Black	3 (1.4 %)	9 (2.2 %)	12 (1.9 %)
	Asian / Oriental	0 (0.0 %)	4 (1.0 %)	4 (0.6 %)
	Other	6 (2.9 %)	13 (3.1 %)	19 (3.0 %)

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Table 28- Summary of demographic characteristics

Symptoms:
Incidences of AF/AFL-related symptoms in the 3 months prior to screening were as follows:

- palpitations, 66.4% in the dronedarone group and 69.1% in the placebo group;
- dizziness, 37.4% and 40.1%, respectively;
- fatigue, 65.9% and 57.5%, respectively;
- chest pain, 28.1% and 24.2%, respectively;
- dyspnea, 59.0% and 51.7%, respectively.

In both groups, the intensity of symptoms was most frequently only moderate or mild.

It is noted that symptoms are usually why a patients seeks medical care in AF/AFL. These are nonspecific symptoms and could relate to a number of different underlying medical conditions.

Heart rate (HR):
The summary of HR, assessed in AF/AFL prior to randomization, is presented in the following table.

	Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
n	198	401	599
Median	99	101	100
Mean	106.3	104.9	105.3
SD	32.3	30.8	31.3
Min - Max	54 - 199	45 - 215	45 - 215

(page 57 EFC4788)

Table 29- Summary of heart rate (bpm) at the time of last 12-lead ECG prior to randomization

Antiarrhythmics:
In the randomized and treated patients population, 66.9% of patients in the dronedarone group and 67.3% in the placebo group, had taken previous antiarrhythmic treatment for AF/AFL.

In 22.6% of study patients, a previous antiarrhythmic drug was stopped due to lack of efficacy. The most frequently used antiarrhythmic were amiodarone (34.1% and 33.7% in dronedarone and placebo patients, respectively), sotalol (20.4% and 25.5%, respectively), Class IC (16.8% and 18.8%, respectively), respectively, Class III (13.2% and 9.1%, respectively), and Class IA (10.3% and 10.1%, respectively).

Cardiovascular history:
In the following table the cardiovascular history is summarized.

	Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
Hypertension	97 (46.6 %)	242 (58.0 %)	339 (54.2 %)
Structural heart disease[a]	94 (45.6 %)	199 (48.5 %)	293 (47.6 %)
Coronary heart disease	44 (21.2 %)	104 (24.9 %)	148 (23.7 %)
Clinically relevant valvular heart disease including mitral valve prolapse	42 (20.2 %)	86 (20.6 %)	128 (20.5 %)
Dilated cardiomyopathy	19 (9.1 %)	34 (8.2 %)	53 (8.5 %)
Pacemaker (only if still in place)	13 (6.3 %)	31 (7.4 %)	44 (7.0 %)
Rheumatic heart disease	8 (3.8 %)	18 (4.3 %)	26 (4.2 %)
Hypertrophic cardiomyopathy	4 (1.9 %)	13 (3.1 %)	17 (2.7 %)
Implantable cardioverter defibrillator (ICD) (only if still in place)	2 (1.0 %)	6 (1.4 %)	8 (1.3 %)
Congenital heart disease	1 (0.5 %)	4 (1.0 %)	5 (0.8 %)

Structural heart disease = coronary heart disease and/or clinically relevant abnormalities at baseline echocardiography
a Because of missing values, percentages were calculated using N=206 for placebo and N=410 for dronedarone group
(page 58 EFC4788)

Table 30- Summary of cardiovascular history

Other baseline cardiovascular findings from a 2D-echocardiogram and physical examination are in the following table.

	Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
2D-echocardiogram			
Left ventricular ejection fraction (%)			
n	195	394	589
Median	60.0	60.0	60.0
Mean	57.21	57.91	57.68
SD	12.24	11.23	11.57
Min - Max	5.5 - 82.0	5.0 - 83.0	5.0 - 83.0
< 35 %	14 / 195 (7.2 %)	15 / 394 (3.8 %)	29 / 589 (4.9 %)
>= 35 %	181 / 195 (92.8 %)	379 / 394 (96.2 %)	560 / 589 (95.1 %)
Cardiovascular clinical examination			
Patients with left CHF	36 (17.3 %)	78 (18.7 %)	114 (18.2 %)
NYHA Class I (Potential)	10 (4.8 %)	28 (6.7 %)	38 (6.1 %)
NYHA Class II (Mild)	26 (12.5 %)	50 (12.0 %)	76 (12.2 %)

(page 59 EFC4788)

Table 31- Summary of baseline cardiology status

The following table summarizes baseline vital signs.

	Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
Systolic blood pressure (mmHg)			
n	208	417	625
Median	130	130	130
Mean	129.8	130.8	130.4
SD	17.4	17.3	17.3
Min - Max	90 - 194	94 - 200	90 - 200
Diastolic blood pressure (mmHg)			
n	208	417	625
Median	76	76	76
Mean	75.7	76.3	76.1
SD	9.1	10.0	9.7
Min - Max	56 - 100	50 - 120	50 - 120
Heart rate (bpm)			
n	208	416	624
Median	64	64	64
Mean	65.4	66.8	66.3
SD	10.6	11.3	11.1
Min - Max	46 - 100	47 - 152	46 - 152

Note: After 3 minutes in supine position. Heart rate measured with a stethoscope for at least 15 seconds
(page 60 EFC4788)

Table 32- Summary of baseline vital signs

The difference between the heart rate on physical exam and ECG can easily be explained by the occurance of not all the heart beats being transmitted in AF/AFL.

Concomitant medication
Patients who received not permitted concomitant medications from the day of first study drug intake up to the day of last study drug intake are summarized in the following table.

	Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
Total forbidden concomitant medications	33 (15.9%)	69 (16.5%)	102 (16.3%)
Vaughan-Williams class I or III antiarrhythmic drugs[a]	6 (2.9%)	17 (4.1%)	23 (3.7%)
Amiodarone	19 (9.1%)	19 (4.6%)	38 (6.1%)
Drugs which can cause Torsades de Pointes	30 (14.4%)	65 (15.6%)	95 (15.2%)
Potent inhibitors of CYP3A4	2 (1.0%)	7 (1.7%)	9 (1.4%)
Substrates of CYP3A4 with a narrow therapeutic margin	1 (0.5%)	2 (0.5%)	3 (0.5%)

Note: Creams, spray and lozenges are not taken into account
a Including Sotalol and excluding Amiodarone
(page 61 EFC4788)

Table 33- Number (%) of patients who received not permitted concomitant medication

The sponsor states that excluding patients who either stopped amiodarone the day of randomization (the protocol allowed amiodarone to be stopped the day of randomization) or started a not permitted concomitant medication on the day of study drug discontinuation, the number of patients who received not permitted concomitant medication was only 44 (10.6%) and 14 (6.7%) in the dronedarone and placebo groups, respectively.

The following table summarizes the number and percentage of patients who received specific permitted concomitant medications.

	Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
Total other specific concomitant medications	207 (99.5%)	411 (98.6%)	618 (98.9%)
Beta blocking agents (except Sotalol)	114 (54.8%)	208 (49.9%)	322 (51.5%)
ACE inhibitors or Angiotensin II receptor antagonists	96 (46.2%)	194 (46.5%)	290 (46.4%)
ACE inhibitors	80 (38.5%)	151 (36.2%)	231 (37.0%)
Angiotensin II receptor antagonists	21 (10.1%)	56 (13.4%)	77 (12.3%)
Digitalis	53 (25.5%)	94 (22.5%)	147 (23.5%)
Digoxin	53 (25.5%)	94 (22.5%)	147 (23.5%)
Calcium antagonists with heart rate lowering effects[a]	55 (26.4%)	103 (24.7%)	158 (25.3%)
Diuretics	65 (31.3%)	150 (36.0%)	215 (34.4%)
Spironolactone	4 (1.9%)	23 (5.5%)	27 (4.3%)
Diuretics other than Spironolactone	65 (31.3%)	149 (35.7%)	214 (34.2%)
Oral anticoagulant	149 (71.6%)	298 (71.5%)	447 (71.5%)
Chronic antiplatelet therapy	88 (42.3%)	191 (45.8%)	279 (44.6%)
Statins	79 (38.0%)	168 (40.3%)	247 (39.5%)
Metabolized by CYP3A4	57 (27.4%)	129 (30.9%)	186 (29.8%)
Not metabolized by CYP3A4	27 (13.0%)	58 (13.9%)	85 (13.6%)
Moderate inhibitors of CYP3A4	58 (27.9%)	105 (25.2%)	163 (26.1%)
NSAID	43 (20.7%)	101 (24.2%)	144 (23.0%)

a Restricted to Diltiazem, Verapamil
(page 62 EFC4788)

Table 34 - Number (%) of patients who received specific permitted concomitant medications

As expected in AF/AFL patients, the most frequently prescribed drugs were oral anticoagulants, and beta-blocking agents.

6.1.4.2.3 Analysis of primary endpoint

The results of the primary analysis are summarized below.

	Placebo (N=208)	**Dronedarone 800 mg (N=417)**
Number of patients with adjudicated first AF/AFL recurrence within 12 months from randomization	146	246
Median time in days (95% CI)	59 ([22;96])	158 ([80;252])
Relative risk[a]	0.725	
95% CI[a]	[0.590;0.890]	
Log-rank's test result (p-value)	0.0017	

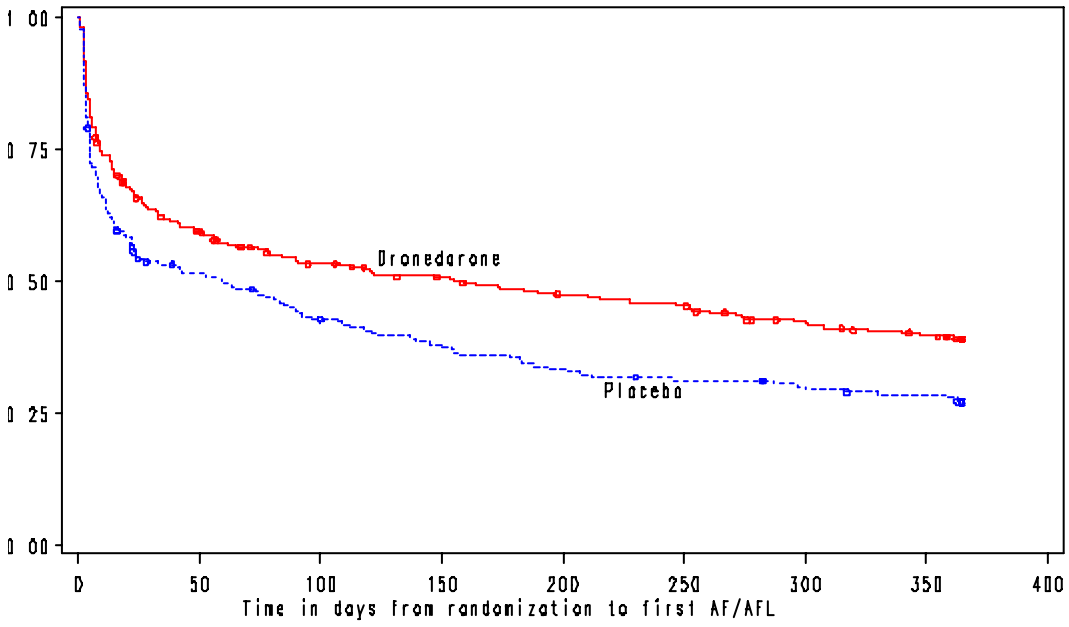
[a] Determined from Cox regression model confirmed by Dr. Valeria Freidlin (page 63 EFC4788)

Table 35- Unadjusted analysis of first AF/AFL recurrence within 12 months

Dronedarone significantly lowered, by 27.5%, the risk of first recurrence of AF/AFL within the 12-month study period compared to placebo in the randomized and treated patients population. The median time from randomization to adjudicated first AF/AFL recurrence in the dronedarone group was 2.7-fold longer than in the placebo group.

At 12 months, taking into account patients censored over time, 61.1% of dronedarone patients had experienced a first AF/AFL recurrence, compared to 72.8% of placebo patient. However, earlier in the protocol (page 50) the sponsor states “It was expected that 60% of patients on placebo in this trial would have an AF/AFL recurrence.” Therefore, dronedarone does not do much better than what was expected from the placebo population.

Below are the cumulative incidence curves showing this.



(figure provided by Dr. Valeria Freidlin)

Figure 6- Primary efficacy endpoint, time to first AF/AFL

Baseline covariates analysis
The adjusted relative risks based on baseline prognostic factors are summarized for the primary endpoint in the following table.

Prognostic factor	Risk	Adjusted relative risk[a]		
		Relative risk	95% CI	p-value
Treatment	Dronedarone / Placebo	0.714	[0.581;0.879]	0.0014
Convsr	Yes / No	1.587	[1.257;2.005]	0.0001
Amio	Yes / No	1.185	[0.926;1.516]	0.178
Shd	Yes / No	0.862	[0.703;1.059]	0.157

[a] Determined from Cox regression model
Convsr: electrical cardioversion, ibutilide infusion or overdrive pacing for the last AF/AFL episode in the 5 days prior to randomization
Amio: chronic treatment with amiodarone preceding randomization
Shd: structural heart disease
(page 65 EFC4788)

Table 36- Adjusted relative risk for adjudicated first AF/AFL recurrence within 12 months by prognostic factors.

This above table shows that treatment effect was significant when adjusted for pre-specified baseline prognostic factors. The recurrence rate was 1.587 times higher in patients with electrical cardioversion, ibutilide infusion or overdrive pacing for the last AF/AFL episode in the 5 days prior to randomization than in other patients (p = 0.0001).

Relative risks in each prognostic factor subcategory (yes/no) are summarized for the primary endpoint in the following table.

Prognostic factor	Category	Number of patients				Unadjusted relative risk[a] Dronedarone/Placebo		
		Placebo		Dronedarone 800 mg				
		N	Nb of events	N	Nb of events	Relative risk	95% CI	p-value
Convsr	Yes	46	40	90	61	0.652	[0.436;0.973]	0.03627
	No	162	106	327	185	0.756	[0.596;0.961]	0.02209
Amio	Yes	43	35	82	48	0.549	[0.355;0.851]	0.0073
	No	165	111	335	198	0.779	[0.617;0.983]	0.03540
Shd	Yes	94	64	199	117	0.773	[0.570;1.049]	0.098
	No	112	80	211	123	0.685	[0.517;0.909]	0.0087

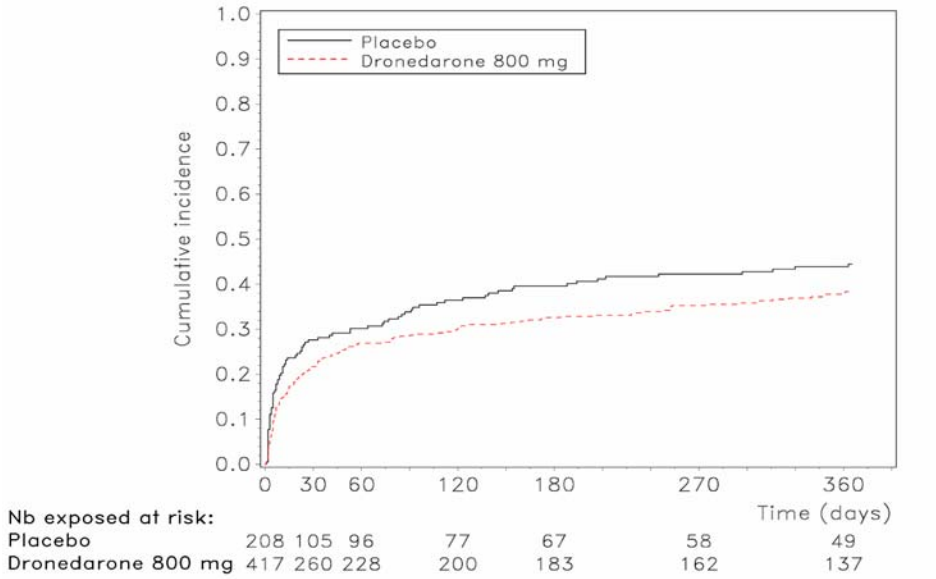
a Determined from Cox regression model
Convsr: electrical cardioversion, ibutilide infusion or overdrive pacing for the last AF/AFL episode in the 5 days prior to randomization
Amio: chronic treatment with oral amiodarone preceding randomization
Shd: structural heart disease
(page 65 EFC4788)

Table 37- Unadjusted relative risk for adjudicated first AF /AFL recurrence within 12 months by prognostic factor subcategories

The above table shows that being converted by electrical cardioversion, ibutilide infusion or overdrive pacing prior to randomization was of benefit for the dronedarone patients. Also, the use of chronic oral amiodarone preceding randomization and the lack of structural heart disease decreased the risk of the occurrence of AF/AFL in this group.

6.1.4.2.4 Secondary efficacy endpoints

6.1.4.2.4.1 Symptomatic AF/AFL among adjudicated first AF/AFL recurrence
The adjudicated first AF/AFL recurrence was associated with symptoms in about 62% of patients, consistently in both groups as shown in the Prentice cumulative incidence curves below.



Competing events: symptomatic adjudicated first AF/AFL recurrence and asymptomatic adjudicated first AF/AFL recurrence
(page 68 EFC4788)

Figure 7- Prentice cause-specific cumulative incidence curves for adjudicated first AF/AFL recurrence – randomized and treated patients population

Dronedarone significantly delayed the time to symptomatic adjudicated first AF/AFL recurrence within 12 months from randomization (Log-rank test, p = 0.021).

6.1.4.2.4.2. Ventricular rate assessed at time of adjudicated first AF/AFL recurrence
The following table summarizes HR assessed at the time of adjudicated first AF/AFL recurrence.

	Placebo (N=208)	Dronedarone 800 mg (N=417)
TTEM recording ECG method		
n	102	188
Median	114	101
Mean	116.6	104.6
SD	31.9	27.1
Min - Max	56 - 226	57 - 173
Whatever recording ECG method		
n	146	246
Median	105	100
Mean	110.6	102.7
SD	32.2	28.3
Min - Max	55 - 226	46 - 217

Note: Heart rate values obtained on only 1 RR interval are not taken into account
(page 69 EFC4788)

Table 38- Summary of heart rate (bpm) assessed at time of adjudicated first AF/AFL recurrence during study period up to Day 365 – randomized and treated patients population

The sponsor states that at time of first recurrence dronedarone patients had significantly lower mean HR based on the TTEM method, p = 0.0009, ANOVA. However, this statistician differs stating that analysis based on the subgroup (TTEM method) was not prespecificied. Therefore, analysis based on all date (all ECG's submitted) should be used. This analysis showed that dronedarone was only numerically (p = 0.078) better than placebo relative to heart rate.

Also, it is important to note that clinically the heart rate should be lowered to a range of 60 to 80 bpm in order to be considered improved. Therefore, the mean rate of 102 is far from what is clinically considered improved.

6.1.4.2.4.3. Time between steady state and adjudicated first AF/AFL recurrence
The following table summarizes the unadjusted analysis of time from Day 5 midnight to the adjudicated first AF/AFL recurrence in the modified randomized and treated patients population.

	Placebo (N=146)	Dronedarone 800 mg (N=327)
Number of patients with adjudicated first AF/AFL recurrence within 12 months from randomization	87	161
Median time in days (95% CI)	152 ([104;292])	342 ([248;.])
Relative risk[a]	0.743	
95% CI[a]	[0.572;0.964]	
Log-rank's test result (p-value)	0.02443	

a Determined from Cox regression model confirmed by Dr. Valeria Freidlin)
(page 70 EFC4788)

Table 39- Unadjusted analysis of time from steady state to adjudicated first AF/AFL recurrence within 12 months from randomization

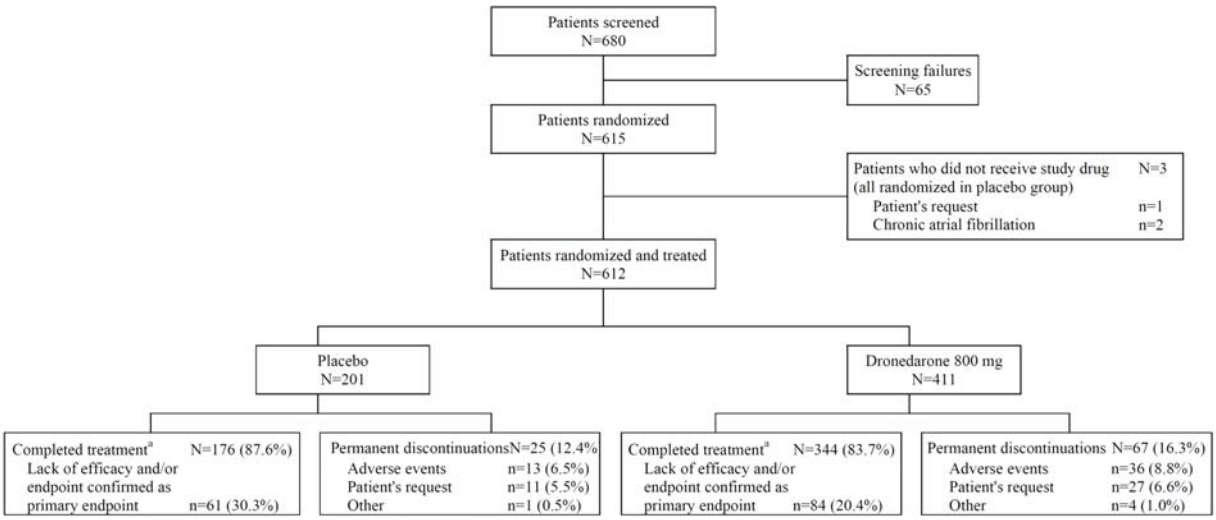
Dronedarone significantly lowered, by 26%, the risk of recurrence of AF/AFL considered between Day 5 midnight and 12 months post randomization. The median time to adjudicated first AF/AFL recurrence in the dronedarone group was 2.3-fold longer than in the placebo group.

6.1.4.2.4.4. Pharmacokinetics
The steady state of dronedarone and SR35021 plasma concentrations was reached by Day 7.
The PK characteristics of dronedarone and its major active circulating metabolite SR35021 in the patients of the present study, as well as the effect of gender, age and CYP3A4 moderate inhibitor were consistent with those already reported in healthy subjects or patients. This is discussed in the pharmacokinetic review.

6.1.4.2.5. The Adonis Study Conclusions
Dronedarone 800 mg daily (400 mg BID) significantly delayed the first AF/AFL recurrence. It also delayed the symptomatic first recurrence. However, these reviewers disagree with the Sponsor that dronedarone significantly reduced ventricular rate at the time of first recurrence.

6.1.4.3. EURIDIS (EFC3153)
This study is essentially identical to the ADONIS.

6.1.4.3.1. Overview
This multinational study was conducted in 65 active centers in 12 European countries between November 2001 and August 2003. The following figure provides a disposition of the patients. There was no statistically significant difference between the treatment groups in the number of premature permanent discontinuations.



a: including patients for whom lack of efficacy and/or endpoint was reported (and endpoint confirmed by adjudication) as the main reason
(page 51 EFC3153)

Figure 8- Disposition of patients

The demographic data for the randomized and treated patients are summarized in the table below.

Parameter		Placebo (N=201)	Dronedarone 800 mg (N=411)	Total (N=612)
Age (years)	n	201	411	612
	Median	63	63	63
	Mean	61.3	62.3	62.0
	SD	10.7	10.0	10.2
	Min - Max	32 - 82	23 - 86	23 - 86
Age (years)[n(%)]	<65	111 (55.2 %)	227 (55.2 %)	338 (55.2 %)
	[65-75[	76 (37.8 %)	139 (33.8 %)	215 (35.1 %)
	>=75	14 (7.0 %)	45 (10.9 %)	59 (9.6 %)
Height (cm)	n	195	407	602
	Median	175	173	173
	Mean	174.6	172.9	173.4
	SD	9.3	9.9	9.8
	Min - Max	152 - 200	148 - 213	148 - 213
Weight (Kg)	n	198	408	606
	Median	85.0	83.0	84.0
	Mean	86.43	83.84	84.68
	SD	14.78	14.39	14.55
	Min - Max	61.0 - 168.0	50.0 - 165.0	50.0 - 168.0
Gender [n(%)]	Male	140 (69.7 %)	285 (69.3 %)	425 (69.4 %)
	Female	61 (30.3 %)	126 (30.7 %)	187 (30.6 %)
Race [n(%)]	Caucasian	201 (100 %)	409 (99.5 %)	610 (99.7 %)
	Asian / Oriental	0 (0.0 %)	2 (0.5 %)	2 (0.3 %)

Table 40- Summary of demographic characteristics

6.1.4.3.2. Medical history

Symptoms:
Incidences of AF/AFL-related symptoms in the 3 months prior to screening were as follows:

- palpitations, 65.0% in the dronedarone group and 66.7% in the placebo group;
- dizziness, 30.2% and 29.4%, respectively;
- fatigue, 46.2% and 42.8%, respectively;
- chest pain, 23.1% and 24.9%, respectively;
- dyspnea, 44.5% and 41.3%, respectively.

In both groups, the intensity of symptoms were most frequently moderate or mild.

Heart rate:
The summary of HR, assessed in AF/AFL prior to randomization, is presented in the following table.

	Placebo (N=201)	Dronedarone 800 mg (N=411)	Total (N=612)
n	195	394	589
Median	99	97	98
Mean	103.3	102.2	102.6
SD	31.6	28.8	29.8
Min - Max	45 - 198	51 - 187	45 - 198

Note: Heart rate values obtained on only 1 RR interval are not taken into account
(page 55 EFC3153)

Table 41- Summary of heart rate (bpm) at the time of last 12-lead ECG in AF/AFL prior to randomization

Antiarrhythmics:
In the randomized and treated patients population, 79.3% of patients in the dronedarone group and 78.6% in the placebo group, had taken previous antiarrhythmic treatment for AF/AFL.
In 39.5% of study patients, a previous antiarrhythmic drug was stopped due to lack of efficacy.
The most frequently used antiarrhythmics were Class II (33.3% and 30.3% in dronedarone and placebo patients, respectively), sotalol (31.4% and 29.4%, respectively), Class IC (29.2% and 34.3%, respectively), and amiodarone (24.6% and 27.9%, respectively).

6.1.4.3.3. Cardiovascular history
The cardiovascular history of randomized and treated patients is summarized in the following table.

	Placebo (N=201)	Dronedarone 800 mg (N=411)	Total (N=612)
Hypertension	108 (53.7 %)	255 (62.0 %)	363 (59.3 %)
Structural heart disease[a] Coronary heart disease	65 (33.3 %) 31 (15.4 %)	149 (36.3 %) 91 (22.1 %)	214 (35.4 %) 122 (19.9 %)
Clinically relevant valvular heart disease including mitral valve prolapse	19 (9.5 %)	50 (12.2 %)	69 (11.3 %)
Pacemaker (only if still in place)	7 (3.5 %)	33 (8.0 %)	40 (6.5 %)
Dilated cardiomyopathy	11 (5.5 %)	16 (3.9 %)	27 (4.4 %)
Hypertrophic cardiomyopathy	8 (4.0 %)	10 (2.4 %)	18 (2.9 %)
Rheumatic heart disease	6 (3.0 %)	7 (1.7 %)	13 (2.1 %)
Congenital heart disease	2 (1.0 %)	9 (2.2 %)	11 (1.8 %)
Implantable cardioverter defibrillator (ICD) (only if still in place)	3 (1.5 %)	0 (0.0 %)	3 (0.5 %)

Structural heart disease = coronary heart disease and/or clinically relevant abnormalities at baseline echocardiography
a Because of missing values, percentages were calculated using N=195 for placebo group and N=410 for dronedarone group
(page 56 EFC3153)

Table 42- Summary of the cardiovascular history

In the above table differences can be seen among the two groups in regards to hypertension, coronary artery disease, and clinically relevant heart disease including mitral valve prolapse. A summary of the baseline cardiology status is shown on the following table.

	Placebo (N=201)	Dronedarone 800 mg (N=411)	Total (N=612)
2D-echocardiogram			
Left ventricular ejection fraction (%)			
n	191	400	591
Median	60.0	60.0	60.0
Mean	59.83	59.57	59.65
SD	9.37	10.25	9.97
Min - Max	20.0 - 84.0	15.0 - 93.4	15.0 - 93.4
< 35 %	2 / 191 (1.0 %)	8 / 400 (2.0 %)	10 / 591 (1.7 %)
>= 35 %	189 / 191 (99.0 %)	392 / 400 (98.0 %)	581 / 591 (98.3 %)
Cardiovascular clinical examination			
Patients with left CHF	37 (18.4 %)	65 (15.8 %)	102 (16.7 %)
NYHA Class I (Potential)	16 (8.0 %)	19 (4.6 %)	35 (5.7 %)
NYHA Class II (Mild)	21 (10.4 %)	46 (11.2 %)	67 (10.9 %)

(page 57 EFC3153)

Table 43- Summary of baseline cardiology status

The summary of the baseline vital signs are provided in the table below.

	Placebo (N=201)	Dronedarone 800 mg (N=411)	Total (N=612)
Systolic blood pressure (mmHg)			
n	200	411	611
Median	130	130	130
Mean	131.4	134.5	133.4
SD	17.0	17.4	17.3
Min - Max	92 - 181	90 - 192	90 - 192
Diastolic blood pressure (mmHg)			
n	200	411	611
Median	80	80	80
Mean	79.1	80.7	80.2
SD	9.7	9.1	9.3
Min - Max	50 - 100	50 - 101	50 - 101
Heart rate (bpm)			
n	199	411	610
Median	64	65	64
Mean	66.8	67.3	67.1
SD	11.3	11.9	11.7
Min - Max	48 - 127	47 - 130	47 - 130

(page 58 EFC3151)

Table 44- Summary of baseline vital signs

6.1.4.3.4. Concomitant medication

Patients who received not permitted concomitant medications from the day of first study drug intake up to the day of last study drug intake are summarized in the following table.

	Placebo (N=201)	Dronedarone 800 mg (N=411)	Total (N=612)
Total forbidden concomitant medications	26 (12.9%)	43 (10.5%)	69 (11.3%)
Vaughan-Williams class I or III antiarrhythmic drugs[a]	8 (4.0%)	20 (4.9%)	28 (4.6%)
Amiodarone	17 (8.5%)	24 (5.8%)	41 (6.7%)
Drugs which can cause Torsades de Pointes	26 (12.9%)	42 (10.2%)	68 (11.1%)
Potent inhibitors of CYP3A4	0 (0.0%)	3 (0.7%)	3 (0.5%)
Substrates of CYP3A4 with a narrow therapeutic margin	0 (0.0%)	3 (0.7%)	3 (0.5%)

Note: Creams, spray and lozenges are not taken into account
a Including Sotalol and excluding Amiodarone
(page 59 EFC3153)

Table 45- Number (%) of patients who received not permitted concomitant medication

Excluding patients who either stopped amiodarone the day of randomization (the protocol allowed amiodarone to be stopped the day of randomization) or started a not permitted concomitant medication on the day of study drug discontinuation, the number of patients who

received not permitted concomitant medications was only 14 (3.4%) and 6 (3.0%) in the dronedarone and placebo groups, respectively.

In the following table are the number and percent of patients who received permitted concomitant medications.

	Placebo (N=201)	Dronedarone 800 mg (N=411)	Total (N=612)
Total other specific concomitant medications	196 (97.5%)	395 (96.1%)	591 (96.6%)
Beta blocking agents (except Sotalol)	124 (61.7%)	245 (59.6%)	369 (60.3%)
ACE inhibitors or Angiotensin II receptor antagonists	94 (46.8%)	215 (52.3%)	309 (50.5%)
ACE inhibitors	79 (39.3%)	176 (42.8%)	255 (41.7%)
Angiotensin II receptor antagonists	22 (10.9%)	50 (12.2%)	72 (11.8%)
Digitalis	55 (27.4%)	79 (19.2%)	134 (21.9%)
Digoxin	42 (20.9%)	51 (12.4%)	93 (15.2%)
Digitalin	12 (6.0%)	24 (5.8%)	36 (5.9%)
Digitalis other than Digoxin or Digitalin	1 (0.5%)	4 (1.0%)	5 (0.8%)
Calcium antagonists with heart rate lowering effects[a]	23 (11.4%)	36 (8.8%)	59 (9.6%)
Diuretics	60 (29.9%)	121 (29.4%)	181 (29.6%)
Spironolactone	14 (7.0%)	10 (2.4%)	24 (3.9%)
Diuretics other than Spironolactone	58 (28.9%)	119 (29.0%)	177 (28.9%)
Oral anticoagulant	142 (70.6%)	273 (66.4%)	415 (67.8%)
Chronic antiplatelet therapy	64 (31.8%)	135 (32.8%)	199 (32.5%)
Statins	52 (25.9%)	95 (23.1%)	147 (24.0%)
Metabolized by CYP3A4	28 (13.9%)	59 (14.4%)	87 (14.2%)
Not metabolized by CYP3A4	29 (14.4%)	44 (10.7%)	73 (11.9%)
Moderate inhibitors of CYP3A4	23 (11.4%)	36 (8.8%)	59 (9.6%)
NSAID	19 (9.5%)	31 (7.5%)	50 (8.2%)

a Restricted to Diltiazem, Verapamil
(page 60 EFC 3153)

Table 46- Number (%) of patients who received specific permitted concomitant medications

6.1.4.3.5. Primary endpoint

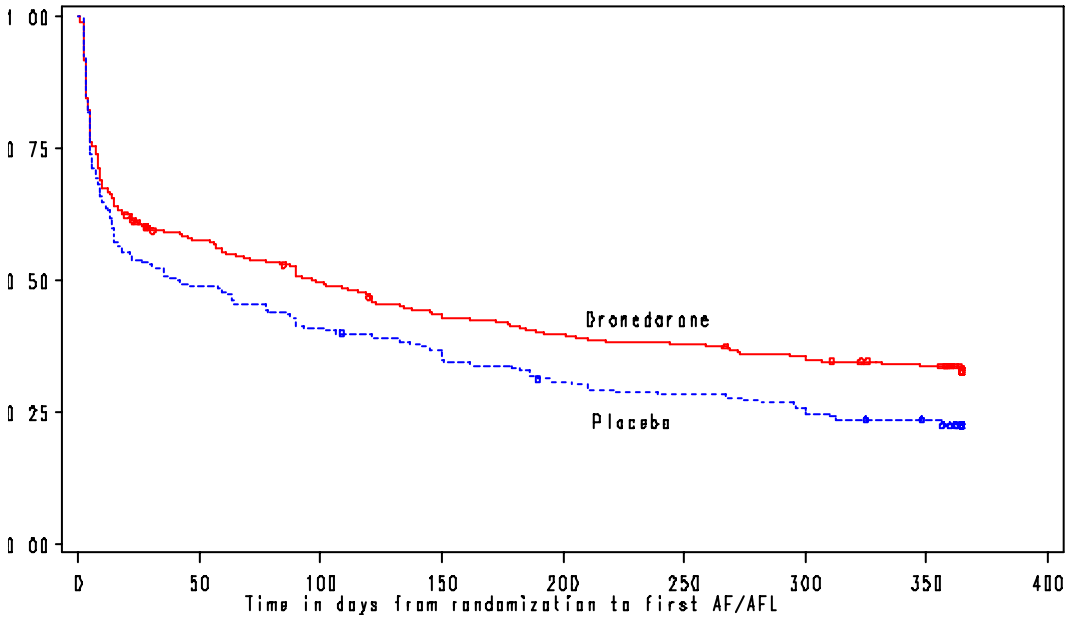
The results of the primary analysis of the primary endpoint are in the following table.

	Placebo (N=201)	Dronedarone 800 mg (N=411)
Number of patients with adjudicated first AF/AFL recurrence within 12 months from randomization	155	272
Median time in days (95% CI)	41 ([16;87])	96 ([61;133])
Relative risk (Dronedarone / Placebo)[a]	0.784	
95% CI[a]	[0.644;0.955]	
Log-rank's test result (p-value)	0.01383	

a Determined from Cox regression model and confirmed by Dr. Valeria Freidlin
(page 61 EFC3153)

Table 47- Unadjusted analysis of time to adjudicated first AF/AFL recurrence within 12 months

Dronedarone significantly lowered, by 22%, the risk of first recurrence of AF/AFL within the 12-month study period compared to placebo in the randomized and treated patients population. The median time from randomization to adjudicated first AF/AFL recurrence in the dronedarone group was 2.3-fold longer than in the placebo group. This is also shown in the figure below.



(Figure provided by Dr. Valeria Freidlin)

Figure 9- Primary efficacy endpoint, time to first AF/AFL

Secondary analysis of the primary endpoint
At 12 months of treatment (Prentice estimates), 65.5% of patients experienced a first AF/AFL recurrence in the dronedarone group as compared to 76.5% in the placebo group. Adjusted relative risks based on baseline prognostic factors are summarized for the primary endpoint in the following table.

Prognostic factor	Risk	Adjusted relative risk[a]		
		Relative risk	95% CI	p-value
Treatment	Dronedarone / Placebo	0.801	[0.656;0.978]	0.02959
Convsr	Yes / No	1.147	[0.942;1.397]	0.173
Amio	Yes / No	0.850	[0.651;1.109]	0.231
Shd	Yes / No	1.000	[0.819;1.221]	1.000

a Determined from Cox regression model
Convsr: electrical cardioversion, ibutilide infusion or overdrive pacing for the last AF/AFL episode in the 5 days prior to randomization
Amio: chronic treatment with amiodarone preceding randomization
Shd: structural heart disease
(page 63 EFC3153)

Table 48- Adjusted relative risk of time to adjudicated first AF/AFL recurrence within 12 months by prognostic factors

Treatment effect was significant when adjusted for pre-specified baseline prognostic factors. None of the 3 baseline prognostic factors had a significant effect on time to recurrence.

Relative risks in each prognostic factor subcategory (yes/no) are summarized for the primary endpoint in following table.

Prognostic factor	Category	Number of patients				Unadjusted relative risk[a] Dronedarone/Placebo		
		Placebo		Dronedarone 800 mg				
		N	Nb of events	N	Nb of events	Relative risk	95% CI	p-value
Convsr	Yes	75	59	153	105	0.823	[0.598;1.133]	0.233
	No	126	96	258	167	0.764	[0.594;0.982]	0.03567
Amio	Yes	32	25	66	41	0.688	[0.418;1.134]	0.143
	No	169	130	345	231	0.800	[0.645;0.992]	0.04166
Shd	Yes	65	51	149	100	0.814	[0.581;1.141]	0.233
	No	130	98	261	172	0.794	[0.620;1.018]	0.069

a Determined from Cox regression model
Convsr: electrical cardioversion, ibutilide infusion or overdrive pacing for the last AF/AFL episode in the 5 days prior to randomization
Amio: chronic treatment with amiodarone preceding randomization
Shd: structural heart disease
(page 63 EFC31532)

Table 49- Unadjusted relative risk to adjudicated first AF/AFL recurrence within 12 months by prognostic factor subcategories

6.1.4.3.6. Secondary endpoints

AF/AFL related symptoms
Two patients in the dronedarone group, without indication of whether the recurrence was symptomatic, were considered asymptomatic in this analysis. Adjudicated first AF/AFL recurrence was associated with symptoms in 55.1% of patients in the dronedarone group, versus 61.3% in the placebo group. At the end of treatment, the intensity of symptoms were reported as significantly lower in the dronedarone group.

Ventricular rate assessed at time of adjudicated first AF/AFL recurrence
The following table summarizes HR assessed at the time of adjudicated first AF/AFL recurrence.

	Placebo (N=201)	Dronedarone 800 mg (N=411)
TTEM recording ECG method		
n	117	199
Median	115	100
Mean	117.5	102.3
SD	29.1	24.7
Min - Max	70 - 204	53 - 173
Whatever recording ECG method		
n	154	269
Median	109	95
Mean	112.1	99.5
SD	29.4	25.0
Min - Max	62 - 204	53 - 173

Note: Heart rate values obtained on only 1 RR interval are not taken into account
(page 67 EFC3153)

Table 50- Summary of heart rate (bpm) assessed at time of adjudicated first AF/AFL recurrence during study period up to Day 365

At time of first recurrence dronedarone patients had statistically lower mean HR (TTEM method, $p<0.0001$, ANOVA; but this is not clinically significant as it is not within the acceptable rate at rest of 60 to 80 bpm.

Pharmacokinetics
Dronedarone significantly lowered, by 29%, the risk of recurrence of AF/AFL considered between Day 5 midnight and 12 months post randomization. The median time to adjudicated first AF/AFL recurrence in the dronedarone group was 1.8-fold longer than in the placebo group.
The steady state of dronedarone and SR35021 plasma concentrations was reached by Day 7.

6.1.4.3.7. The Euridis Study Conclusions

Dronedarone 800 mg daily (400 mg BID) delayed the first symptomatic AF/AFL recurrence. Although it reduced the ventricular heart rate at the first recurrence, this was not clinically significant.

6.1.4.4. The ERATO Study (EFC4508)

This is a supportive study for ventricular rate control in permanent atrial fibrillation.

6.1.4.4.1. Primary endpoint

The results of the primary analysis of the primary endpoint are shown in following table.

		Placebo (N=89)	Dronedarone 800 mg (N=85)
Baseline	Mean	90.6	86.5
	SEM	1.5	1.4
D14	Mean	90.2	76.2
	SEM	1.5	1.4
Change from baseline(a)	Mean	0.7	-11.0
	95%CI(b)	[-1.9;3.3]	[-13.5;-8.5]
Treatment effect(a)	Mean	-11.7	
	95%CI(b)	[-14.8;-8.5]	
	p-value(b)	$22x10^{-14}$	

(a) Change from baseline and treatment effect (difference between Dronedarone 800 mg and Placebo groups) are adjusted for baseline heart rate value, age and type of baseline standard treatment (beta-blocker, heart rate lowering calcium antagonist, digitalis)
(b) Following multiple imputation technique using Rubin's rule [4 (4.7%) dronedarone and 2 (2.2%) placebo patients had missing data at baseline and were evaluated on Day 14, and 5 (5.9%) dronedarone and 5 (5.6%) placebo patients were evaluated at baseline and had missing data on Day 14, 1 (1.2%) dronedarone patient had missing data at baseline and on Day 14]
(page 57 EFC4508)

Table 51- 24-hour Holter heart rate (bpm)

The decrease from baseline in 24-hour Holter HR on Day 14 in the dronedarone group was significantly more pronounced than the change from baseline observed in the placebo group (ANCOVA, $p<0.0001$). The presence/absence at baseline of beta blockers, calcium antagonists and digitalis (each tested separately) had no significant effect on the primary endpoint analysis. However, this was not supported in the ADONIS and EURIDIS trials above.

6.1.4.4.2. Ventricular rate during exercise

		Placebo (N=89)	Dronedarone 800 mg (N=85)
Baseline	N	87	82
	Mean	131.6	124.6
	SEM	2.9	2.3
D14	N	84	75
	Mean	130.0	103.3
	SEM	2.9	2.3
Change from baseline(a)	N	84	74
	Mean	-2.2	-25.6
	95%CI	[-6.7;2.4]	[-30.1;-21.1]
Treatment effect(a)	Mean	-23.4	
	95%CI	[-28.9;-17.9]	
	p-value	$25x10^{-15}$	

(a) Change from baseline and treatment effect (difference between Dronedarone 800 mg and Placebo groups) are adjusted for baseline heart rate value, age and type of baseline standard treatment (beta-blocker, heart rate lowering calcium antagonist, digitalis)
(page 59 EFC4508)

Table 52- Heart rate at sub-maximal exercise (bpm)

		Placebo (N=89)	Dronedarone 800 mg (N=85)
Baseline	N	88	84
	Mean	162.4	152.6
	SEM	3.6	2.9
D14	N	86	76
	Mean	159.6	129.7
	SEM	3.7	3.1
Change from baseline(a)	N	86	76
	Mean	-2.9	-27.4
	95%CI	[-8.0;2.3]	[-32.5;-22.3]
Treatment effect(a)	Mean	-24.5	
	95%CI	[-30.8;-18.3]	
	p-value	$1x10^{-12}$	

(a) Change from baseline and treatment effect (difference between Dronedarone 800 mg and Placebo groups) are adjusted for baseline heart rate value, age and type of baseline standard treatment (beta-blocker, heart rate lowering calcium antagonist, and digitalis)
(page 59 EFC4508)

Table 53- Heart rate at maximal exercise (bpm)

6.1.4.4.3. The Erato Study Conclusions

Dronedarone 800 mg daily (400 mg BID) significantly decreased HR at steady state (Day 14) and long term (Month 4), compared with placebo. On Day 14, while decreases from baseline in HR at sub-maximal and maximal exercise were significantly greater with dronedarone versus

placebo, the changes from baseline in maximal exercise duration were not different between the 2 treatment groups. This study confirms the lack of efficacy of dronedarone in ventricular rate control in patients with atrial fibrillation.

6.1.4.5. The DAFNE Study (DRI3550)

This was a dose-ranging study of the efficacy and safety of dronedarone for the maintenance of sinus rhythm in patients undergoing cardioversion for atrial fibrillation.

6.1.4.5.1. Results
There was no statistically significant dose effect was observed in the number of shocks or in the energy necessary to obtain sinus rhythm.

	Cox's model results p-value		
Comparison	**Treatment group**	**Covariate SHD**	**Covariate AFD**
800 mg versus placebo	0.0010	0.4137	0.6043
1200 mg versus placebo	0.8106	0.5019	0.3439
1600 mg versus placebo	0.1209	0.0860	0.0923

SHD = presence of structural heart disease, AFD = duration of the current AF episode
(page 79 DRI3550)

Table 54- Time to Atrial Fibrillation Recurrence - Comparison of Each Treatment Group versus Placebo:

A highly statistically significant treatment effect was observed in the 800 mg group (p = 0.0010). No statistically significant effects were observed in the covariate analysis of SHD or AFD.

6.1.4.5.1 Conclusions
In this study there was no dronedarone dose effect for maintenance of sinus rhythm. The lack of dose effect cannot be explained by any pharmacokinetic related issues. However, dronedarone 800 mg/day (400 mg. b.i.d.) was superior to placebo for this endpoint. The sponsor should consider the implementation of another controlled study with a wider dose range (e.g. 50mg bid to 800mg).

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

In the Andromeda Study among the patients on the study drug dronedarone, there were more deaths, more hospitalizations and more hospitalizations for acute cardiovascular reasons than in the patients on placebo. Although the Sponsor attributes this increase in mortality and morbidity to the lack of ACE inhibitors or Angiotensin II receptor antagonists in the dronedarone patients, these reviewers do not concur with the sponsor's conclusions. The percentage for both groups receiving ACE inhibitors or Angiotensin II receptor antagonists was similar, dronedarone 93.5% and placebo 94.3%, during the study.

In the Adonis study dronedarone 800 mg daily (400 mg BID) significantly delayed the first AF/AFL recurrence. It also delayed the symptomatic first recurrence. However, these reviewers disagree with the sponsor that dronedarone significantly reduced ventricular rate at the time of first recurrence. In the Euridis study which was identical to the Adonis, dronedarone 800 mg daily (400 mg BID) delayed the first symptomatic AF/AFL recurrence. Although it reduced the ventricular heart rate at the first recurrence, this was not clinically significant.

In the Erato study dronedarone 800 mg daily (400 mg BID) significantly decreased HR at steady state (Day 14) and long term (Month 4), compared with placebo. On Day 14, while decreases from baseline in HR at sub-maximal and maximal exercise were significantly greater with dronedarone versus placebo, the changes from baseline in maximal exercise duration were not different between the 2 treatment groups. This study confirms the lack of efficacy for dronedarone in ventricular rate control in atrial fibrillation.

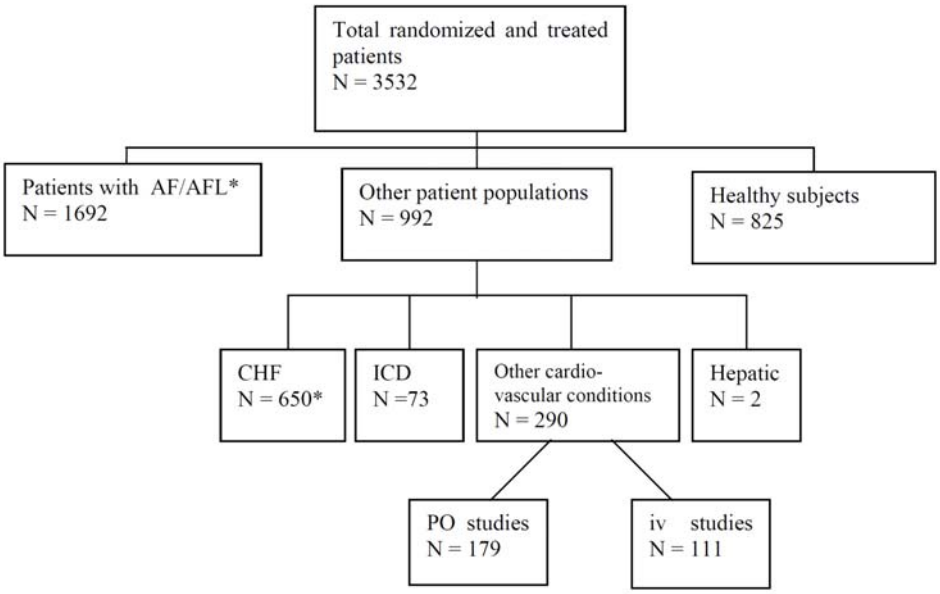
In the Dafne study there was no dronedarone dose effect for maintenance of sinus rhythm. The lack of dose effect cannot be explained by any pharmacokinetic related issues. However, dronedarone 800 mg/day (400 mg b.i.d.) was superior to placebo for the maintenance of sinus rhythm. We concur with Dr. Williams, recommendations that the sponsor should consider the implementation of another controlled study with a wider dose range (e.g. 50mg bid to 800mg).

Before dronedarone can be shown to be safe and efficacious, the Athena Study (EFC5555) must be completed with favorable results. This study, "A Placebo-Controlled, Double-blind, Parallel Arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of Cardiovascular Hospitalization or Death from any cause in patients with atrial fibrillation/atrial flutter (AF/AFL)," plans to enroll almost 4000 patients 70 years old or older.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This safety review is essentially divided into three sections: The Andromeda Study which included patients with congestive heart failure (CHF), the studies pertaining to atrial fibrillation/flutter (AF/AFL), and the studies in normal volunteers. An overview of all the studies included for safety is shown in the following diagram.



*23 patients in EFC4966/ANDROMEDA and 11 patients in EFC4508/ERATO, from centers 616004 and 616003 respectively, are counted in this figure; hereafter they are excluded from all analyses presented (unless otherwise specified) due to a major violation in GCP which raised doubts about the integrity of the data from these centers.
(page 312 Module 2.7.4 Summary)

Figure 10- Overall disposition of subjects/patients in the completed clinical studies

7.1.1 Deaths

7.1.1.1. Deaths in the ANDROMEDA study (EFC4966)
The primary objective of this study was to evaluate whether dronedarone reduces death from any cause or hospitalizations for worsening heart failure in patients with moderate to "severe" congestive heart failure (CHF) and left ventricular dysfunction (LVD), when added to usual evidence-based treatments for CHF, over a minimum period of 12 months as compared to placebo. A secondary objective was to evaluate whether dronedarone reduces death from any cause. Another secondary objective was whether dronedarone reduces arrhythmic/sudden death.

7.1.1.1.1 Analysis of primary endpoint: death or hospitalization for worsening of heart failure
The results of the primary analysis which was death or hospitalization for worsening of heart failure up to January 16, 2003 are summarized in the following table. This is a very troublesome table showing that dronedarone increased by 38% the risk of death or hospitalization for heart failure as compared to placebo.

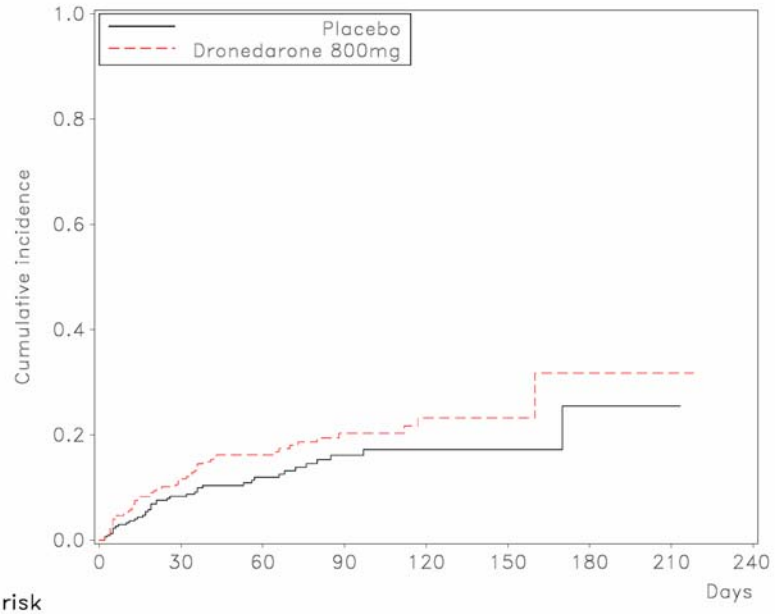
	Placebo (N=317)	**Dronedarone 800 mg (N=310)**
Number of patients who died or who have been hospitalized for worsening heart failure	40	53
Relative risk[a]	1.38	
95% CI[a]	[0.918 ; 2.088]	
Log-rank's test result (p-value)	0.118	

a Determined from unadjusted Cox regression model
(page 67 EFC4966)

Table 55- Analysis of time from randomization to death or hospitalization for worsening of heart failure up to January 16, 2003 (excluding center 616004)

All patients randomized in center 616004 (n = 23) were excluded from the main analysis population by the Sponsor due to a major violation in good clinical practice (GCP) documented in this center, raising doubts about the integrity of the data provided by this center. In Supplement No. 015, the sponsor states there were 23 patients in this center. Eleven patients were randomized to receive dronedarone and 12 were in the placebo group. Among these patients none of them experienced hospitalization for worsening of heart failure or death up to January 16, 2003. Therefore, there was no primary efficacy event at this center.

The analysis of time from randomization to death or hospitalization for worsening of heart failure up to January 16, 2003 (excluding center 616004) is also shown in the Kaplan-Meier cumulative incidence curve below.



Nb exposed at risk								
Placebo	317	234	159	87	41	16	6	1
Dronedarone 800 mg	310	232	151	87	49	19	4	1

(page 67 EFC 4966)

Figure 11- Kaplan-Meier incidence curves to January 16, 2003 (excluding c. 616004)

Secondary supportive analysis of primary endpoint
The adjusted relative risks based on prognostic factors for the primary endpoint are summarized in the following table.

Prognostic factor	Risk	Adjusted relative risk[a]		
		Relative risk	95% CI	p-value
ACE inhibitor or A II receptor antagonist	Intake / No intake	0.32	[0.192 ; 0.520]	579E-8
Baseline creatinine clearance[b]	>= 50 ml/min / < 50 ml/min	0.46	[0.271 ; 0.793]	0.00499
Baseline NYHA	> II / II	1.75	[1.061 ; 2.881]	0.02823
Digitalis	Intake / No intake	1.58	[1.024 ; 2.423]	0.03876
Weight (Kg)	Continuous parameter	1.01	[0.996 ; 1.025]	0.150
Treatment	Dronedarone / Placebo	1.29	[0.841 ; 1.989]	0.241
Beta-blocker[c]	Intake / No intake	1.28	[0.799 ; 2.038]	0.308
Baseline WMI[d]	Continuous parameter	1.01	[0.388 ; 2.636]	0.983
Spironolactone	Intake / No intake	1.00	[0.649 ; 1.544]	0.996

Note: intake of medications has been analyzed as time dependent variable
a Determined from Cox regression model
b Creatinine clearance estimate using Cockroft formula
c Excluding Sotalol
d WMI is used to estimate LVEF, with LVEF = WMIx30 (5)
(page 68 EFC4966)

Table 56- Post hoc adjusted relative risk of death or hospitalization for worsening of heart failure by prognostic factors up to January 16, 2003 (excluding center 616004)

The following table shows the unadjusted relative risk of death or hospitalization for worsening of heart failure by prognostic factor subcategories up to January 16, 2003. In this table the patients with a higher baseline creatinine clearance have a greater risk with dronedarone than with placebo.

Prognostic factor	Category	Number of patients: Placebo N	Placebo Nb of events	Dronedarone 800 mg N	Dronedarone 800 mg Nb of events	Unadjusted relative risk[a] Dronedarone/Placebo: Relative risk	95% CI	p-value
ACE inhibitor or A II receptor antagonist	Intake	289	31	261	36	1.33	[0.821 ; 2.149]	0.247
	No intake [b]	28	9	49	17	0.99	[0.440 ; 2.226]	0.980
Baseline creatinine clearance	<50 ml/min	128	25	133	29	1.12	[0.658 ; 1.918]	0.671
	>=50 ml/min	179	13	168	21	1.85	[0.924 ; 3.714]	0.08244
Baseline NYHA	II	121	9	131	15	1.58	[0.689 ; 3.600]	0.281
	>II	196	31	179	38	1.34	[0.835 ; 2.156]	0.225
Digitalis	Intake	107	18	90	23	1.43	[0.770 ; 2.646]	0.258
	No intake [b]	210	22	220	30	1.37	[0.789 ; 2.372]	0.265
Weight	<78 kg	162	24	154	25	1.10	[0.629 ; 1.930]	0.735
	>=78 kg	155	16	156	28	1.85	[0.997 ; 3.421]	0.05114
Beta-blocker [c]	Intake	227	29	222	36	1.33	[0.813 ; 2.162]	0.259
	No intake [b]	90	11	88	17	1.52	[0.710 ; 3.256]	0.281
Baseline WMI	<1	181	18	145	29	2.05	[1.137 ; 3.687]	0.01698
	>=1	136	22	165	24	0.92	[0.513 ; 1.638]	0.770
Spironolactone	Intake	154	21	132	18	1.07	[0.570 ; 2.020]	0.827
	No intake [b]	163	19	178	35	1.66	[0.952 ; 2.909]	0.07413

a Determined from Cox regression
b No intake is co-medication either never taken or prematurely stopped (i.e. prior to endpoint or censoring date)
c Excluding Sotalol
(page 70 EFC4966)

Table 57- Unadjusted relative risk of death or hospitalization for worsening heart failure by prognostic factors up to January 16, 2003 (excluding center 616004)

A sensitivity analysis performed on all randomized and treated patients (including center 616004) is shown in the following table. This analysis supported the primary efficacy analysis which excluded center 616004. No deaths in the dronedarone treatment group were recorded at the center 616004.

	Placebo (N=329)	Dronedarone 800 mg (N=321)
Number of patients who died or who have been hospitalized for worsening heart failure	40	53
Relative risk[a]	1.38	
95% CI[a]	[0.918 ; 2.088]	
Log-rank's test result (p-value)	0.119	

a Determined from unadjusted Cox regression model
(page 125 EFC4966)

Table 58- Analysis of time from randomization to death or hospitalization for worsening heart failure up to 16 January 2003, including center 616004

7.1.1.1.2. Death from any cause

In the following table are the results of the analysis of death from any cause up to January 16, 2003. This is a very troublesome table showing that dronedarone significantly (p = 0.027) increased, by 113%, the risk of death from any cause as compared to placebo.

	Placebo (N=317)	**Dronedarone 800 mg (N=310)**
Number of patients who died	12	25
Relative risk[a]	2.13	
95% CI[a]	[1.071 ; 4.247]	
Log-rank's test result (p-value)	0.02717	

(page 71 EFC4966) (This analysis was confirmed by Dr. Valeria Freidlin)

Table 59- Analysis of death up to January 16, 2006, (excluding center 616004)

This analysis was confirmed by Dr. Valeria Freidlin. In this reviewer's analysis p = 0.025 in log-rank test and relative risk (hazard ratio) = 2.15 with the 95% CI (1.081, 4.28) was in favor of placebo.

The primary causes of death up to January 16, 2003, as adjudicated by the Critical Events Committee (CEC) are summarized in the following table. The majority of deaths in both treatment groups were of cardiovascular origin. This table shows among the dronedarone patients there is a worsening of congestive heart failure and an increase in documented arrhythmias.

	Placebo (N=12)	**Dronedarone 800 mg (N=25)**
Cardiovascular death	9 (75%)	24 (96%)
Myocardial infarction	2 (16.7%)	0 (0.0%)
Worsening CHF	2 (16.7%)	10 (40%)
Documented arrhythmia	2 (16.7%)	6 (24%)
Procedure related	0 (0.0%)	1 (4%)
Other cardiovascular reason	0 (0.0%)	2 (8%)
Presumed cardiovascular reason	3 (25%)	5 (20%)
Non cardiovascular death	2 (16.7%)	1 (4%)
Cancer	1 (8.3%)	1 (4%)
Other non cardiovascular reason [a]	1 (8.3%)	0 (0.0%)
Non adjudicated death [b]	1 (8.3%)	0 (0.0%)

(page 73 EFC4966)

Table 60- Number (%) of patients according to adjudicated primary cause of death up to January 16, 2003 (excluding center 616004)

In both treatment groups the majority of deaths were of cardiovascular origin. Within the dronedarone group, non-sudden deaths accounted for the majority of deaths as shown in the table below.

	Placebo (N=9)	Dronedarone 800 mg (N=24)
Sudden death unwitnessed	3 (33.3%)	3 (12.5%)
Sudden death witnessed	3 (33.3%)	7 (29.2%)
Non-sudden death	3 (33.3%)	14 (58.3%)

(page 73) EFC4966)

Table 61- Number (%) of patients according to adjudicated timing of cardiovascular deaths up to January 16, 2003 (excluding center 616004)

The Sponsor submitted the following post hoc covariate analyes which were not prespecified in the protocol. The table below summarizes the post hoc adjusted relative risk of death by prognostic factors up to January 16, 2003. According to the Sponsor, the most important risk factor for death was the absence of treatment with ACE inhibitor or Angiotensin II receptor antagonist in the dronedarone group. However, the reviewers believe these covariate analyses are difficult to interpret because: 1. the analyses were not prespecified and therefore are data driven; 2. ACE inhibitor and A II receptor antagonist intake were not baseline characteristics and therefore, this relationship cannot be determined; and 3.the Table 6 on page 26 shows that there was a very small (0.8 %) difference between the groups relative to treatment with ACE inhibitors or Angiotensin II receptor antagonists.

		Adjusted relative risk[a]		
Prognostic factor	Risk	Relative risk	95% CI	p-value
ACE inhibitor or A II receptor antagonist	Intake / No intake	0.21	[0.097 ; 0.432]	0.00003
Treatment	Dronedarone / Placebo	1.83	[0.887 ; 3.782]	0.102
Baseline creatinine clearance[b]	>= 50 ml/min / < 50 ml/min	0.65	[0.267 ; 1.604]	0.353
Beta-blocker[c]	Intake / No intake	0.79	[0.386 ; 1.624]	0.525
Weight (Kg)	Continuous parameter	0.99	[0.967 ; 1.018]	0.557
Baseline NYHA	> II / II	1.18	[0.555 ; 2.501]	0.669
Digitalis	Intake / No intake	1.10	[0.536 ; 2.268]	0.792
Baseline WMI[d]	Continuous parameter	1.18	[0.247 ; 5.666]	0.834
Spironolactone	Intake / No intake	1.05	[0.511 ; 2.170]	0.888

Note: intake of medications has been analyzed as time dependent variable
a Determined from Cox regression model
b Creatinine clearance estimate using Cockroft formula
c Excluding Sotalol
d WMI is used to estimate LVEF, with LVEF = WMIx30 (5)
(page 74 EFC4966)

Table 62- Post hoc adjusted relative risk of death by prognostic factors up to January 16, 2003 (excluding center 616004)

In the following table is the unadjusted relative risk by prognostic factor subcategories from randomization to death up to January 16, 2003. This table shows that in the unadjusted analysis, dronedarone treatment significantly increased the risk of death in patients with moderate to severe renal insufficiency (baseline creatinine clearance <50 mL/minute). Also, in the dronedarone group there was significantly increased death with more severe heart failure (NYHA class >II), in the patients with no intake of ACE inhibitor/AII receptor antagonist, or with spironolactone, and with baseline WMI <1.

In the main analysis population up to January 17, 2003, 34 dronedarone patients and 18 placebo patients died. This analysis was consistent with the analysis up to January 16, 2003; dronedarone significantly (p = 0.019) increased, by 96%, the risk of death.

		Number of patients				Unadjusted relative risk[a] Dronedarone/Placebo		
		Placebo		Dronedarone 800 mg				
Prognostic factor	Category	N	Nb of events	N	Nb of events	Relative risk	95% CI	p-value
ACE inhibitor or A II receptor antagonist	Intake	281	10	249	10	1.14	[0.472 ; 2.737]	0.774
	No intake [b]	36	2	61	15	5.06	[1.157 ; 22.177]	0.03131
Baseline creatinine clearance	<50 ml/min	128	6	133	17	2.70	[1.065 ; 6.867]	0.03644
	>=50 ml/min	179	5	168	6	1.36	[0.412 ; 4.492]	0.614
Beta-blocker [c]	Intake	221	7	209	12	1.85	[0.728 ; 4.699]	0.196
	No intake [b]	96	5	101	13	2.34	[0.834 ; 6.587]	0.106
Weight	<78 kg	162	9	154	14	1.63	[0.705 ; 3.768]	0.253
	>=78 kg	155	3	156	11	3.72	[1.035 ; 13.345]	0.04409
Baseline NYHA	II	121	5	131	7	1.28	[0.405 ; 4.029]	0.676
	>II	196	7	179	18	2.77	[1.156 ; 6.625]	0.02234
Digitalis	Intake	101	2	89	12	6.45	[1.443 ; 28.802]	0.01470
	No intake [b]	216	10	221	13	1.27	[0.555 ; 2.892]	0.574
Baseline WMI	<1	181	4	145	15	4.60	[1.526 ; 13.868]	0.00671
	>=1	136	8	165	10	1.05	[0.415 ; 2.674]	0.912
Spironolactone	Intake	150	6	134	8	1.58	[0.547 ; 4.552]	0.399
	No intake [b]	167	6	176	17	2.55	[1.007 ; 6.480]	0.04840

a Determined from Cox regression
b No intake is co-medication either never taken or prematurely stopped (i.e. prior to endpoint or censoring date)
c Excluding Sotalol
(page 75 EFC4966)

Table 63- Unadjusted relative risk by prognostic factor subcategories for death up to January 16, 2003, (excluding center 616004)

The analysis performed 6 months after discontinuation of inclusions and ongoing study

drug treatment, July 17, 2003, showed a similar number of deaths in both treatment groups: 42 patients in the dronedarone group, and 39 in the placebo group. The cumulative incidence curves are presented in the figure below. The number of deaths due to worsening heart failure was similar in both treatment groups: 15 patients in the dronedarone group, and 13 in the placebo group. To these reviewers the significance of this is unknown.

Analysis of the per protocol population supported the results of the main population analysis. In the table below is the efficacy response data of the secondary efficacy parameters per-protocol population up to January 16, 2003, regarding death from any cause.

Primary cause of death	Placebo (N=294)	Dronedarone 800 mg (N=278)
Total (a)	11	21
Missing cause	1 (9.1 %)	0 (0.0 %)
Cardiac death		
Sudden death - Witnessed	2 (18.2 %)	5 (23.8 %)
Sudden death - Alive within 24 H prior death	1 (9.1 %)	0 (0.0 %)
Sudden death - Arrhythmic death	1 (9.1 %)	0 (0.0 %)
Sudden death - Other	0 (0.0 %)	1 (4.8 %)
Worsening CHF	1 (9.1 %)	8 (38.1 %)
Cardiac procedure	0 (0.0 %)	1 (4.8 %)
Myocardial infarction	2 (18.2 %)	1 (4.8 %)
Other cardiac death	0 (0.0 %)	1 (4.8 %)
Vascular death		
Other vascular death	0 (0.0 %)	1 (4.8 %)
Non-cardiovascular death	2 (18.2 %)	2 (9.5 %)
Unknown cause	1 (9.1 %)	1 (4.8 %)

(page 3202, Appendix 16.2.6.2.2.1.1.7 EFC4966)

Table 64- Summary of local primary cause of death January 16, 2003, per protocol population

The above table shows the dronedarone patients had an increase in sudden death (probably an arrhythmia) and also shows a worsening of congestive heart failure. According to the Sponsor, among the arrhythmic/sudden deaths there were no reported cases of torsades de pointes.

The following table shows the efficacy response data of the secondary efficacy parameters of the per-protocol population a month later regarding death from any cause. This table reveals an increase in death from worsening of CHF.

Primary cause of death	Placebo (N=294)	Dronedarone 800 mg (N=278)
Total (a)	16	28
Missing cause	2 (12.5 %)	0 (0.0 %)
Cardiac death		
Sudden death - Witnessed	2 (12.5 %)	5 (17.9 %)
Sudden death - Alive within 24 H prior death	1 (6.3 %)	0 (0.0 %)
Sudden death - Arrhythmic death	2 (12.5 %)	0 (0.0 %)
Sudden death - Other	0 (0.0 %)	2 (7.1 %)
Worsening CHF	4 (25.0 %)	11 (39.3 %)
Cardiac procedure	0 (0.0 %)	1 (3.6 %)
Myocardial infarction	2 (12.5 %)	2 (7.1 %)
Other cardiac death	0 (0.0 %)	1 (3.6 %)
Vascular death		
Hemorrhagic stroke	0 (0.0 %)	1 (3.6 %)
Other vascular death	0 (0.0 %)	1 (3.6 %)
Non-cardiovascular death	2 (12.5 %)	3 (10.7 %)
Unknown cause	1 (6.3 %)	1 (3.6 %)

(page 3224 Appendix 16.2.6.2.2.2.1.7. EFC4966)

Table 65- Summary of local primary cause of death February 16, 2003, per protocol population

7.1.1.1.3 Listing of all deaths among patients receiving dronedarone in Andromeda Study

Table 66- Deaths among patients receiving dronedarone in Andromeda Study

Table (15.4.2) 2 - Listing of all deaths - randomized and treated patients population (Treatment as received – Dronedarone 800 mg)

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208101019		2003-01-17(2)	e	2003-11-14(303)							
208102001	*	2003-01-17(129)	c	2003-02-02(145)	P 3	General disorders and administration site conditions	Death (Death)	2003-02-02(145)	No	Presumed cardiovascular reason	Sudden death unwitnessed
208102003		2002-09-17(2)	e	2003-11-18(429)							
208102007		2002-10-13(12)	a b	2002-10-14(13)	T 2	General disorders and administration site conditions	Sudden death (Sudden death - unwittnessed)	2002-10-14(13)	No	Presumed cardiovascular reason	Sudden death unwitnessed
208103009	*	2002-10-14(20)	a b	2002-10-14(20)	T 2	Cardiac disorders	Cardiac failure (Worsening chf)	2002-10-14(20)	No	Worsening CHF	Non sudden death
208103017		2002-12-16(33)	a b	2002-12-16(33)	T 2	General disorders and administration site conditions	Sudden death (Sudden dead)	2002-12-16(33)	No	Documented arrhythmia	Sudden death witnessed
208104007		2003-01-17(36)	c	2003-02-16(66)	T 2	Cardiac disorders	Cardiac failure (Worsening heart failure)	2002-12-16(4)	No	Worsening CHF	Non sudden death
208105002		2002-08-27(8)	d	2003-02-18(183)	P 2	Cardiac disorders	Cardiac failure (Worsening heart failure)	2002-12-27(130)	No	Worsening CHF	Non sudden death

(page 150 EFC4966) continued

Table 66- continued

(continued)

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208105003	*	2002-10-15(41)	b	2002-11-01(58)	T 2	Cardiac disorders	Cardiac failure (Worsening heart failure)	2002-10-23(49)	No	Worsening CHF	Non sudden death
208106011		2002-11-13(3)	a b	2002-11-14(4)	T 2	Gastrointestinal disorders	Mesenteric occlusion (Mesentery thrombosis)	2002-11-14(4)	No	Other cardiovascular reason	Non sudden death
208108003		2003-01-17(139)	d	2003-06-07(280)	P 4	Cardiac disorders	Cardiac failure (Progression in heart failure)	2003-06-01(274)	No	Worsening CHF	Non sudden death
208108006		2002-12-26(112)	a b	2002-12-26(112)	T 2	Cardiac disorders	Cardiac failure (Worsening chf)	2002-12-09(95)	No	Documented arrhythmia	Sudden death witnessed
208111002	*	2002-09-09(28)	a b	2002-09-09(28)	T 2	Cardiac disorders	Ventricular tachycardia (Ventricular tachycardia (cardiac arrest (death)))	2002-09-07(26)	No	Documented arrhythmia	Sudden death witnessed
208112001		2002-09-11(30)	a b	2002-09-11(30)	T 2	General disorders and administration site conditions	Sudden death (Sudden death)	2002-09-11(30)	No	Presumed cardiovascular reason	Sudden death un-witnessed

Continued

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Table 66- continued

(continued)

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208112010		2002-11-01(5)	a b	2002-11-01(5)	T 2	Cardiac disorders	Myocardial infarction (Myocardial infarction)	2002-11-01(5)	No	Presumed cardiovascular reason	Sudden death unwitnessed
208114018		2003-01-17(45)	a c	2003-01-21(49)	T 2	Cardiac disorders	Cardiac failure (Worsening of heart failure)	2003-01-14(42)	No	Worsening CHF	Non sudden death
208114019		2003-01-17(40)	c	2003-02-04(58)	T 3	Cardiac disorders	Acute myocardial infarction (Ami worsening heart failure)	2003-01-24(47)	No	Procedure related	Non sudden death
208116008		2002-11-04(5)	a b	2002-11-10(11)	T 2	Cardiac disorders	Cardiac arrest (Cardiac arrest)	2002-11-10(11)	No	Presumed cardiovascular reason	Sudden death witnessed
208116011		2003-01-05(18)	c	2003-02-08(52)	P 3	Cardiac disorders	Cardiac failure (Worsening chf)	2003-02-01(45)	No	Presumed cardiovascular reason	Non sudden death
208118003		2003-01-01(45)	d	2003-07-01(226)	P 4	Cardiac disorders	Cardiogenic shock (Cardiogenic shock)	2003-06-29(224)	No	Presumed cardiovascular reason	Non sudden death
208121014		2003-01-15(2)	c	2003-01-27(14)	T 3	Renal and urinary disorders	Renal tubular disorder (Acute tubular interstitial nephropathy)	2003-01-17(4)	No	Worsening CHF	Non sudden death

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Table 66- continued

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208124007		2002-12-13(1)	d	2003-06-05(175)	P 4	Cardiac disorders	Acute myocardial infarction (Acute myocardial infarct)	2003-06-05(175)	No	Presumed cardiovascular reason	Sudden death unwitnessed
208126005		2003-01-17(155)	d	2003-06-14(303)	P 4	Cardiac disorders	Cardiac failure (Worsening heart failure)	2003-06-13(302)	No	Presumed cardiovascular reason	Non sudden death
208126010		2002-12-15(33)	a b	2002-12-23(41)	T 2	Cardiac disorders	Myocardial ischaemia (Ischaemic heart disease)	2002-12-09(27)	No	Procedure related	Non sudden death
208128001		2003-01-17(134)	d	2003-03-27(203)	P 4	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung neoplasm malignant (Lung cancer)	2003-03-27(203)	No	Cancer	
208129004		2002-09-09(19)	a b	2002-09-09(19)	T 2	Cardiac disorders	Ventricular fibrillation (Possibly ventricular fibrillation)	2002-09-09(19)	Yes	Documented arrhythmia	Sudden death witnessed
208129009		2003-01-16(73)	e	2003-07-22(260)	P 5	General disorders and administration site conditions	Death (Dead at admission to hospital)	2003-07-22(260)	No	Presumed cardiovascular reason	Sudden death un-witnessed

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Table 66- continued

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208130011		2003-01-16(43)	e	2003-07-23(231)	P 4	Infections and infestations	Sepsis (Sepsis)	2003-07-04(212)	No	Primary infection disease	
208131001	*	2002-10-02(21)	b	2002-10-19(38)	P 2	Cardiac disorders	Cardiac disorder (Terminal heart disease)	2002-10-19(38)	No	Worsening CHF	Non sudden death
208131003		2002-12-12(63)	d	2003-03-10(151)	P 4	Cardiac disorders	Cardiac arrest (Asystole)	2003-03-10(151)	No	Documented arrhythmia	Sudden death witnessed
208131011		2003-01-16(7)	c	2003-02-06(28)	T 2	Nervous system disorders	Cerebrovascular accident (Apoplexia cerebri)	2003-01-14(5)	No	Stroke	Non sudden death
208133010	*	2003-01-15(6)	a c	2003-01-21(12)	T 2	Nervous system disorders	Cerebrovascular accident (Stroke / apoplexia cerebri)	2003-01-14(5)	No	Stroke	Non sudden death
208137001		2002-10-31(81)	b	2002-12-20(131)	T 2	Investigations	Blood creatinine increased (Increased creatinin)	2002-08-19(8)	No	Worsening CHF	Non sudden death
			b	2002-12-20(131)	P 2	Cardiac disorders	Cardiac failure (Worsening of heart failure)	2002-12-17(128)	No	Worsening CHF	Non sudden death

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Table 66- continued

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208137006		2003-01-16(18)	a c	2003-01-20(22)	T 3	General disorders and administration site conditions	Sudden death (Sudden death. found dead in his chair, in hospital, section showed pneumonia)	2003-01-20(22)	No	Primary infection disease	
528002004		2003-01-16(94)	d	2003-05-27(225)	P 4	Cardiac disorders	Ventricular fibrillation (Ventricle fibrillation)	2003-05-27(225)	No	Documented arrhythmia	Sudden death witnessed
578304003		2002-10-09(13)	a b	2002-10-10(14)	T 2	Cardiac disorders	Cardiac failure (Increasing heart failure)	2002-10-09(13)	No	Worsening CHF	Non sudden death
578304006		2003-01-10(72)	a b	2003-01-15(77)	T 2	Infections and infestations	Bronchitis (Bronchitis)	2002-12-19(50)	No	Cancer	
616002003		2002-10-21(21)	b b	2002-11-22(53) 2002-11-22(53)	T 2 T 2	Cardiac disorders Respiratory, thoracic and mediastinal disorders	Cardiac failure (Worsening of heart failure) Respiratory failure (Respiratory insufficiency)	2002-10-22(22) 2002-10-25(25)	Yes No	Worsening CHF Worsening CHF	Non sudden death Non sudden death
616004012	1 *	2003-01-16(50)	c	2003-02-15(80)	P 3	Cardiac disorders	Cardiopulmonary failure (Cardio-pulmonary insufficiency)	2003-02-04(69)	No	Procedure related	Non sudden death

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Table 66- continued

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
752206001		2002-12-12(71)	a b	2002-12-14(73)	T 2	Gastrointestinal disorders	Peritonitis (Peritonitis)	2002-12-12(71)	No	Other cardiovascular reason	Non sudden death
752210007		2002-12-20(12)	a b	2002-12-28(20)	T 2	General disorders and administration site conditions	Sudden death (Sudden death)	2002-12-28(20)	No	Presumed cardiovascular reason	Non sudden death
752211001		2002-12-11(42)	a b	2002-12-19(50)	T 2	Cardiac disorders	Cardiac failure (Worsening heart failure)	2002-11-20(21)	No	Worsening CHF	Non sudden death
752213001		2002-10-11(1)	a b	2002-10-12(2)	T 2	Cardiac disorders	Cardiac arrest (Cardiac arrest)	2002-10-12(2)	Yes	Documented arrhythmia	Sudden death witnessed
752215002		2002-11-27(50)	a b	2002-11-27(50)	T 2	Cardiac disorders	Cardiac failure (Worsening heart failure)	2002-11-13(36)	No	Worsening CHF	Non sudden death
752215004		2002-11-19(2)	a b	2002-11-19(2)	T 2	Cardiac disorders	Cardiac failure (Worsening heart failure)	2002-11-19(2)	No	Worsening CHF	Non sudden death

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Table 66- continued

(continued)

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
752220003		2002-12-14(68)	a b	2002-12-14(68)	T 2	Cardiac disorders	Cardiac arrest (Cardiac arrest)	2002-12-14(68)	No	Documented arrhythmia	Sudden death witnessed
752220004		2002-12-16(62)	a b	2002-12-16(62)	T 2	Cardiac disorders	Cardiac failure (Worsening chf)	2002-12-13(59)	No	Worsening CHF	Non sudden death

Note: For all deaths, only AEs leading to death are listed. Deceased patients with no AE leading to death are also listed.
Day 1 is the day of first study drug intake, ## As assessed by the investigator, *: Patient excluded from per-protocol population, I: Patient from center 616004, N: AE occurred before 1st admin., T: AE occurred between 1st admin. and last admin. + 10 days, P: AE occurred after last admin. + 10 days, 2: AE occurred between 1st admin. and 16/01/2003, 3: AE occurred between 17/01/2003 and 17/02/2003, 4: AE occurred between 18/02/2003 and 17/07/2003, 5: AE occurred after 17/07/2003, a: Death between 1st admin. and last admin. + 10 days, b: Death between 1st admin. and 16/01/2003, c: Death between 17/01/2003 and 17/02/2003, d: Death between 18/02/2003 and 17/07/2003, e: Death after 17/07/2003
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7.1.1.1.4 Deaths among the patients receiving placebo

Table 67- List of deaths among the patients receiving placebo

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208102009		2002-11-18(39)	b	2002-12-29(80)	T 2	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Prostate cancer (Malignant prostate cancer)	2002-11-18(39)	No	Cancer	
208102019		2003-01-22(14)	d	2003-05-29(141)							
208103002		2002-07-28(4)	a b	2002-07-29(5)	T 2	Cardiac disorders	Myocardial infarction (Myocardial infarction)	2002-07-29(5)	No	Myocardial infarction	Non sudden death
208103005		2002-09-09(13)	c	2003-01-17(143)							
208103011		2002-10-15(6)	a b	2002-10-15(6)	T 2	General disorders and administration site conditions	Asthenia (Weakness)	2002-10-14(5)	No	Worsening CHF	Sudden death witnessed
			a b	2002-10-15(6)	T 2	Cardiac disorders	Cardiac arrest (Asystole)	2002-10-15(6)	No	Worsening CHF	Sudden death witnessed
208103024		2003-01-17(12)	d	2003-05-15(130)	P 4	General disorders and administration site conditions	Sudden death (Sudden death)	2003-05-15(130)	No	Documented arrhythmia	Sudden death unwitnessed

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Table 67- continued

Table (15.4.2) 1 - Listing of all deaths - randomized patients population (treatment as received - placebo) (continued)

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208105005		2002-12-08(75)	d	2003-03-16(173)	P 4	Vascular disorders	Hypotension (Hypotension)	2003-03-12(169)	No	Worsening CHF	Non sudden death
			d	2003-03-16(173)	P 4	Cardiac disorders	Cardiac failure (Worsening heart failure)	2003-03-12(169)	No	Worsening CHF	Non sudden death
208105007		2003-01-17(66)	c	2003-02-12(92)	T 3	Cardiac disorders	Cardiac failure (Worsening heart failure)	2003-01-20(69)	No	Worsening CHF	Non sudden death
208106002		2003-01-17(157)	d	2003-03-11(210)	N	Investigations	Blood creatinine increased (High p-creatininium 347 mcmol/l)	2002-08-13(0)	No	Worsening CHF	Non sudden death
			d	2003-03-11(210)	P 4	Cardiac disorders	Cardiac failure (Worsening chf)	2003-03-04(203)	No	Worsening CHF	Non sudden death
208107002		2002-12-03(89)	d	2003-04-23(230)							
208107011		2003-01-16(36)	d	2003-03-25(104)	P 4	Metabolism and nutrition disorders	Diabetic foot (Worsening of diabetic wound)	2003-03-06(85)	No	Presumed cardiovascular reason	Sudden death witnessed
208110007		2003-01-17(121)	e	2003-07-27(312)	P 5	Cardiac disorders	Cardiac failure (Worsening heart failure)	2003-07-26(311)	No	Worsening CHF	Non sudden death

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Table 67- continued

Table (15.4.2) 1 - Listing of all deaths - randomized patients population (treatment as received - placebo) (continued)

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208111015		2003-01-16(39)	d	2003-03-20(102)	P 4	Vascular disorders	Hypotension (Hypotension)	2003-03-18(100)	No	Worsening CHF	Non sudden death
			d	2003-03-20(102)	P 4	Respiratory, thoracic and mediastinal disorders	Pulmonary oedema (Pulmonary oedema)	2003-03-19(101)	No	Worsening CHF	Non sudden death
208111015		2003-01-16(39)	d	2003-03-20(102)	P 4	Cardiac disorders	Cardiac failure (Worsening heart failure)	2003-03-19(101)	No	Worsening CHF	Non sudden death
208112009		2003-01-17(82)	d	2003-03-08(132)	P 4	Cardiac disorders	Cardiac arrest (Cardiac arrest)	2003-03-08(132)	No	Documented arrhythmia	Sudden death witnessed
208114005		2002-12-21(75)	a b	2002-12-22(76)	T 2	Vascular disorders	Gangrene (Bed sore leading to gangrena right foot)	2002-10-29(22)	No	Other non cardiovascular reason	
208114016		2003-01-17(58)	a c	2003-01-20(61)	T 3	Cardiac disorders	Ventricular fibrillation (Ventricular fibrillation)	2003-01-20(61)	No	Documented arrhythmia	Sudden death witnessed
208114020		2003-01-17(30)	d	2003-04-07(110)	P 4	Cardiac disorders	Ventricular fibrillation (Ventricular fibrillation)	2003-04-07(110)	No	Documented arrhythmia	Sudden death witnessed

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Table 67- continued

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208115007		2003-01-17(52)	e	2003-07-31(247)	P 4	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung neoplasm (Right side central lung tumor with compression of trachea)	2003-07-15(231)	No	Presumed non cardiovascular reason	
208117015	*	2003-01-17(3)	d	2003-03-28(73)	P 4	Cardiac disorders	Cardiac failure congestive (Increasing congestive heart failure)	2003-03-20(65)	No	Worsening CHF	Non sudden death
208119008		2002-12-09(26)	d	2003-03-03(110)	P 4	General disorders and administration site conditions	Sudden death (Sudden death)	2003-03-03(110)	No	Presumed cardiovascular reason	Sudden death witnessed
208120001		2002-09-03(20)	d	2003-04-20(249)							
208121004	*	2002-10-25(12)	c	2003-01-25(104)	P 2	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to central nervous system (Metastasis cerebrum)	2003-01-12(91)	No	Cancer	
208125008		2003-01-17(45)	d	2003-06-06(185)	P 4	General disorders and administration site conditions	Sudden death (Sudden death)	2003-06-06(185)	No	Presumed cardiovascular reason	Sudden death unwitnessed

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Table67- continued

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208126003		2002-12-31(170)	a b	2002-12-31(170)	T 2	Cardiac disorders	Cardiac arrest (Cardiac arrest)	2002-12-31(170)	No	Documented arrhythmia	Sudden death witnessed
208126009	*	2002-12-03(36)	d	2003-02-21(116)	P 4	Cardiac disorders	Cardiac arrest (Cardiac arrest)	2003-02-21(116)	No	Worsening CHF	Non sudden death
208126011		2003-01-09(53)	a b	2003-01-09(53)	T 2	Cardiac disorders	Cardiac arrest (Cardiac arrest)	2003-01-09(53)	No	Presumed cardiovascular reason	Sudden death unwitnessed
208131002		2002-12-24(78)	a b	2002-12-25(79)	T 2	Cardiac disorders	Cardiac failure (Worsening heart failure)	2002-12-12(66)	No	Worsening CHF	Non sudden death
208132004	*	2003-01-17(82)	d	2003-04-27(182)	P 4	Injury, poisoning and procedural complications	Femur fracture (Collum femoris fracture)	2003-04-22(177)	No	Worsening CHF	Non sudden death
208133009	*	2003-01-14(5)	d	2003-05-11(122)	P 4	Cardiac disorders	Cardiac arrest (Cardiac arrest)	2003-05-11(122)	No	Documented arrhythmia	Sudden death witnessed
348002004		XXXX-XX-XX(13)	a b	2002-12-02(13)	T 2	Cardiac disorders	Myocardial infarction (Myocardial infarction)	2002-12-02(13)	No	Myocardial infarction	Non sudden death

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Table 67- continued

Table (13.4.2) 1 - Listing of all deaths - randomized patients population (treatment as received = placebo) (continued)

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
348003004		2003-01-17(80)	a c	2003-01-25(88)	T 3	Cardiac disorders	Cardiac failure (Worsening of congestive heart failure)	2003-01-20(83)	No	Worsening CHF	Non sudden death
578303001		2003-01-17(137)	d	2003-05-06(246)	P 4	Cardiac disorders	Myocardial infarction (Myocardial infarction)	2003-05-05(245)	No	Myocardial infarction	Non sudden death
578307002		2003-01-13(36)	a b	2003-01-13(36)	T 2	General disorders and administration site conditions	Sudden death (Sudden death)	2003-01-13(36)	No	Presumed cardiovascular reason	Sudden death unwitnessed
616002008	*	2002-12-13(26)	a b	2002-12-13(26)	T 2	General disorders and administration site conditions	Sudden death (Sudden death)	2002-12-13(26)	Yes	Presumed cardiovascular reason	Sudden death unwitnessed
752205003		2003-01-17(65)	d	2003-03-05(112)	P 4	Vascular disorders	Shock (Circulation failure due to heart failure and multiple infarctions)	2003-03-03(110)	No	Worsening CHF	Non sudden death
752206002		2002-10-31(22)	b	2003-01-06(89)							
752206005		2003-01-16(57)	d	2003-02-25(97)	P 3	Cardiac disorders	Cardiac failure (Worsening chf)	2003-02-11(83)	No	Worsening CHF	Non sudden death

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Table 67- continued

Table (13.4.2) 1 - Listing of all deaths - randomized patients population (treatment as received = placebo) (continued)

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
752210005		2003-01-02(35)	d	2003-05-19(172)	P 4	Cardiac disorders	Myocardial infarction (Myocardial infarction)	2003-05-19(172)	No	Myocardial infarction	Non sudden death
752215003		2002-10-21(7)	a b	2002-10-21(7)	T 2	General disorders and administration site conditions	Sudden death (Sudden death)	2002-10-21(7)	No	Documented arrhythmia	Sudden death witnessed
752216002		2003-01-16(65)	d	2003-06-01(201)	P 4	General disorders and administration site conditions	Multi-organ failure (Multi organ failure probably due to liver malignancy)	2003-05-29(198)	No	Cancer	
752217002		2003-01-16(56)	a c	2003-01-20(60)	T 3	General disorders and administration site conditions	Multi-organ failure (Multi organ failure)	2003-01-20(60)	No	Worsening CHF	Non sudden death

Note: For all deaths, only AEs leading to death are listed. Deceased patients with no AE leading to death are also listed. # Day 1 is the day of first study drug intake, ## As assessed by the investigator, *: Patient excluded from per-protocol population, I: Patient from center 616004, N: AE occurred before 1st admin., T: AE occurred between 1st admin. and last admin. + 10 days, P: AE occurred after last admin. + 10 days, 2: AE occurred between 1st admin. and 16/01/2003, 3: AE occurred between 17/01/2003 and 17/02/2003, 4: AE occurred between 18/02/2003 and 17/07/2003, 5: AE occurred after 17/07/2003, a: Death between 1st admin. and last admin. + 10 days, b: Death between 1st admin. and 16/01/2003, c: Death between 17/01/2003 and 17/02/2003, d: Death between 18/02/2003 and 17/07/2003, e: Death after 17/07/2003
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7.1.2 Other Serious Adverse Events

7.1.2.1. Patients in the ANDROMEDA Study

The following table provides an overview of the Treatment Emergent Adverse Events (TEAE) during this study.

	Placebo (N=317)		Dronedarone 400 mg BID (N=310)	
Patients with any TEAE (a)	214	(67.5%)	220	(71.0%)
Patients with any serious TEAE	118	(37.2%)	128	(41.3%)
Deaths (b)	12	(3.8%)	25	(8.1%)
Patients permanently discontinued study drug for any TEAE (a)(c)(d)	28	(8.8%)	58	(18.7%)

(a) Including SAEs
(b) Patients who died from first study drug intake up to the 16 January 2003
(c) According to the 'End of treatment' form
(d) Whatever the period
(page 360 Module 2.7.4 Summary)

Table 68- Overview of main treatment emergent events [number (%) of patients] up to January 16, 2003

This table show that among the patients treated with dronedarone there were more treatment emergent adverse events, more patients with serious treatment emergent adverse events, more deaths, and more patients who permanently discontinued their drug for treatment emergent adverse events compared to placebo.

Hospitalization for worsening of heart failure
An analysis of the time to first hospitalization for worsening heart failure up to January 16, 2003, is summarized in the following table. Although the Sponsor states that "There was no statistically significant difference between groups in first hospitalization for worsening heart failure," it is apparent from this table that more patients on dronedarone were hospitalized (39 = 13%) as compared to placebo (31 = 10%).

	Placebo (N=317)	Dronedarone 800 mg (N=310)
Number of patients hospitalized for worsening heart failure	31	39
Log-Rank	0.271	

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Table 69- Analysis of time to first hospitalization for worsening of heart failure up to January 16, 2003 (excluding center 616004)

The following table provides an analysis of acute cardiovascular reasons from randomization to the first hospitalization up to January 16, 2003. This table shows that more dronedarone patients (71 = 23%) were hospitalized for cardiovascular reasons as compared to placebo (50 = 16%).

	Placebo (N=50)	**Dronedarone 800 mg (N=71)**
Worsening CHF	30 (60%)	35 (49.3%)
Myocardial ischemia	8 (16%)	13 (18.3%)
Ventricular arrhythmia	2 (4%)	3 (4.2%)
Supraventricular arrhythmia	1 (2%)	4 (5.6%)
Stroke	3 (6%)	4 (5.6%)
Other cardiovascular reason	4 (8%)	9 (12.7%)
Presumed cardiovascular reason	2 (4%)	3 (4.2%)

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Table 70- Number (%) of patients according to adjudicated primary cause of the first hospitalization for acute cardiovascular reasons up to January 16, 2003 (excluding c.616004)

Among patients with a recent "severe" episode of CHF, there were marked differences in frequency between the dronedarone treated patients and the placebo group for cardiac disorders, GI disorders and laboratory findings. The most common treatment emergent adverse events (with incidence ≥10% in at least 1 treatment group) in this population of patients with a recent severe episode of CHF were cardiac disorders, GI disorders, laboratory results, infections and infestations, and respiratory thoracic and mediastinal disorders. Among the TEAEs with an incidence ≥ 2%, there were more cardiac failure and blood creatinine increased in the dronedarone 400 mg BID group. This is shown in the following table.

Table 71- Number (%) of patients with TEAEs for preferred term with incidence ≥ 2% in either treatment group presented by system organ class up to January 16, 2003

MedDRA (6.1) Organ Class **Preferred term**	**Placebo (N=317)**		**Dronedarone 400 mg BID (N=310)**	
Any Class any event	214	(67.5%)	220	(71.0%)
Cardiac disorders				
Any event	76	(24.0%)	105	(33.9%)
Cardiac failure	24	(7.6%)	46	(14.8%)
Angina pectoris	11	(3.5%)	12	(3.9%)
Ventricular tachycardia	3	(0.9%)	9	(2.9%)
Atrial fibrillation	12	(3.8%)	3	(1.0%)
Gastrointestinal disorders				
Any event	42	(13.2%)	65	(21.0%)
Diarrhoea	15	(4.7%)	26	(8.4%)
Nausea	9	(2.8%)	14	(4.5%)
Investigations				
Any event	28	(8.8%)	54	(17.4%)
Blood creatinine increased	7	(2.2%)	35	(11.3%)
Infections and infestations				
Any event	50	(15.8%)	46	(14.8%)
Pneumonia	23	(7.3%)	14	(4.5%)
Respiratory, thoracic and mediastinal disorders				
Any event	39	(12.3%)	46	(14.8%)
Cough	12	(3.8%)	15	(4.8%)
Dyspnoea	9	(2.8%)	9	(2.9%)
Nervous system disorders				
Any event	27	(8.5%)	28	(9.0%)
Dizziness	12	(3.8%)	11	(3.5%)
Vascular disorders				
Any event	11	(3.5%)	19	(6.1%)
Hypotension	4	(1.3%)	10	(3.2%)
Metabolism and nutrition disorders				
Any event	18	(5.7%)	18	(5.8%)
General disorders and administration site conditions				
Any event	17	(5.4%)	17	(5.5%)
Musculoskeletal and connective tissue disorders				
Any event	16	(5.0%)	15	(4.8%)
Skin and subcutaneous tissue disorders				
Any event	11	(3.5%)	14	(4.5%)
Renal and urinary disorders				
Any event	8	(2.5%)	14	(4.5%)
Psychiatric disorders				
Any event	9	(2.8%)	11	(3.5%)

Continued

Table 71- continued

MedDRA (6.1) Organ Class Preferred term	Placebo (N=317)		Dronedarone 400 mg BID (N=310)	
Blood and lymphatic system disorders				
Any event	5	(1.6%)	11	(3.5%)
Anaemia	5	(1.6%)	10	(3.2%)
Injury, poisoning and procedural complications				
Any event	2	(0.6%)	9	(2.9%)
Reproductive system and breast disorders				
Any event	1	(0.3%)	4	(1.3%)
Eye disorders				
Any event	4	(1.3%)	2	(0.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Any event	7	(2.2%)	1	(0.3%)
Ear and labyrinth disorders				
Any event	0	(0%)	1	(0.3%)
Surgical and medical procedures				
Any event	10	(3.2%)	0	(0%)
Hepatobiliary disorders				
Any event	6	(1.9%)	0	(0%)

Note: A patient can have AEs in more than one system organ class and in more than one preferred term
(pages 361-2 Module 2.7.4 Summary)

7.1.1.2 Deaths in the AF/AFL Studies (ADONIS, EURIDIS, ERATO and DAFNE)

7.1.1.2.1. Baseline characteristics of AF/AFL patients
An overview of the all the patients in the AF/AFL program is shown in the diagram below.

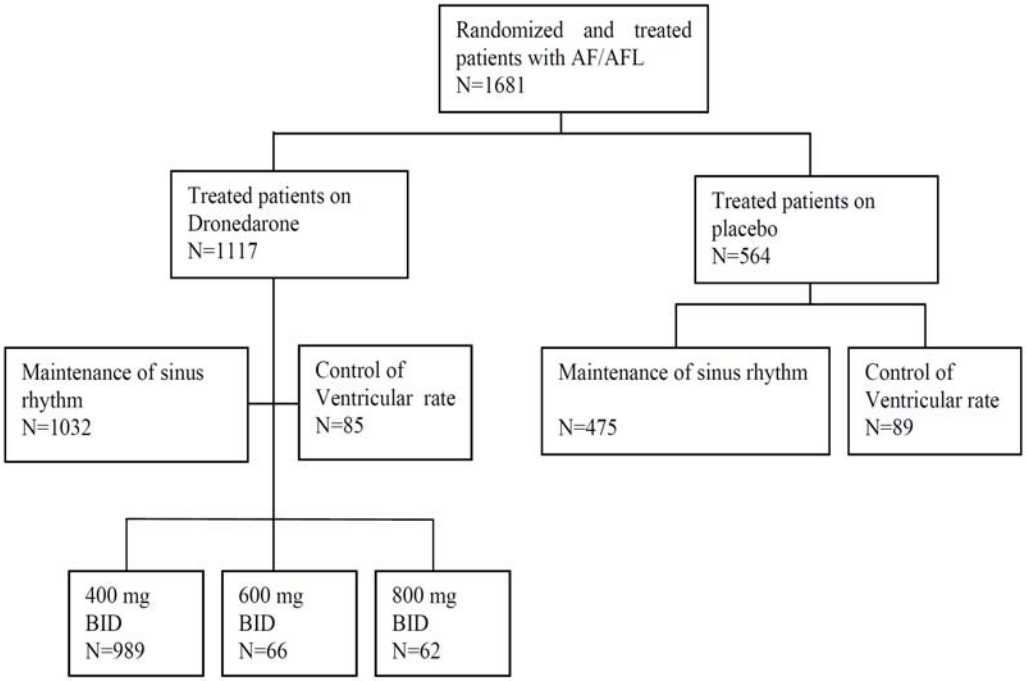

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Figure 12- Patient disposition in patients with AF/AFL

The following table summarizes the number of randomized patients exposed to treatment according to study day in patients with AF/AFL.

Days	Placebo	Dronedarone 400 mg BID	Dronedarone 600 mg BID	Dronedarone 800 mg BID
D1	564	989	66	62
D30	446	833	23	23
D60	420	782	21	20
D120	374	724	19	16
D180	316	661	12	9
D270	235	546	0	0
D360	100	283	0	0

Note: Protocols: DRI3550 (DAFNE), EFC3153 (EURIDIS), EFC4788 (ADONIS), EFC4508 (ERATO)
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Table 72- Number of patients who were on study drug from Day 1 to Day 360

This clinical reviewer feels that only 283 patients treated for a year on a drug that will be utilized for a chronic illness is a very small number to evaluate safety of a new drug for patients that will be exposed long term. This may also be why the Sponsor did not see some of the side effects that are seen with amiodarone because of this low number of patients exposed to the drug for 360 days.

An overview of all the treated patients for AF /AFL is shown in the table below.

Parameter		Placebo (N=564)	Dronedarone 400 mg BID (N=989)	Dronedarone 600 mg BID (N=66)	Dronedarone 800 mg BID (N=62)	Total (N=1681)
Age (years)	n	564	989	66	62	1681
	Median	65	65	64	66	65
	Mean	63.3	63.6	64.2	63.7	63.5
	SD	10.7	10.8	8.6	10.8	10.7
	Min - Max	30 - 87	20 - 88	39 - 79	29 - 80	20 - 88
Age (years) [n(%)]	<65	274 (48.6%)	490 (49.5%)	34 (51.5%)	30 (48.4%)	828 (49.3%)
	[65-75[	223 (39.5%)	344 (34.8%)	21 (31.8%)	24 (38.7%)	612 (36.4%)
	>=75	67 (11.9%)	155 (15.7%)	11 (16.7%)	8 (12.9%)	241 (14.3%)
Height (cm)	n	552	976	65	61	1654
	Median	173	173	172	171	173
	Mean	173.2	172.8	171.6	170.3	172.8
	SD	9.8	10.4	8.8	10.5	10.1
	Min - Max	142 - 200	138 - 213	141 - 190	147 - 209	138 - 213
Weight (kg)	n	561	986	66	61	1674
	Median	85.0	85.0	83.5	80.5	84.5
	Mean	86.17	85.80	84.39	83.03	85.76
	SD	16.76	17.09	16.31	14.49	16.86
	Min - Max	51.0 - 168.0	35.0 - 185.9	54.0 - 136.0	55.0 - 135.0	35.0 - 185.9
BMI (Kg/m²) [n(%)]	<30	382 (69.2%)	649 (66.6%)	45 (69.2%)	40 (65.6%)	1116 (67.6%)
	>=30	170 (30.8%)	325 (33.4%)	20 (30.8%)	21 (34.4%)	536 (32.4%)
	Missing	12	15	1	1	29
Gender [n(%)]	Male	388 (68.8%)	684 (69.2%)	48 (72.7%)	40 (64.5%)	1160 (69.0%)
	Female	176 (31.2%)	305 (30.8%)	18 (27.3%)	22 (35.5%)	521 (31.0%)
Race [n(%)]	Caucasian	554 (98.2%)	960 (97.1%)	65 (98.5%)	62 (100.0%)	1641 (97.6%)
	Black	4 (0.7%)	10 (1.0%)	0 (0.0%)	0 (0.0%)	14 (0.8%)
	Asian/Oriental	0 (0.0%)	6 (0.6%)	1 (1.5%)	0 (0.0%)	7 (0.4%)
	Other	6 (1.1%)	13 (1.3%)	0 (0.0%)	0 (0.0%)	19 (1.1%)

Note: protocols: DRI3550 (DAFNE), EFC3153 (EURIDIS), EFC4788 (ADONIS), EFC4508 (ERATO)
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Table 73- Summary of demographic characteristics of patients with AF/AFL

From this above table it is clear that the studied population was quite young compared to the population at large with the real risk, as the incidence of atrial fibrillation increases with each decade. Therefore, although there were not many deaths in these studies, it is not a representative population of the patients who may utilize this drug.

Another table showing how healthy the patients were in the AF/AFL studies is following.
In the baseline cardiovascular examination there were no patients in moderate or severe CHF.
In fact, almost all the patients had a LVEF $\geq$ 35.

	Placebo (N=564)	Dronedarone 400 mg BID (N=989)	Dronedarone 600 mg BID (N=66)	Dronedarone 800 mg BID (N=62)	Total (N=1681)
2D-Echocardiogram - Left ventricular ejection fraction (%)					
n	531	944	65	59	1599
Median	60.0	60.0	55.0	55.0	60.0
Mean	57.48	58.17	54.29	53.68	57.62
SD	10.99	10.68	11.70	11.07	10.89
Min - Max	5.5 - 84.0	5.0 - 93.4	35.0 - 88.0	31.0 - 82.0	5.0 - 93.4
LVEF<35%	19 / 531 (3.6%)	25 / 944 (2.6%)	0 / 65 (0.0%)	1 / 59 (1.7%)	45 / 1599 (2.8%)
LVEF>=35%	511 / 531 (96.2%)	918 / 944 (97.2%)	65 / 65 (100.0%)	58 / 59 (98.3%)	1552 / 1599 (97.1%)
Cardiovascular clinical examination					
Patients with left CHF	122 (21.6%)	196 (19.8%)	17 (25.8%)	15 (24.2%)	350 (20.8%)
NYHA classification [n(%)]					
Class I (Potential)	41 (7.3%)	67 (6.8%)	10 (15.2%)	7 (11.3%)	125 (7.4%)
Class II (Mild)	81 (14.4%)	129 (13.0%)	7 (10.6%)	8 (12.9%)	225 (13.4%)

Note: protocols: DRI3550 (DAFNE), EFC3153 (EURIDIS), EFC4788 (ADONIS), EFC4508 (ERATO)
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Table 74- Number (%) of patients according to cardiovascular examination

7.1.1.2.2. Deaths of patients on dronedarone

The following table provides an overview of deaths during each time period. The incidence of deaths was similar in the dronedarone 400 mg BID and placebo groups during the study period.

Number of deaths	Placebo	Dronedarone 400 mg BID	Dronedarone 600 mg BID	Dronedarone 800 mg BID
Between randomization and 1st administration	1/568 (0.2%)	1/992 (0.1%)	0/ 66 (0.0%)	0/ 62 (0.0%)
On randomized and treated patients				
During treatment 95% CI	3/564 (0.5%) [0.1% - 1.5%]	9/989 (0.9%) [0.4% - 1.7%]	0/ 66 (0.0%) [0.0% - 5.4%]	0/ 62 (0.0%) [0.0% - 5.8%]
Post treatment up to the planned end of study	3/561 (0.5%)	3/980 (0.3%)	0/ 66 (0.0%)	0/ 62 (0.0%)
During study 95% CI	6/564 (1.1%) [0.4% - 2.3%]	12/989 (1.2%) [0.6% - 2.1%]	0/ 66 (0.0%) [0.0% - 5.4%]	0/ 62 (0.0%) [0.0% - 5.8%]
Reported after the planned end of study *	0	3	0	1

Note: One patient died during the screening period
Note: Patients from study center 616003 are excluded from results. No death occurred in this center
* Data no longer collected systematically
Note: protocols: DRI3550 (DAFNE), EFC3153 (EURIDIS), EFC4788 (ADONIS), EFC4508 (ERATO)
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Table 75- Number (%) of deaths according to analysis periods in patients with AF/AFL

Table 76- Listing of all deaths of patients treated with dronedarone

Patient Number	Last study drug intake date [day(a)]	Death	Characteristics of the adverse events related to death				
		Date [day(a)]	MedDRA (7.0) organ class	Preferred Term (Verbatim)	Onset date [day(a)]	Onset time	Relation to study drug(b)
Treatment as received: Dronedarone 400 mg BID							
003153528005001	2002-12-25(323)	2003-03-30(418) (3)	Respiratory, thoracic and mediastinal disorders	Dyspnoea (Dyspnoea)	2002-12-26(324)	XX:XX	No

(Continued)

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Table 76- continued

Patient Number	Last study drug intake date(day(a))	Death	Characteristics of the adverse events related to death				
		Date [day(a)]	MedDRA (7.0) organ class	Preferred Term (Verbatim)	Onset date[day(a)]	Onset time	Relation to study drug(b)
003153528006007	2002-02-09(3)	2002-02-09(3) (1)	General disorders and administration site conditions	Sudden death (Sudden death)	2002-02-09(3)	XX:XX	Yes
003153528011027	2003-05-08(310)	2003-05-10(312) (1)	Cardiac disorders	Myocardial infarction (Myocardial infarction)	2003-05-08(310)	XX:XX	No
004508250004003	2003-04-01(8)	2003-04-01(8) (1)	General disorders and administration site conditions	Sudden death (Sudden death)	2003-04-01(8)	13:15	Yes
004508528009007	2003-09-02(169)	2003-09-23(190) (2)	Gastrointestinal disorders	Diverticular perforation (Perforated diverticulitis)	2003-09-08(175)	XX:XX	No
004788032005005	2002-10-26(66)	2002-10-27(67) (1)	Cardiac disorders	Cardiac failure congestive (Congestive heart failure nyha iii)	2002-10-10(50)	11:00	No
	2002-10-26(66)	2002-10-27(67) (1)	Cardiac disorders	Ventricular fibrillation (Ventricular fibrillation)	2002-10-27(67)	XX:XX	No
004788036002010	2002-05-23(95)	2002-05-23(95) (1)	General disorders and administration site conditions	Sudden death (Sudden death)	2002-05-23(95)	09:05	Yes
004788124011006	2002-11-13(86)	2003-01-08(142) (2)	General disorders and administration site conditions	Sudden cardiac death (Sudden cardiac death)	2003-01-08(142)	17:30	No
004788124032005	2002-06-29(66)	2002-08-20(118) (3)	Respiratory, thoracic and mediastinal disorders	Acute pulmonary oedema (Acute pulmonary oedema)	2002-08-08(106)	XX:XX	No
	2002-06-29(66)	2002-08-20(118) (3)	Infections and infestations	Enterococcal sepsis (Septicemia enterococcus)	2002-08-08(106)	13:08	No
004788710006002	2002-04-12(19)	2002-04-12(19) (1)	General disorders and administration site conditions	Sudden death (Death)	2002-04-12(19)	13:00	No

(Continued)

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Table 76- continued

Patient Number	Last study drug intake date [day(a)]	Death	Characteristics of the adverse events related to death				
		Date [day(a)]	MedDRA (7.0) organ class	Preferred Term (Verbatim)	Onset date [day(a)]	Onset time	Relation to study drug(b)
004788710006004	2003-03-21(299)	2003-03-22(300) (1)	Cardiac disorders	Atrioventricular block complete (Third degree heart block)	2003-03-21(299)	20:00	No
004788840002004	2002-09-19(221)	2002-09-22(224) (1)	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastatic neoplasm (Suspected metastatic liver + lung carcinoma-primary site unknown confirmed for ct scan)	2002-06-22(132)	XX:XX	No
004788840010006	2002-09-20(60)	2003-02-13(206) (3)	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Multiple myeloma (Multiple myeloma exacerbation)	2003-02-13(206)	XX:XX	No
004788840021013	2002-11-25(187)	2003-06-02(376) (3)	Cardiac disorders	Cardiac failure congestive (Worsening congestive heart failure)	2003-05-24(367)	XX:XX	No
004788840040011	2003-03-XX(288)	2003-03-17(288) (1)	General disorders and administration site conditions	Sudden death (Sudden death)	2003-03-17(288)	XX:XX	No
Treatment as received: Dronedarone 800 mg BID							
003550528005008	2000-04-17(162)	2000-05-13(188) (2)	Injury, poisoning and procedural complications	Injury (Trauma)	2000-04-17(162)	XX:XX	No

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7.1.1.2.2. Deaths in patients treated on placebo

Table 77- Listing of all deaths for patients treated with placebo

Patient Number	Last study drug intake date [day(a)]	Death	Characteristics of the adverse events related to death				
		Date [day(a)]	MedDRA (7.0) organ class	Preferred Term (Verbatim)	Onset date [day(a)]	Onset time	Relation to study drug(b)
Treatment as received: Placebo							
004508528005004	2003-11-25(57)	2004-01-09(102) (2)	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bronchioloalveolar carcinoma (Diffuse broncho-alveolar cell carcinoma in both lungs)	2003-11-12(44)	XX:XX	No
004788124024042	2002-12-16(117)	2002-12-16(117) (1)	General disorders and administration site conditions	Sudden death (Sudden death)	2002-12-16(117)	XX:XX	Yes
004788124028001	2002-08-29(206)	2002-10-16(254) (2)	Vascular disorders	Circulatory collapse (Vascular collapse-not otherwise specified)	2002-10-16(254)	XX:XX	No
004788840002008	2002-10-04(82)	2002-10-04(82) (1)	Cardiac disorders	Cardiac arrest (Death secondary to cardiac arrest - previously reported as hypertensive cardiomyopathy, previously reported as death)	2002-10-04(82)	14:57	Yes
004788840036006	2002-10-23(140)	2002-12-24(202) (2)	Cardiac disorders	Cardiac failure congestive (Worsening congestive heart failure)	2002-10-23(140)	02:34	No
	2002-10-23(140)	2002-12-24(202) (2)	Renal and urinary disorders	Renal insufficiency (Renal failure)	2002-11-04(152)	05:30	No
004788840040010	2002-05-27(15)	2002-05-28(16) (1)	Nervous system disorders	Cerebrovascular accident (Cerebral vascular accident)	2002-05-27(15)	XX:XX	No

(a) Day related to first study drug as day 1
(b) As assessed by the investigator
(1) Death occurred from first study drug intake up to last study drug intake + 10 days
(2) Death occurred after last study drug intake + 10 days up to end of study date
(3) Death occurred after end of study date
No death after D365 but before end of study in EURIDIS/ADONIS
Note: Protocols: DRI3550 (DAFNE), EFC3153 (EURIDIS), EFC4788 (ADONIS), EFC4508 (ERATO)
(pages 514-6 Module 2.7.4 Summary)

7.1.1.2.3. Other serious Adverse Events in Patients in the AF/AFL studies

There was a dose response for GI disorders with a difference in the incidence of GI disorders between the placebo (0.5%) and the dronedarone 400 mg BID group (1.9%). For cardiac disorders the overall incidence of SAEs was similar in the placebo and dronedarone 400 mg BID groups. In the dronedarone 400 mg group, GI hemorrhages and GI signs and symptoms accounted for most of the SAEs. Almost all of the patients who experienced GI hemorrhage in the dronedarone 400 mg BID group took an oral anticoagulant (OAC) concomitantly.

One patient in the ADONIS study taking dronedarone 400 mg BID experienced an anaphylactic reaction, and 1 patient in the DAFNE study taking dronedarone 800 mg BID experienced an anaphylactic shock.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1. Patients in the AF/AFL studies
The overall incidence of AEs leading to permanent discontinuation of study drug was similar among all treatment groups, except for GI disorders and laboratory results (Investigations). Gastrointestinal disorders were the main reason for discontinuation in the dronedarone 800 mg BID group (11.3% of patients). The most frequent AEs (i.e., ≥ 1%) leading to permanent study drug discontinuation by high level group term (HLGT) in the dronedarone 400 mg BID group were cardiac arrhythmias, and epidermal and dermal conditions. However, their incidence was not different from that of placebo. There was a difference between placebo and dronedarone 400 mg BID groups for HLGT renal and urinary tract investigations and urinalyses.

There was an overall dose response observed in patients with any treatment-emergent adverse event (TEAE) and in patients who permanently discontinued study drug for any AE as shown in the following table.

	Placebo (N=564)	Dronedarone 400 mg BID (N=989)	Dronedarone 600 mg BID (N=66)	Dronedarone 800 mg BID (N=62)
Patients with any TEAE (a)	340 (60.3%)	660 (66.7%)	42 (63.6%)	45 (72.6%)
Patients with any serious TEAE	79 (14.0%)	133 (13.4%)	4 (6.1%)	8 (12.9%)
Deaths (b)	3 (0.5%)	9 (0.9%)	0 (0.0%)	0 (0.0%)
Patients permanently discontinued study drug for any AE (a)(c)(d)	34 (6.0%)	96 (9.7%)	4 (6.1%)	14 (22.6%)

(a) Including SAEs
(b) Deaths which occurred from first study drug intake up to last study drug intake plus 10 days
(c) According to 'End of treatment' form
(d) Events started before the first study drug intake were taken into account
Note: Protocols: DRI3550 (DAFNE), EFC3153 (EURIDIS), EFC4788 (ADONIS), EFC4508 (ERATO)
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Table 78- Overview of main treatment emergent events [number (%) of patients] excluding the occurrence of AF/AFL

A summary of AEs leading to permanent discontinuation of study drug according to MedDRA organ classes and preferred terms is provided in the following table.

MedDRA (7.0) Organ Class Preferred term	Placebo (N=564)		Dronedarone 400 mg BID (N=989)		Dronedarone 600 mg BID (N=66)		Dronedarone 800 mg BID (N=62)	
Any Class any event	340	(60.3%)	660	(66.7%)	42	(63.6%)	45	(72.6%)
Gastrointestinal disorders								
Any event	90	(16.0%)	188	(19.0%)	13	(19.7%)	22	(35.5%)
Diarrhoea	23	(4.1%)	66	(6.7%)	5	(7.6%)	18	(29.0%)
Nausea	17	(3.0%)	39	(3.9%)	2	(3.0%)	5	(8.1%)
Abdominal pain upper	9	(1.6%)	20	(2.0%)	1	(1.5%)	1	(1.6%)
Abdominal pain	6	(1.1%)	19	(1.9%)	1	(1.5%)	2	(3.2%)
Vomiting	4	(0.7%)	17	(1.7%)	1	(1.5%)	2	(3.2%)
Dyspepsia	7	(1.2%)	13	(1.3%)	2	(3.0%)	0	(0%)
Infections and infestations								
Any event	95	(16.8%)	194	(19.6%)	7	(10.6%)	7	(11.3%)
Nasopharyngitis	18	(3.2%)	37	(3.7%)	3	(4.5%)	2	(3.2%)
Upper respiratory tract infection	6	(1.1%)	29	(2.9%)	0	(0%)	1	(1.6%)
Influenza	17	(3.0%)	25	(2.5%)	1	(1.5%)	2	(3.2%)
Nervous system disorders								
Any event	81	(14.4%)	144	(14.6%)	4	(6.1%)	6	(9.7%)
Headache	38	(6.7%)	52	(5.3%)	2	(3.0%)	3	(4.8%)
Dizziness	17	(3.0%)	34	(3.4%)	1	(1.5%)	3	(4.8%)
Investigations								
Any event	49	(8.7%)	133	(13.4%)	10	(15.2%)	8	(12.9%)
Blood creatinine increased	1	(0.2%)	22	(2.2%)	1	(1.5%)	0	(0%)
Hepatic enzyme increased	6	(1.1%)	12	(1.2%)	3	(4.5%)	1	(1.6%)
Blood urea increased	1	(0.2%)	4	(0.4%)	2	(3.0%)	2	(3.2%)
Electrocardiogram QT prolonged	0	(0%)	3	(0.3%)	1	(1.5%)	2	(3.2%)
Cardiac disorders								
Any event	62	(11.0%)	123	(12.4%)	12	(18.2%)	13	(21.0%)
Bradycardia	8	(1.4%)	26	(2.6%)	1	(1.5%)	4	(6.5%)
Angina pectoris	12	(2.1%)	20	(2.0%)	0	(0%)	1	(1.6%)
Palpitations	5	(0.9%)	11	(1.1%)	4	(6.1%)	3	(4.8%)
Cardiac failure congestive	4	(0.7%)	13	(1.3%)	3	(4.5%)	1	(1.6%)
Cardiac failure	3	(0.5%)	8	(0.8%)	3	(4.5%)	1	(1.6%)
Atrial tachycardia	7	(1.2%)	5	(0.5%)	0	(0%)	3	(4.8%)
General disorders and administration site conditions								
Any event	60	(10.6%)	130	(13.1%)	6	(9.1%)	6	(9.7%)
Oedema peripheral	23	(4.1%)	42	(4.2%)	1	(1.5%)	1	(1.6%)
Fatigue	14	(2.5%)	27	(2.7%)	3	(4.5%)	2	(3.2%)
Musculoskeletal and connective tissue disorders								
Any event	61	(10.8%)	126	(12.7%)	2	(3.0%)	3	(4.8%)
Back pain	9	(1.6%)	33	(3.3%)	0	(0%)	1	(1.6%)
Arthralgia	9	(1.6%)	31	(3.1%)	0	(0%)	1	(1.6%)
Pain in extremity	5	(0.9%)	21	(2.1%)	0	(0%)	0	(0%)

(Continued)

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Table 79- Number (%) of patients with TEAEs with incidence ≥ 2% for all patients with AF/AFL

MedDRA (7.0) Organ Class Preferred term	Placebo (N=564)		Dronedarone 400 mg BID (N=989)		Dronedarone 600 mg BID (N=66)		Dronedarone 800 mg BID (N=62)	
Respiratory, thoracic and mediastinal disorders								
Any event	58	(10.3%)	117	(11.8%)	2	(3.0%)	9	(14.5%)
Cough	8	(1.4%)	22	(2.2%)	1	(1.5%)	3	(4.8%)
Dyspnoea	12	(2.1%)	23	(2.3%)	0	(0%)	1	(1.6%)
Skin and subcutaneous tissue disorders								
Any event	36	(6.4%)	94	(9.5%)	4	(6.1%)	6	(9.7%)
Vascular disorders								
Any event	35	(6.2%)	62	(6.3%)	1	(1.5%)	3	(4.8%)
Hypertension	14	(2.5%)	24	(2.4%)	1	(1.5%)	1	(1.6%)
Injury, poisoning and procedural complications								
Any event	29	(5.1%)	57	(5.8%)	1	(1.5%)	2	(3.2%)
Psychiatric disorders								
Any event	16	(2.8%)	52	(5.3%)	2	(3.0%)	1	(1.6%)
Eye disorders								
Any event	15	(2.7%)	29	(2.9%)	2	(3.0%)	2	(3.2%)
Metabolism and nutrition disorders								
Any event	29	(5.1%)	28	(2.8%)	3	(4.5%)	1	(1.6%)
Hypokalaemia	3	(0.5%)	3	(0.3%)	2	(3.0%)	0	(0%)
Renal and urinary disorders								
Any event	15	(2.7%)	26	(2.6%)	1	(1.5%)	0	(0%)
Reproductive system and breast disorders								
Any event	11	(2.0%)	24	(2.4%)	1	(1.5%)	1	(1.6%)
Ear and labyrinth disorders								
Any event	5	(0.9%)	20	(2.0%)	3	(4.5%)	2	(3.2%)
Vertigo	1	(0.2%)	13	(1.3%)	3	(4.5%)	2	(3.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Any event	11	(2.0%)	22	(2.2%)	0	(0%)	0	(0%)
Endocrine disorders								
Any event	9	(1.6%)	13	(1.3%)	0	(0%)	1	(1.6%)
Blood and lymphatic system disorders								
Any event	0	(0%)	14	(1.4%)	0	(0%)	0	(0%)
Hepatobiliary disorders								
Any event	6	(1.1%)	7	(0.7%)	1	(1.5%)	0	(0%)
Surgical and medical procedures								
Any event	5	(0.9%)	8	(0.8%)	0	(0%)	0	(0%)
Immune system disorders								
Any event	2	(0.4%)	5	(0.5%)	1	(1.5%)	2	(3.2%)
Congenital, familial and genetic disorders								
Any event	0	(0%)	1	(0.1%)	0	(0%)	0	(0%)

Note: A patient can have AEs in more than one system organ class and in more than one preferred term
Note: Protocols: DRI3550 (DAFNE), EFC3153 (EURIDIS), EFC4788 (ADONIS), EFC4508 (ERATO)
(page 358 Module 2.7.4 Summary)

Table 79- continued

Among the TEAEs with an incidence ≥ 2% (in at least 1 treatment group) there was a dose response, with a trend toward a higher incidence in dronedarone groups compared to placebo, for diarrhea, blood creatinine increased, blood urea increased, ECG QT-interval prolonged, palpitations, bradycardia and vertigo. Among the TEAEs with a dose response, there was a difference between placebo and dronedarone 400 mg BID for diarrhea, blood creatinine increased and vertigo. Considering the other TEAEs with an incidence ≥ 2%, only back pain and upper respiratory tract infection showed an apparent difference in incidence between placebo and the dronedarone 400 mg BID group.

Syncope were reported at a similar incidence in placebo (0.5%) and dronedarone 400 mg BID (0.7%) groups. The incidence of cerebrovascular accident or transient ischemic attack (TIA) in this population at risk for such events, was the same (0.2%) for TIA in both placebo and dronedarone 400 mg BID groups and for cerebrovascular accident was lower in dronedarone dose groups (0.1% in dronedarone 400 mg BID group, none in 600 mg BID and 800 mg BID group) compared to placebo (0.4%).

7.1.1.3. Deaths and Adverse events in normal volunteers
There were no significant adverse events or deaths in the volunteer studies or the drug interaction studies.

7.1.4 Immunogenicity

Not applicable.

7.1.5 Human Carcinogenicity

Not applicable.

7.1.6 Special Safety Studies

Not applicable.

7.1.7 Withdrawal Phenomena and/or Abuse Potential

Not applicable

7.1.8 Human Reproduction and Pregnancy Data

Not applicable.

7.1.9 Assessment of Effect on Growth

Not applicable.

7.1.10 Overdose Experience

Not applicable.

7.1.11 Postmarketing Experience

Not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

"The dose" was determined from the DAFNE trial. The Sponsor chose 400 mg B.I.D. although the Agency recommended a dosing sequence be made available. Doses from 50 mg. to 800 mg. should be investigated as discussed in Dr. Williams' review of the DAFNE study.

8.2 Drug-Drug Interactions

The PK/PD drug interaction is shown in the following table from Dr. Kumi's Review.

Drug	Classification	Effect of co-administration		
		PD (either or both drugs)	Dronedarone	Other Drug
	Miscellaneous			
digoxin	PGP substrate	NA	NA	↑ 2.5 fold
pantoprazole	decrease gastric pH	NA	↔	NA
theophylline	CYP1A2 substrate	NA	↔	↓ 20 %
	CYP3A function			
rifampicin	inducer	None	↓ 80 %	NA
dilitiazem	weak inhibitor	↑ repolarization time	↑ 60 %	NA
nifedipine	weak inhibitor	Lowered blood pressure	↑ 20 %	NA
grapefruit juice	moderate inhibitor	NA	↑ 3-fold	NA
ketoconazole	strong inhibitor	↑ PR, no effect on QT	↑ ≥ 9-fold	NA
verapamil	Substrate, inhibitor	↑ repolarization time	↑ 40 %	↑ 40 %
nisoldipine	substrate	↔	↔	↑ 100 %
simvastatin	substrate	↔	↔	↑ 4-fold
ethinylestradiol	substrate	NA	NA	↑ 25 %
levonorgestrel	substrate	NA	NA	↑ 18 %
	CYP2C9 function			
losartan	substrate	↑ heart rate	↔	↔
S-warfarin/R-warfarin	substrate	↑ INR by 7 %	↔	↑ AUC 11 %
	CYP2D6 function			
metoprolol	Substrate	↓ cardiac contractility	NA	↑ 60 -150 %
propranolol	substrate	↓ HR, DBP, SBP	↔	↑ 16 to 33 %

(page 7 Dr. Robert Kumi's Review)

Table 80- PK/PD drug-drug Interaction

8.3 Special Populations

From Dr. Robert Kumi's Review:

• ***Renal Insufficiency:*** The effect of impaired renal function was not evaluated in the dronedarone program
• ***Hepatic insufficiency:*** The effect of impaired hepatic function has not been evaluated, but there is an ongoing study to evaluate this patient population.
• ***Gender:*** Relative to elderly males, elderly females have exposures that are approximately 30 % higher.
• ***Age:*** Relative to healthy young males, healthy elderly males have exposures that are about 40 % higher
• ***Race:*** Relative to healthy male Caucasians, healthy Asian (Japanese) males have exposures that are about 100 % higher

8.4 Pediatrics

The Sponsor requested March 9, 2005 a deferral of pediatric studies with dronedarone. The Division responded on April 1, 2005 to the sponsor's request, agreeing to a deferral of pediatric studies with dronedarone in patients less than 16 years of age for rhythm and rate

control in patients with atrial fibrillation/atrial flutter.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

A literature review of the available pharmacological treatments for AF/AFL was completed, as well as a review of amiodarone and the early studies pertaining to dronedarone.

8.7 Postmarketing Risk Management Plan

Not applicable.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

This NDA pertains to an important chronic medical problem, atrial fibrillation and/or flutter (AF/AFL). The incidence has been shown to increase with age and, therefore, as the population ages there will be an increase in the incidence of AF/AFL.

In the clinical submission of this NDA, the Sponsor has included five studies for efficacy. They are seeking two indications at this time: patients will remain longer in normal sinus rhythm on dronedarone compared to patients on placebo and if AF/AFL reoccurs while patients are on dronedarone their ventricular rate will be slower.

The DAFNE study was utilized by the Sponsor to determine the dose. Although the Agency as early as 1999 advised the Sponsor to provide a dosing range rather than a fixed dose, the Sponsor choose not to heed this advice. In the DAFNE study does greater than 400 mg twice a day (BID) did not appear as efficacious as that dose. Although the Sponsor was advised to study lower doses they failed to do this.

The ERATO trial evaluated ventricular rate control. In this study and in the Sponsor's two pivotal studies, the ADONIS and EURIDIS, the rate is not improved to the clinically acceptable range of 60 to 80 bpm at rest and 90 to 115 bpm with exercise. In the ERATO study, the patients on dronedarone showed no improvement over placebo in an exercise test revealed.

In the ADONIS and ERUIDIS studies the Sponsor evaluated surrogate markers for AF/AFL. The patients, when they had symptoms, used a transtelephonic device to transmit their ECG. The Sponsor did demonstrate in these two studies that patients taking dronedarone remain longer in normal sinus rhythm compared to placebo. However, their ventricular rate is not lowered in these studies to a clinically acceptable range should they revert to AF/AFL. The population chosen for these studies was relatively young and in good health.

In these reviewers' opinion, the critical study is the ANDROMEDA Study which investigated patients with a previous episode of "severe" congestive heart failure (CHF). This study has clinical endpoints, death and hospitalizations, and not surrogate markers. The drug dronedarone statistically significantly ($p \leq 0.027$) increased the risk of death from any cause and the risk of hospitalization for acute cardiovascular reasons as compared to placebo.

Although the Sponsor has another large ongoing trial in patients who are 70 or older with AF/AFL, at this time these reviewers must recommend that this NDA because of the increase in mortality that dronedarone is NOT APPROVABLE. Finally, in evaluating the risk/benefit ratio, there is very little benefit to be gained from this drug which has been shown to statistically significantly increase the risk of death in older, sicker patients.

9.2 Recommendation on Regulatory Action

NOT APPROVABLE

9.3 Labeling Review

To be completed in the future.

9.4 Comments to Applicant

There are two main comments for the Sponsor:

1. The ongoing trial EFC5555 must show both efficacy and safety.
2. Other doses in the range of 50 mg to 800 mg should be investigated.

10 APPENDICES

10.1 Review of Individual Study Reports

Study: ANtiarrhythmic trial with DROnedarone in Moderate to severe CHF Evaluating morbidity DecreAse (ANDROMEDA), (EFC4966)

Study Dates: Planned dates were June 12, 2002 through August 19, 2003. However, the premature end of study drug treatment and randomizations was January 16, 2003. These patients were studied for an additional 6 months, to July 17, 2003.

Study Population: patients with moderate to "severe" congestive heart failure with left ventricular dysfunction.

Design: A multicenter, multinational, double-blind, randomized, parallel-group, placebo-controlled study of the efficacy of dronedarone 800 mg daily (400 BID), for reducing death or hospitalizations for worsening of heart failure in patients with symptomatic CHF (NYHA class II – IV) and moderate to severe systolic LVD defined as WMI $\leq$ 1.2.

In addition to the blinded Steering Committee (SC) responsible for the conduct of the trial, a central, independent data safety monitoring board (DSMB) monitored the safety of patients in the study, and an independent, blinded Critical Events Committee (CEC) adjudicated the causes of deaths and hospitalizations.

Study centers: 72 active centers in 6 European countries: Denmark, Hungary, the Netherlands, Norway, Poland, and Sweden

Objectives:
Primary: To evaluate whether dronedarone reduces death from any cause or hospitalizations for worsening heart failure in patients with moderate to severe congestive heart failure (CHF) and left ventricular dysfunction (LVD), when added to usual evidence-based treatments for CHF, over a minimum period of 12 months as compared to placebo.

Secondary objectives were to evaluate whether dronedarone:
• reduces death from any cause;
• reduces hospitalization for worsening heart failure;
• reduces hospitalization for acute cardiovascular reasons;
• reduces arrhythmic/sudden death;
• is effective in maintaining sinus rhythm in the target population.

Both the safety and tolerability of dronedarone versus placebo patients were to be evaluated.

Pharmacokinetic objective:
Dronedarone and SR35021 plasma levels at steady state were documented.

Interim analysis
The safety of patients included in the study will be monitored by the DSMB. No efficacy interim analysis for the study was planned.

Number of patients evaluated:
Planned: 1,000
Main analysis population: Randomized: 627; Treated: 627; Efficacy: 627 Safety: 627

On January 16, 2003, 7 months after randomization of the first patient, the inclusion of patients into the study was discontinued following a recommendation of the Data Safety Monitoring Board (DSMB), because of the higher number of deaths observed in the patients randomized to dronedarone compared to placebo. Following a second safety analysis (February 17, 2003), the DSMB recommended follow-up of mortality, major clinical events, and renal function for all the patients up to July 17, 2003 (6 months after the end of inclusions).

All patients randomized in center 616004 (n = 23) were excluded by the Sponsor from the main analysis population due to a major violation in good clinical practice (GCP) violation documented in this center, raising doubts about the integrity of the data provided by this center.

Inclusion criteria:
a) Age ≥18 years;
b) patients hospitalized with symptomatic CHF, current New York Heart Association (NYHA) class II-IV, requiring treatment with a diuretic, who had had within the last month at least 1 episode of dyspnea or fatigue at rest, or on slight exertion, corresponding to NYHA class III or IV;
c) wall motion index (WMI) ≤1.2, determined by a blinded central evaluation of a recorded standard echocardiography, equivalent to a left ventricular ejection fraction (LVEF) ≤35%.

Exclusion criteria:
a) acute pulmonary edema within 12 hours prior to start of study medication;
b) cardiogenic shock, treatment with intrvenous pressor agents or patients on respirator
c) uncorrected hemodynamically significant primary obstructive valvular disease;
d) hemodynamically significant obstructive cardiomyopathy;
e) acute MI during the 7 days preceding randomization (changed to 5 days following Amendment No. 1);
f) a cardiac operation or revascularization procedure [except percutaneous coronary intervention (PCI) following Amendment No. 1] during the month preceding randomization;
g) planned major non-cardiac or cardiac surgery or procedures including surgery for valvular heart disease, coronary artery bypass graft (CABG), or on urgent cardiac transplantation list;
h) acute myocarditis or constrictive pericarditis;
i) history of torsades de pointes;

j) bradycardia <50 bpm and/or PR-interval ≥280 ms at screening (at randomization following Amendment No. 1);
k) QTc-interval >500 ms at screening (at randomization following Amendment No. 1);
l) significant sinus node disease or second or third degree atrioventricular block (AV block) unless treated with a pacemaker;
m) treatment with other class I or III anti-arrhythmic drugs;
n) any illness or disorder other than CHF that could preclude participation or severely limit survival;
o) pregnant women or women of child-bearing potential not on adequate birth control;
p) breastfeeding women;
q) serum potassium <3.5 mmol/L;
r) other conditions/circumstances likely to lead to poor treatment adherence;
s) current participation in another clinical study in which the patient is currently taking an investigational drug or using an investigational device;
t) need of a concomitant medication that was prohibited in this study;
u) previous participation in this study or in other dronedarone studies.

Figure 13- Amended Study Flowchart

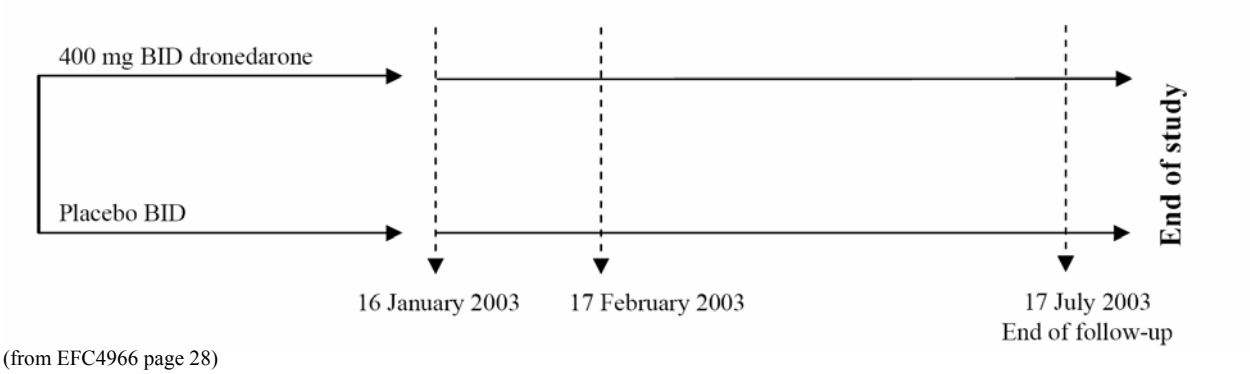
Time	D-6 to D1 (Screening)[1]	D1	D5±2[11]	M1±7D	M3±14D	M6±14D	M9±14D	M12±14D	M15±14D	M18±14D	M21±14D	M24±14D	EOS Visit[9]
Inclusion/Exclusion Criteria	x	x											
Informed Consent	x	x											
Demographic data	x												
Medical history[6]	x												
2D-echocardiography[4]	x												
Chest X-ray[10]	x												
12-lead ECG	x	x	x	x	x	x	x	x	x	x	x	x	x
NYHA	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory **1**[7]	(B-HCG, **SB3**)[3],	H1, SB2	**SB3**	H1, SB2	**SB3**	H1, SB2	**SB3**	H1, SB2	**SB3**	**SB2**		H1, SB2	**SB3**
Laboratory 2[12]	**DIG**[3]	**DIG**	**DIG**	**DIG**	**DIG**	**DIG**	**DIG**	**DIG**		**DIG**		**DIG**	**DIG**
PK at trough[5]				x		x							
Vital signs[8]		x	x	x	x	x	x	x	x	x	x	x	x
IVRS call		x				x		x		x		x	
Dispense study medication		x		x	x	x	x	x	x	x	x		
Drug accountability				x	x	x	x	x	x	x	x	x	x
Symptoms[2]		x	x	x	x	x		x		x		x	
Adverse event reporting & concomitant drugs	x	x	x	x	x	x	x	x	x	x	x	x	x
Endpoints		x	x	x	x	x	x	x	x	x	x	x	x

(from Appendix 1, page 236 of Study EFC4966)

Amended Study Flowchart Footnotes:
1) Full screening data will be recorded on the screening visit CRF for randomized patients, in non randomized patients only demographic data and reason(s) for noninclusion will be collected in a screening log
2) CHF and Arrhythmia related symptoms will be collected in the CRF
3) SB3, DIG, B-HCG in women (pregnancy test, can be replaced by urine test) assessed locally
4) Echocardiography assessed centrally for WMI
5) Must be done just before dosing in approximately 50% of patients. In addition to this, several blood samples (pre-dose, 2h, 4h, 6h, 8h, 10h and 12h postdose) will be taken in a subgroup of about 30 patients recruited at selected centers at M1. One of these samples will be collected as close as possible to the time of 12-lead ECG recording.
6) Includes medical history, previous therapy
7) Biology Laboratory Tests: see section in protocol body
8) Vital signs include: sitting or supine blood pressure and at randomization weight and height

9) End of study (EOS) visit to be completed as close as possible to 1 year treatment of last patient (end of the study)
10) Can be performed one month before to one week after randomization
11) SB3 should be done preferably on D3 whenever possible
12) Laboratory 2, only in patients receiving DIGOXIN.

Figure 14- Main timepoints implemented following January 16, 2003



(from EFC4966 page 28)

Investigational Plan
All potentially eligible patients at each site were to undergo an echocardiography to confirm their eligibility. Eligible patients were randomly allocated to dronedarone treatment or placebo in a 1:1 ratio, in addition to the standard treatment necessary for their condition. Three amendments were written for this study, Amendment No. 1, dated June 26, 2002; Amendment No. 2, dated January 15, 2003; and Amendment No. 3, dated March 7, 2003.

Protocol Amendment 1; dated June 26, 2002:
Reasons for the Amendment:
• Given the high incidence of cardiovascular deaths, including sudden deaths, in the target population, these adverse events are to be considered as expected, for regulatory purposes. Their reporting as serious adverse event (SAEs) is not changed.
• Exclusion of patients with recent acute myocardial infarction is brought from 7 to 5 days to facilitate recruitment.
• Clarifications are given concerning some additional points.

Additional exclusion criteria were included as cited above. Sudden deaths, are to be considered as expected, nevertheless they will always be reported as serious adverse events (SAEs). Changes occurred to the flow chart.

Protocol Amendment 2; dated January 15, 2003:
Reasons for Amendment:

A number of unexpected renal events and/or cardiac failures was noted when reviewing the serious adverse events. Based on an evaluation of individual serious adverse events and a blinded analysis of serum creatinine, the Steering Committee has decided to implement the following changes to ensure patients' safety in the ANDROMEDA study.

To improve patient's safety by:

- paying closer attention to the renal function both with respect to eligibility (exclude patients with poor renal function at baseline because they would not tolerate a further deterioration in renal function) and following renal function more closely in enrolled patients with the purpose of permanently stopping treatment with study medication if the renal function deteriorates.
- routinely measuring serum digoxin (se-digoxin) in participants receiving treatment with digoxin.

The investigator must discontinue study medication if one or more of the following are found:
- PR interval > 0.35 sec or 2° or 3° AV block unless patient has a pacemaker
- Symptomatic bradycardia
- New bundle branch block or increase in QRS duration > 50% compared to baseline
- ECG documented sustained ventricular tachycardia, or TdP.

Study drug will also be permanently discontinued if there is a decrease of creatinine clearance > 20% compared to baseline. For patients already enrolled in the study at the time of the implementation of this amendment (Amendment # 2) the study drug will be permanently discontinued if on the last available laboratory result the creatinine clearance is less than 24 ml/min or reduced by more than 20% compared to baseline. In all patients in whom study drug is discontinued because of decreased creatinine clearance, this parameter will be monitored after study drug discontinuation, at least at week 1, 2 and 4.

Also, changes were made to the study flow chart.

Protocol Amendment 3; March 7, 2003
Reason for the Amendment:
The Steering Committee also decided based on the DSMB's recommendations to maintain a 6-month follow-up of patients after the study drug discontinuation. The objective of this follow-up was to optimize patients' safety and to provide more data for explanatory analyses. It will be done in blinded conditions to avoid possible bias in data collection and will be focused on survival, major clinical events and renal function.

Amendment N°2 of the study protocol dated from January 15th 2003 finalized the day before the DSMB meeting was never circulated nor submitted and is superseded by the present amendment.

Patients must be followed up for 6 months after study treatment discontinuation. In addition to the visits already mentioned in the Letters of instructions to investigators, patients will be seen at least twice: 3 and 6 months following study treatment discontinuation.

Double blind will be maintained during the follow-up period in order to ensure an unbiased collection of data. At the request of the Steering Committee a preliminary statistical analysis will be conducted by a statistician appointed by the Sponsor, in order to understand the reasons leading to premature discontinuation. This analysis will be done once the endpoints have been adjudicated by the Central Event Committee, and after validation of the prospectively defined Statistical Analysis Plan. Full unblinding will occur when all the data has been validated.

The Investigator could discontinue study medication if 1 or more of the following were found:

- PR interval >350 ms or second or third degree AV block unless patient had a pacemaker;
- symptomatic bradycardia;
- new bundle branch block or increase in QRS duration >50% compared to baseline;
- electrocardiogram (ECG) documented sustained ventricular tachycardia (VT), or torsades de pointes;
- other cardiac or non-cardiac AEs which in the Investigator's opinion would be potentially threatening to the patient's safety.

Concomitant therapy
Not permitted therapy:
Vaughan Williams Class I and III anti-arrhythmic drugs (including the beta-blocking agent sotalol) could not be administered during the study and were to be withdrawn for at least 5 plasma half-lives (except for amiodarone) prior to the first administration of study drug.

Patients on amiodarone therapy could be randomized in the study as soon as amiodarone administration was permanently stopped but an ECG was to be performed about 4 hours after administration of study drug to verify good tolerability.

All concomitant drugs which caused torsades de pointes were contraindicated. Such drugs include some phenothiazines, cisapride, bepridil, tricyclic antidepressants, and certain oral macrolides.

Given the involvement of the cytochrome (CYP) 450 3A4 in the metabolism of dronedarone, the concomitant use of grapefruit juice and all potent inhibitors of CYP450 3A4, such as ketoconazole, itraconazole, cyclosporin, clarithromycin, erythromycin, nefazodone and ritonavir, were prohibited. Other drugs which are CYP450 3A4 substrates and have a narrow therapeutic margin, were to be avoided.

Permitted therapy:
No patient was deprived of any necessary therapy as a consequence of participating in this study. It was important that the participants received all accepted evidence-based treatments in accordance with national or international guidelines, such as anti-thrombotic therapy, anti-coagulation, adequate heart failure treatment including diuretics, Angiotensin converting enzyme (ACE) inhibitor or angiotensin II (AII) receptor antagonists in case of poor tolerability, beta-blockers and medication for rate control in patients with AF/FL.

Calcium antagonists with depressant effects on the sinus and AV node (e.g., diltiazem and verapamil) could be used, but with caution, as they could potentiate the depressant effects on conduction. Beta-blockers could also be used with caution. Digoxin could, if necessary, be co-administrated with caution. An interaction study had shown that dronedarone at the dose of 400 mg daily increases plasma levels of digoxin by an average of 30%. Therefore it was expected that patients required and would best tolerate lower doses of digoxin than usual.

If oral anticoagulation was indicated, the international normalized ration (INR) was monitored as required. No interaction between warfarin and dronedarone had been documented in Study INT3353.

An interaction study had shown that dronedarone could increase 4-fold the plasma concentrations of simvastatin, a CYP450 3A4 substrate. The clinical consequences of this PK interaction could not be predicted but the risk of rare side effects such as rhabdomyolysis could be increased.

Cardiovascular examination
A baseline echocardiography was performed in order to select a population with a reduced LVEF. To be eligible, central, blinded evaluation of the screening echocardiography had to confirm a WMI $\leq$ 1.2. No follow-up echocardiographies were planned in the study.

Efficacy assessments
The main efficacy assessments were recordings of death from any cause, or hospitalization for worsening heart failure. Resuscitated cardiac arrest and/or cardiac transplantation were not counted as death in this study. The CEC-adjudicated hospitalizations for worsening heart failure were considered.

Primary efficacy variable:
The primary efficacy endpoint was death from any cause or hospitalization for worsening heart failure.

Secondary efficacy variables:
Secondary endpoints were:

- death from any cause;
- adjudicated hospitalization for worsening heart failure;
- adjudicated hospitalization for acute cardiovascular reasons;
- adjudicated arrhythmic/sudden death;
- AF/AFL.

General statistical approach
All statistical analyses were performed using two-sided tests and/or two-sided confidence intervals (CIs). Unless otherwise specified, Fisher's exact tests were used for qualitative parameters.

Continuous parameters were summarized using mean, standard deviation (SD), median, minimal and maximal values. Categorical parameters were summarized using counts and percentages. In summary tables, patients with missing data were presented when relevant; they were excluded from the calculation of percentages, unless otherwise specified.

Two dates were used as reference dates (Day 1) according to the purpose of the analysis: the date of randomization (efficacy analyses) and the date of first study drug intake (safety analyses). Computed duration expressed in days was calculated as the difference between start and end date plus 1 day.

All statistical summaries and analyses were generated using SAS version 8.2 on unix environment.

Analysis population
Patients were analyzed for efficacy and safety according to the treatment actually received. A patient was considered actually treated with dronedarone as soon as he/she received a tablet of dronedarone.

There were 3 analysis populations.
1. Randomized and treated patients
The randomized and treated patients population corresponds to all randomized patients who received at least 1 study drug administration, either dronedarone or placebo. This population was used for analyses of efficacy and safety parameters.

2. Randomized and treated patients excluding center 616004
Because a major violation in GCP was detected in center 616004, raising doubts about the integrity of the data provided by this center, patients from this center were excluded by the Sponsor from the randomized and treated patients population, due to potentially unreliable data which might have decreased the sensitivity of the analysis of the primary and other safety endpoints. Thus, the main efficacy analysis population was the randomized and treated patients excluding center 616004. This population was also used for all safety analyses.

3. Per-protocol population
The per-protocol (PP) population was all randomized and treated patients, excluding patients from center 616004, or those with a major protocol deviation.

Periods of analysis
Three periods were defined for efficacy and safety analyses according to the main cut-off dates of the trial: “Up to January 16, 2003”, “Up to February 17, 2003” and “Up to July 17, 2003”.

Primary efficacy endpoint
The primary efficacy endpoint was the time to death from any cause or time to hospitalization for worsening heart failure, whichever was earlier.

All deaths were adjudicated except those without a SAE form documenting the AE leading to death. However, all deaths, even if non-adjudicated, were taken into account in the analysis. All hospitalizations declared by the Investigators before February 17, 2003 were adjudicated, except those occurring before randomization, or those which were judged 'planned' by the Study Coordinating Center. Only adjudicated hospitalizations were taken into account in the analysis.

Primary analysis
The primary analysis was based on the "Randomized and treated patients excluding center 616004" population up to January 16, 2003.

The primary analysis was the comparison of the 2 treatment groups using a 2-sided Log-rank asymptotic test (level of significance 0.05). Cumulative incidence functions in each treatment group were calculated using non-parametric Kaplan-Meier estimate as well as the corresponding 95% CIs (with Greenwood's variance) at specified time point.

Cox's proportional hazard model was used to estimate the hazard ratio (labeled in tables "Relative risk") with 95% CIs, if the validity of proportional hazards assumptions was confirmed graphically. The original protocol states that the primary and secondary analyses will not include covariates (Appendix 16.1.1, Sections 10.7.1.2.3 and 10.7.2.2).

Patients with no primary endpoint up to January 16, 2003 were right-censored at the latest date with complete information (on hospitalization and alive status) obtained either on "last contact form" or at the last visit performed, or on January 16, 2003 whichever came first.

Secondary analyses
The primary analysis was also performed up to February 17, 2003. The censoring process was the same as that described for the primary analysis considering the February 17, 2003 cut-off date instead of January 16, 2003.

The Sponsor's post hoc covariate analyses:
The Sponsor submitted post hoc covariate analyses that were not prespecified in the original protocol.
The primary efficacy endpoint was analyzed by the Sponsor using the following covariates: baseline weight, creatinine clearance, WMI, NYHA status, and concomitant intake (up to date of endpoint or censoring) of beta-blocker, digitalis, spironolactone, ACE inhibitors or AII receptor antagonists. First, a Cox proportional hazard model was used with all covariates (intake of concomitant medication was included as time dependent covariates) in order to adjust the treatment effect to variables with possible influence on the endpoint. Then, a Cox proportional hazard model was performed for each subcategory defined by these covariates; in these univariate analyses, intake of co-medication is intake up to the endpoint or censoring date whenever the co-medication started. Kaplan-Meier cumulative incidence curves have been done for each subcategory of the more significant covariates among those defined above. This analysis was performed on the periods "Up to January 16, 2003" and "Up to February 17, 2003".

Sensitivity analysis and per-protocol analysis:

A sensitivity analysis including patients randomized in the Polish center 616004 was done on the periods "Up to January 16, 2003" and "Up to February 17, 2003".

An "on-treatment" analysis was performed in the PP population using a competing risks analysis with model of cause-specific hazards. Competing events were the time of primary endpoint from randomization and the time of last study drug intake plus 10 days. The cumulative incidence functions were calculated separately for the 2 treatment groups with the nonparametric Prentice estimate. The 2 treatment groups were compared for primary endpoint using a 2-sided Log-rank asymptotic test.

Secondary efficacy endpoints
In all time-dependent analyses, the censoring process for secondary endpoints was the same as that described for the primary endpoint. The analyses were performed on the 3 populations unless otherwise specified. An "on-treatment" analysis was performed in the PP population with the same analytical method used for the primary efficacy parameter.

Death from any cause
The analysis consisted of the comparison of the 2 treatment groups using a 2-sided Log-rank asymptotic test. Cumulative incidence functions in each treatment group were calculated using the non-parametric Kaplan-Meier estimate as well as the corresponding 95% CIs (with Greenwood's variance) at specified time point. Cox's proportional hazard model was used to estimate the hazard ratio (labeled in tables "Relative risk") with 95% CIs.

Arrhythmic/sudden deaths
Deaths were considered as arrhythmic deaths when adjudicated as 'Documented arrhythmia'. Sudden deaths were those checked 'sudden death unwitnessed' or 'sudden death witnessed' in the death adjudication form. The time from randomization to an arrhythmic or a sudden death was analyzed with the same method as that described above for the endpoint 'death from any cause'.

Hospitalization for worsening heart failure
The cumulative incidence of first hospitalization for worsening heart failure (adjudication) considering death from any cause as a competing risk was estimated by treatment group and compared by Log-rank test.

The duration in days of the first hospitalization was summarized as a quantitative variable and compared using a Wilcoxon test.

Hospitalizations for acute cardiovascular reasons
The same analyses as those described for the criterion 'Hospitalization for worsening heart failure' were performed for all adjudicated hospitalizations.

Atrial fibrillation/atrial flutter occurrence
Two different analyses were performed according to rhythm status at randomization:

- Patients in AF/AFL at randomization: the analyses focused on cardioversions (spontaneous or electrical);
- Patients in sinus rhythm at randomization: cumulative incidence of AF/AFL recurrence was calculated using Kaplan-Meier estimates.

10.1.2 American-Australian-African trial with DronedarONe In atrial fibrillation or flutter patients for maintenance of Sinus rhythm (ADONIS): EFC4788

Study Dates: November 17, 2001 to September 25, 2003

Study Population: patients with a recent episode of atrial fibrillation or flutter

Study Centers: 101 active centers in 5 countries: USA, Canada, Australia, South Africa and Argentina

Study Design: This was a multicenter, multinational, double-blind, parallel-group study which compared the efficacy of dronedarone versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological, or spontaneous conversion of atrial fibrillation/ atrial flutter (AF/AFL).

Objectives
Primary efficacy objective: The primary objective was to assess the efficacy of dronedarone versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of AF/AFL.

Secondary objectives were:

- to assess the efficacy of dronedarone versus placebo on AF/AFL-related symptoms;
- to assess the efficacy of dronedarone versus placebo on ventricular rate control in case of AF/AFL recurrence;
- to assess the efficacy of dronedarone versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of AF/AFL after the drug plasma level steady state is reached;
- to assess the tolerability of dronedarone versus placebo in the target population.

Secondary pharmacokinetic objectives:
The PK objective was to document dronedarone and SR35021, the main metabolite, trough plasma levels at steady state and to describe the PK of the selected dose in the target population.

Study Design:
This was a multicenter, multinational, double-blind, parallel-group, placebo-controlled, phase 3 study. A total of 552 patients in normal sinus rhythm at randomization, with an ECG-documented history of an AF/AFL episode within the last 3 months, converted electrically, pharmacologically, or spontaneously, were to be randomized.

If, following randomization, AF/AFL recurred, it was recommended that the patient remain in the study according to the following conditions:

- if AF/AFL was not transient, electrical cardioversion while on study drug could be performed to restore sinus rhythm; this applied in particular to the first 5 days following randomization, the time necessary for study drug levels to reach steady state;
- if there was no indication for cardioversion the patient could remain on study drug while in AF/AFL in particular to benefit from the heart rate (HR)-lowering properties of the study drug.

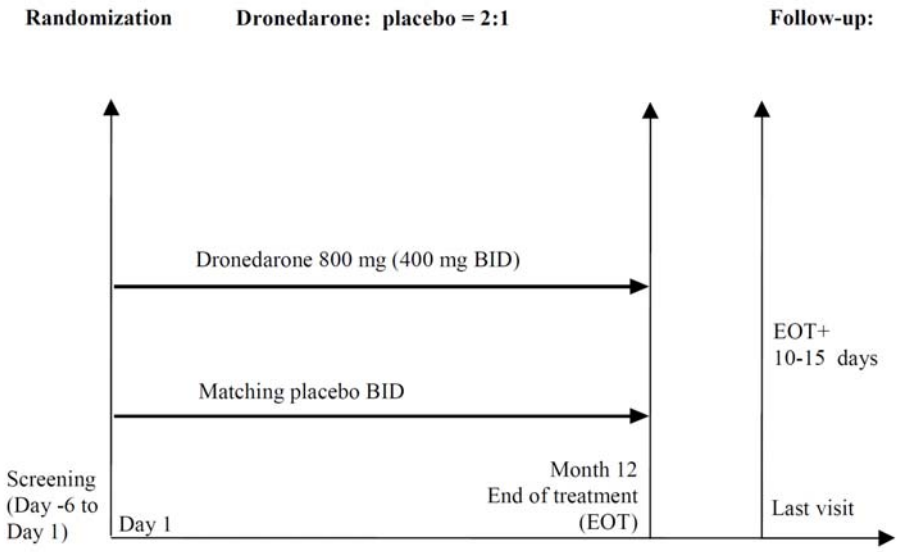


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Figure 15- Overall study design

Amendments:

Three amendments were issued for this study.

Amendment No.1, September 12, 2001, was introduced before the inclusion of any patients. In this Amendment the duration of study participation was revised, the definition of the primary efficacy population was changed, and the time window (12 months from randomization) for the observation of the primary endpoint was clarified.

Amendment No. 2, June 26, 2002, added specifications and recommendations regarding patient safety.

Amendment No. 3, March 3, 2003, gave further instructions regarding concomitant medications and safety.

Central laboratory/electrocardiogram Corelab
A central laboratory/electrocardiogram (ECG) Corelab, MDS Pharma Services, 95560 Baillet-en-France, was responsible for the following:

- reception and interpretation of transtelephonic electrocardiogram monitoring (i.e., TTEM) tracings recorded and transmitted by patients by phone;
- reading of 12-lead ECG tracings recorded by the investigational sites;
- adjudication of the primary endpoint by a group of 4 senior cardiologists;
- collection of frozen pharmacokinetic (PK) samples from the sites, storage and periodic transfer of the frozen samples to Sanofi-Synthelabo;
- assessment of biological safety parameters.

The procedure for central reading, and for the adjudication of the primary endpoint, was validated by an international expert in the field of cardiac arrhythmia

Randomization center
The S-Clinica Randomization center, B1050 Brussels, Belgium, provided the interactive voice response system (IVRS) for the following functions:

- randomization of patients using a stochastic minimization procedure;
- reallocation of treatments at Month 6 (M6);
- treatment replacement;
- recording of permanent study drug discontinuation;
- determination of investigational product needs;
- unblinding of treatment.

Steering Committee
The Steering Committee (SC) consisted of 9 members, 8 international experts in the field of cardiac arrhythmia, 1 of whom was the chairman, and 1 member from the Sponsor.
The main functions of the SC were:

- to provide advice on scientific and clinical aspects of the study protocol and related documents;
- to oversee the good conduct of the study, as well as its analysis and scientific reporting;
- to resolve policy issues that might be encountered during the study.

The SC members, who were blinded in regards to treatment groups, met to review and discuss the study at regular intervals.

Data safety monitoring board
The independent data safety monitoring board (DSMB) included 3 members:
2 international experts in cardiac arrhythmia and 1 in clinical pharmacology, who was the chairman.
The primary responsibility of the DSMB was to protect the welfare of patients participating in the study, through:

- immediate reviews of serious adverse events (SAEs) leading to death;
- regular review of monthly line listings using the Council for international organization of medical sciences (CIOMS) format;
- biannual review of the complete safety database;

- interim analysis of the primary efficacy endpoint when half of the expected events had been observed;
- recommendations based on reviews, to the SC and the Sponsor, in regards to protocol modifications, study continuation, or early study termination (conclusion forms).

Two parallel groups of patients were allocated according to central randomization to dronedarone 400 mg BID or placebo. Placebo was selected to document efficacy in the absence of a widely recognized first-line therapy for maintenance of sinus rhythm in AF/AFL patients. In order to appropriately document safety, randomization was performed in a 2 (dronedarone): 1 (placebo) ratio to maximize the number of patients on study drug, and follow-up was prolonged up to 12 months.

The detection of AF/AFL recurrences was based on a centralized review of transtelephonic electrocardiogram monitoring (TTEM) and 12-lead electrocardiogram (ECG) with adjudication of the first AF/AFL recurrence by a group of 4 senior cardiologists of ECG Corelab.

Inclusion criteria were: patients of either sex, aged 21 years or greater, in sinus rhythm for at least 1 hour at the time of randomization and with at least 1 ECG-documented AF/AFL episode in the last 3 months.

Exclusion criteria:
a) women of childbearing potential not on adequate birth control: Pregnant women and breast-feeding women could not be included (Amendment No. 1);
b) documented AF/AFL episode motivating inclusion in the study starting and not persisting beyond 10 days after an acute condition known to cause AF/AFL (e.g., alcohol intake, thyrotoxicosis, infection, myocardial infarction, pericarditis, pulmonary embolism, cardiac surgery);
c) history of torsades de pointes;
d) bradycardia <50 bpm at the screening ECG;
e) PR-interval ≥0.28 seconds at screening;
f) high degree atrioventricular (AV) block (2nd degree or higher), or significant sinus node disease (documented pause of 3 seconds or more) without a permanent pacemaker implanted;
g) treatment with other Class I or III antiarrhythmic drugs;
h) clinically overt congestive heart failure (CHF) with New York Heart Association (NYHA) Class III or IV at the time of randomization;
i) clinically relevant hematologic, hepatic [alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin >2 times the upper limit of normal at screening], gastrointestinal (GI), renal [serum creatinine ≥150 µmol/L (i.e., 1.7 mg/dL) at screening], pulmonary, endocrinologic (in particular thyroid) or psychiatric disease;
j) ongoing potentially dangerous symptoms when in AF/AFL such as angina pectoris, transient ischemic attacks, stroke, syncope, as judged by the Investigator;
k) patients in whom amiodarone prescribed for sinus rhythm maintenance was discontinued for inefficacy;
l) patients in whom 3 or more Class I or III antiarrhythmic drugs prescribed for sinus rhythm maintenance were discontinued for inefficacy;

m) patients known to have chronic AF/AFL defined as continuous AF/AFL for more than 12 months;
n) patients in whom a contraindicated concomitant treatment was mandatory;
o) patients thought to be unable to use the TTEM system as scheduled in the study protocol;
p) patients unable to sign an informed consent;
q) hypokalemia (plasma potassium <3.5 mmol/L) and hypomagnesemia (plasma magnesium <0.7 mmol/L) had to be corrected before inclusion (Amendment No. 1).

Prior and concomitant therapy
Not permitted:
Vaughan-Williams-Singh Class I and III antiarrhythmic drugs (including sotalol) other than the study drug were not to be administered during the study and had to be withdrawn for at least 5 plasma half-lives prior to the first study drug administration.

Patients on nonchronic (including intravenous) amiodarone or chronic amiodarone therapy (defined as a cumulative dose of 20 or more 200 mg tablets in the last 2 months) could be randomized as soon as amiodarone was stopped. In these patients, an ECG was to be performed about 4 hours after the first study drug administration to verify good tolerability.

All concomitant drugs which can cause torsades de pointes were contraindicated. Such drugs include some phenothiazines, cisapride, bepridil, tricyclic antidepressants, and certain oral macrolides.

Given the involvement of the CYP450 3A4 cytochrome in the metabolism of dronedarone, the concomitant use of grapefruit juice and all potent inhibitors of CYP450 3A4, such as ketoconazole, itraconazole, cyclosporin, clarithromycin, erythromycin, nefazodone and ritonavir, were prohibited. Other drugs which are CYP450 3A4 substrates and have a narrow therapeutic margin were to be avoided.

Permitted:
Calcium antagonists with depressant effects on the sinus and AV node (e.g., diltiazem and verapamil) could be used with caution, as a potentiation of the depressant effects on conduction is possible.

Beta-blockers could be used with caution (except sotalol which was contraindicated) as a potentiation of the depressant effects is possible: concomitant administration was to start with low doses of beta-blockers and increased only after ECG verification confirming good tolerability.

Digoxin, if necessary, could be concomitantly administered with caution (concomitant administration had to start with low doses of digoxin, and digoxin plasma levels monitored locally, especially at the beginning of the coadministration): an interaction study (INT2634) has shown that dronedarone at the dose of 400 mg daily increases digoxin plasma levels by an average of 30%.

If oral anticoagulation was indicated, the international normalized ratio (INR) to be monitored locally, although no interaction between warfarin and dronedarone had been documented.

An interaction study has shown that dronedarone can increase 4-fold the plasma concentrations of simvastatin, a CYP450 3A4 substrate. The clinical consequences of this PK interaction cannot be predicted, the risk of rare side effects such as rhabdomyolysis could be increased. In case of unexplained muscle pain, tenderness, or weakness occurring during concomitant therapy with a statin, the patients were to consult the Investigator immediately. The statin and the study drug were to be discontinued if myopathy was diagnosed or suspected (cf. Amendment No. 2).

The study flow chart is following.

Table 81- Study flow chart

	Screening D-6 to D1	D1[i]	D7 ±2	D14 ±3	D21 ±3	M2 ±5D	M4 ±5D	M6 ±5D	M9 ±5D	M12 ±5D[m]	EOT[g]	EOT+ (10-15) D[h]
Informed consent	X											
Medical history[a]	X											
Cardiovascular examination	X											
Notification of symptoms[b]	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X[l]
12-lead ECG[k]	X	X	X	X	X	X	X	X	X	X	X	X[l]
Laboratory tests[d]	B1,B2, B3		B2		B1,B2, B3		B1,B2, B3		B1,B2, B3		B1,B2, B3	
PK			X[f]		X[f]		X[f]		X[f]		X[f]	
Chest X-ray	X							X			X	
2D-echocardiogram	X											
IVRS calls[j]		X						X			X	
Randomization		X										
Dispense study drug		X				X	X	X	X			
Treatment with study drug		◄----	----	----	----	----	----	----	----	----	----►	
TTEM[e]		◄----	----	----	----	----	----	----	----	----	----	----►
Adverse events & concomitant drugs	◄----	----	----	----	----	----	----	----	----	----	----►	

a: Includes: cardiovascular history, review of ECGs
b: Palpitations, dizziness, fatigue, chest pain, dyspnea
c: Weight, supine blood pressure and HR
d: B1: full blood count [red blood cells (RBC), white blood cells (WBC) with differential, platelets]
B2: glucose, electrolytes (Na+, K+, Cl- , Ca++, Mg++), urea, creatinine, AST, ALT, gamma-glutamyl transferase (GGT), CPK, alkaline phosphatase, bilirubin
B3: free triiodothyronine, free thyroxine (FT3, FT4), thyroid stimulating hormone (TSH; ultra sensitive method), triglycerides, cholesterol
e: Transtelephonic ECG monitoring (TTEM x 2 10 minutes apart) in case of symptoms and at the following times: Days 2, 3, 5, M3, M5, M7, M10
f: PK: sampling for study drug assay just before morning dosing (trough) and in case of AE leading to drug discontinuation
g: EOT visit at M12 after randomization or following premature discontinuation
h: The follow-up (EOT + 10 to 15 days) visit was to take place 10 to 15 days after study drug discontinuation
i: Baseline (just before first study drug administration)
j: IVRS
k: If the 12-lead ECG shows the first AF/AFL recurrence, a second recording was done 10 minutes after the first
l: TTEM instead of 12-lead ECG and vital signs not collected if telephone visit
m: Replaced by the EOT visit if patient still on treatment
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Efficacy assessments
Atrial fibrillation:
Atrial fibrillation is defined as the absence of P-waves and fine oscillations of the electrocardiographic baseline (fibrillatory waves) associated with an irregular ventricular rhythm (except in paced patients).

Atrial flutter:
Atrial flutter is defined by a characteristic regular flutter wave pattern (F-waves) with an atrial rate between 240 to 360 bpm.

Assessments for the primary endpoint:
The primary endpoint of the study was the time from randomization to first documented AF/AFL recurrence defined as an episode lasting 10 minutes or more, as indicated by 2 consecutive 12-lead ECG or TTEM tracings recorded approximately 10 minutes apart and both showing AF/AFL. The ECG Corelab centralized the reception of TTEMs and 12-lead ECGs and adjudicated the primary endpoint by reviewing tracings.

12-lead electrocardiogram:
At each visit, the Investigator recorded a 12-lead ECG. If this ECG showed the first AF/AFL recurrence, a second ECG was recorded 10 minutes after the first in order to confirm that the primary endpoint was reached.

All ECGs required by the study protocol were sent to the ECG Corelab for central reading which included: underlying rhythm, HR, PR-, QRS-, QT-, QTc-intervals. Results were then communicated to the centers by the Corelab.

Transtelephonic electrocardiogram monitoring:
Enrolled patients were given a transtelephonic electrocardiogram monitoring (TTEM) device for the duration of the study. Patients were asked to record their ECG at times planned and in case of symptoms that might be related to cardiac arrhythmia. Each time, 2 tracings (10 minutes apart) were to be recorded. After recording, the patient was to call the ECG Corelab to transmit the tracings by phone. Tracings were analyzed by the ECG Corelab for rhythm and HR.

Symptoms:
The presence of symptoms (palpitations, dizziness, fatigue, chest pain, dyspnea) was to be reported, each time an ECG (12-lead or TTEM) was recorded. If any symptom was present, the patient was considered as symptomatic.

At each visit, the presence and details of symptoms since last visit, were recorded independently of the AF/AFL status of the patient.

Atrial fibrillation/AFL and AF/AFL-related symptoms were not to be reported as AEs unless 1 or more of the seriousness criteria were met.

Twelve-lead electrocardiogram
Twelve-lead ECGs were recorded using the investigational center's own equipment. All ECGs were assessed for heart rhythm, HR, PR-, QRS-, QT-, and QTc-interval was derived using the Bazett and Fridericia formulae (QTcB and QTcF).

Clinical laboratory assessments
Blood samples were drawn according to the schedule provided in the study flow chart, prepared and sent to the Central laboratory. The following parameters were determined:

- liver function: ALT, AST, alkaline phosphatase, GGT, total bilirubin;
- renal function: creatinine, urea;
- electrolytes: calcium, chloride, potassium, sodium, magnesium;
- metabolism: glucose, CPK, total cholesterol, triglycerides;
- WBC: basophils, eosinophils, lymphocytes, monocytes, neutrophils, WBC count;
- RBC and platelets: RBC count, platelet count;
- endocrinology: FT3, FT4, TSH.

Chest X-ray
Although pulmonary side effects are not expected with dronedarone, in case of new onset clinical or X-ray abnormalities, the patients were to be seen by a lung specialist; lung function tests could be performed, looking for a restrictive pattern with impaired CO-transfer.

Cardiovascular examination
A cardiovascular examination was performed at screening to verify eligibility, and included NYHA classification assessment.

2D-echocardiogram
The echocardiogram was performed at screening to measure the following parameters:
left atrium diameter, end-diastolic, end-systolic left ventricular diameters, end-diastolic septal and posterior wall myocardial thickness, left ventricular ejection fraction (LVEF), and valvular abnormalities as per Amendment No. 1.

According to the Sponsor, the TTEM and 12-lead ECG procedures used in this study allowed thorough documentation of arrhythmias as cardiac rhythm was documented during the study both at predefined intervals and in the case of symptoms.

Efficacy variables
The primary efficacy variable was the time in days elapsed between randomization and the first documented AF/AFL recurrence within 12 months from randomization. An AF/AFL recurrence was defined as an episode lasting 10 minutes or more, as indicated by 2 consecutive 12-lead ECGs or TTEM tracings recorded approximately 10 minutes apart, both showing AF/AFL, and

confirmed by the ECG Corelab responsible for the adjudication of the first recurrence based on the analysis of all ECGs and/or TTEMs.

The secondary efficacy variables were the following:

- symptomatic AF/AFL among the adjudicated first AF/AFL recurrence;
- ventricular rate assessed at the time of the adjudicated first AF/AFL recurrence;
- time elapsed in days between Day 5 midnight (steady state) and the adjudicated first AF/AFL recurrence within 12 months from randomization.

Pharmacokinetic assessments:
Trough (just before dosing) plasma concentrations of dronedarone (SR33589) and SR35021 were planned to be assessed in all patients, at steady state at visits Day 7 ± 2, Day 21 ± 3, M4 ± 5 days, M9 ± 5 days and M12 ± 5 days.

General statistical approach:
All statistical analyses were performed using two-sided tests and/or two-sided confidence intervals (CIs). Unless otherwise specified, Fisher's exact tests were used for qualitative parameters.

Continuous parameters were summarized using mean, standard deviation (SD), median, minimal and maximal values. Categorical parameters were summarized using counts and percentages.

Analysis populations:
Patients were analyzed for efficacy and for safety according to the treatment group assigned by the IVRS at randomization, i.e., as randomized.

Randomized and treated patients population (Intent-to-treat, ITT)
The randomized and treated patients population corresponds to the all randomized patients who received at least 1 study drug administration, either dronedarone or placebo.

Per-protocol population
The per-protocol population (PP) corresponds to the randomized and treated patients with no major protocol deviations and who had not reached the primary efficacy endpoint between randomization and the first study drug intake.

Primary efficacy endpoint:
For all analyses on the primary endpoint, only the results of the adjudication were taken into account. The primary efficacy endpoint was the time in days from the randomization to the adjudicated first AF/AFL recurrence within 12 months post randomization.

Primary analysis
The primary analysis was the comparison of the 2 treatment groups using a 2-sided Log-rank asymptotic test. A Type I error of 0.0492 was considered due to the interim analysis conducted when half of the expected events had been accumulated. Cumulative incidence functions in each

treatment group were calculated using the nonparametric Kaplan-Meier estimate as well as the corresponding 95% CIs (with Greenwood's variance estimated) at each scheduled time point. The hazard ratio (labeled in tables "Relative risk") with the 95% CI, was estimated using the Cox model with treatment group as the only factor.

Patients with no documented AF/AFL recurrence up to the end of study or up to Day 365 whichever came first, were considered as right-censored data.

Secondary analyses
Competing risks analysis on the per-protocol population:
An 'on-treatment' analysis was performed in the PP population using a competing risks analysis with model of cause-specific hazards. Competing events were: the time of adjudicated first AF/AFL recurrence within 12 months from randomization and the time of last study drug intake plus 10 days. The cumulative incidence functions were calculated separately for the 2 treatment groups with the nonparametric Prentice estimate. 95% CIs for cumulative adjudicated first AF/AFL recurrence event incidence were computed at each scheduled time point [Keiding and Andersen formula with delta method's variance estimated]. The 2 treatment groups were compared for adjudicated first AF/AFL recurrence event using a 2-sided Log-rank asymptotic test.

Baseline covariate analysis:
The primary efficacy endpoint was further analyzed using the following 3 binary baseline prognostic factors for recurrence of AF/AFL, to examine if treatment effect varied with subgroup or covariate:

- electrical cardioversion, ibutilide infusion or overdrive pacing for the last AF/AFL episode in the 5 days prior to randomization;
- chronic treatment with amiodarone;
- structural heart disease: structural heart disease was considered present if the patient has coronary heart disease and/or clinically relevant abnormalities at baseline echocardiography.

In the randomized and treated patients population, for each prognostic factor category, Kaplan-Meier cumulative incidence curves were provided per treatment group and hazard ratio (with 95% CI) was estimated using the Cox model. In order to test the treatment effect adjusted for covariate prognostic factors, a Cox model with the treatment group and the 3 prognostic factors as covariates was used.

In the PP population, an unadjusted "on-treatment" analysis was done using the competing risk method as described in the above subsection (competing risks analysis in the PP population). For each prognostic factor subcategory, Prentice cumulative incidence curves were provided per treatment group.

Secondary efficacy endpoints:
Analysis of AF/AFL-related symptoms

The analyses were performed in the randomized and treated patient population. Patients reported to be symptomatic at the time of the primary endpoint were summarized.

The primary endpoint was investigated according to presence/absence of symptoms through a survival competing risks analysis with a model of cause-specific hazards. The competing events were the time of symptomatic primary endpoint and the time of asymptomatic primary endpoint. The cumulative incidence functions were calculated separately for the 2 treatment groups with nonparametric Prentice estimate. The 2 treatment groups were compared for presence of symptoms using a 2-sided Log-rank asymptotic test.

Atrial fibrillation/AFL-related symptoms collected in the CRF at each visit (patients not necessarily in confirmed AF/AFL) were described according to intensity. An intensity index was calculated for each patient and summarized by visit; the 2 treatment groups were compared using a nonparametric Wilcoxon's rank test.

Analysis of ventricular rate at time of primary endpoint
Ventricular rate (obtained on 2 or more consecutive RR intervals on ECG) assessed at the time of the primary endpoint was analyzed in the randomized and treated patients population (modified randomized and treated patients population), as a continuous variable; first whatever the ECG method (12-lead ECG/TTEM) and considering only patients for whom primary endpoint was detected on TTEM. The 2 treatment groups were compared using a 2-way ANOVA with treatment group, ECG recording method, and their interaction.

10.1.3 SR33589B: EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm (EURIDIS)

Study Dates:19 November 2001 through 14 August 2003

Study Population: patients with a recent episode of atrial fibrillation or atrial flutter

Design: Multicenter, multinational, double-blind, parallel-group study, comparing dronedarone versus placebo for maintenance of normal sinus rhythm after pharmacological or spontaneous conversion of atrial fibrillation/atrial flutter

Overall study design and plan:
This study was identical to the ADONIS Study except that it was a European trial with 65 active centers in 12 countries: Netherlands, Germany, Poland, Hungary, Italy, France, Czech Republic, Belgium, Spain, Denmark, Finland and United Kingdom.

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Gail Moreschi
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MEDICAL OFFICER

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-913	Submission Date(s): 06/10/2005
Brand Name (proposed)	Multac
Generic Name	Dronedarone hydrochloride
Reviewer	Robert O. Kumi, Ph.D.
Team Leader	Patrick Marroum, Ph.D.
OCPB Division	1
ORM division	Cardiovascular and Renal Drug Products
Sponsor	Sanofi-Aventis
Relevant IND(s)	49,484
Submission Type; Code	N_000
Formulation; Strength(s)	Tablet, 400 mg
Class/Indication	Anti-arrhythmic/ Rhythm control in patients with atrial fibrillation or atrial flutter, to maintain normal sinus rhythm or to decrease ventricular rate

Briefing Date: 03/27/2005
Briefing Attendees: Raj Madabushi, Joga Gobburu, Phil Colangelo, Mehul Mehta, Christine Garnett, Gail Moreschi, Avi Karkowsky, John Lazor, Hank Malinowski, Nhi Beasley, Peter Hinderling, John Hunt, Norman Stockbridge, Kavita Johal, Albert Chen and Nallani Srikanth

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1 Executive Summary

In NDA 21-913, Multac (dronedarone hydrochloride) is proposed for rhythm control in patients with atrial fibrillation or atrial flutter, to maintain normal sinus rhythm or to decrease ventricular rate. Dronedarone HCl is a benzofuran derivative in the same class as amiodarone, an approved antiarrhythmic agent. Dronedarone is an anti-arrhythmic agent that has electrophysiological properties associated with all four Vaughan-Williams classes. Multac will be marketed as a 400 mg strength tablet. The proposed dronedarone dosage is 400 mg twice daily; each dose should be given with or shortly after the morning and evening meal. According to the applicant, Multac treatment can be initiated in an outpatient setting; additionally, with the proper precautions, Multac can be initiated as soon as amiodarone therapy is stopped or following therapy with Class I and Class III anti-arrhythmic. Numerous clinical and nonclinical studies were conducted to support the Multac NDA including three pivotal trials in the target patient population, over 40 clinical pharmacology (pharmacokinetic studies), and over 10 in vitro studies. The clinical studies were conducted in healthy subjects and various patient groups; dronedarone was administered orally as well as intravenously in these studies.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the information submitted to NDA 21-913. The clinical pharmacology and biopharmaceutics information provided in NDA 21-913 is acceptable. However, the applicant should adequately address the following comments:

Comments to Sponsor

- Please indicate when results from the hepatic impairment study, POP5820, will be submitted to the Agency. Without this information, the product labeling will be restrictive in this patient population
- You have not adequately addressed the issue of dose-response in the target population; therefore dosage adjustment is not feasible during dronedarone therapy.
- You have not provided sufficient permeability information to support dronedarone designation as BCS 2. Please provide all available information that demonstrate dronedarone is a high permeability compound.
- The dissolution methodology is acceptable, however, we do not agree with your dissolution specification. Based on the data provided the following specification is more appropriate: 1) Not less than 25 % and not more than 50 % is dissolved within 30 minutes 2) Q = 80 at 90 minutes
- In future submissions, any concentrations and/or subjects that have been excluded from the analysis should be maintained in the datasets. For this analysis, the sponsor identified 123 concentrations (from 10 subjects) as outliers and excluded these observations from the dataset.
- Please refer to the attached, revised label for detailed labeling recomendations

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Over 40 studies were included in the clinical pharmacology and biopharmaceutics development program for the use of dronedarone in patients with atrial fibrillation or atrial flutter; in these studies dronedarone was administered by the oral and intravenous route. Additionally, dronedarone was evaluated in over 10 in vitro studies. Studies included in NDA 21-913 are presented in Appendix 4.1; not all of the submitted studies were reviewed because they were not required for evaluation of the proposed indication.

Key Clinical Pharmacology and Biopharmaceutics Findings and Information

1. **Dronedarone Pharmacokinetics (ADME)**

Absorption/absolute bioavailability and general pharmacokinetics (PK)

- Dronedarone ***absolute oral bioavailability*** (BA) following administration of a capsule formulation (800 mg) is approximately 15 %, but this value may not be reflective of the absolute oral BA of the to be marketed tablet formulation (proposed 400 mg dose) due to differing food effect (formulation dependent) and dose-dependent pharmacokinetics oral administration
- Administration of ***food*** increases mean dronedarone absorption from approximately 2- (low fat meal) to 5-fold (high fat meal)
- Dronedarone exposure increased in a ***greater than dose proportional manner*** following single and multiple dose administration. For a two-fold increase in dose, the exposure increased by 2.5 to 3.5-fold over the 200 to 1600 dose range
- ***Steady state*** is achieved approximately seven days after repeated administration of 400 mg dronedarone twice daily
- The mean accumulation ratio is ~ 2.6 at the proposed dosage
- Dronedarone exhibits dose- and time-dependent PK
- Dronedarone has limited properties associated with PGP substrate status

Distribution

- Dronedarone is approximately 99 % bound to plasma proteins at therapeutic drug concentrations; the main binding component is albumin
- Following single dose administration of IV dronedarone (40 – 80 mg), the volume of distribution associated with the terminal elimination phase was 2500 – 3400 L

Metabolism and P-glycoprotein

In vitro information

- Dronedarone metabolism was mainly mediated by CYP3A, yielding the major metabolite, SR35021
- Dronedarone has a low inhibitory potential towards major CYPs, including on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. The most inhibitory potential was towards CYP3A4 (I/Ki ~ 0.01) and CYP2D6 (I/Ki ~ 0.06)
- Dronedarone exhibited similar PGP inhibitory potential as cyclosporine A by preventing the efflux of two PGP substrates, digoxin and vincristine

In vivo information
Dronedarone is extensively metabolized following dronedarone administration and negligible amounts of intact dronedarone are present in the feces. N-debutylation appears to be the main metabolic pathway of dronedarone, leading to the formation of SR35021; however additional processes occur including oxidation of SR35021, oxidative deamination, and direct oxidation. Ultimately, several metabolites (> 30) are formed and excreted in the urine and feces. SR35021 is not detected following IV administration, suggesting that it is formed mainly presystemically during first pass.

Properties of metabolites
The activities of all the identified metabolites (n > 30) were not tested; however, the major metabolite, SR35021 is 3 to 10 times less potent than dronedarone. SR35021 plasma levels are approximately half that of dronedarone; other individual metabolites account for < 3 % of the administered dronedarone dose. Based on the low exposure of the metabolites, they are unlikely to impact overall activity associated with dronedarone administration, unless they are individually or collectively more potent than dronedarone.

Overall, SR35021 exhibited PK properties (accumulation, half-life, volume of distribution) that were similar to that of dronedarone.

<u>Excretion (Elimination)</u>

- Mass balance indicates that orally administered dronedarone is ultimately excreted in the urine (6 %) and feces (84 %) primarily as metabolites. No unchanged dronedarone was excreted in the urine. Similar findings were obtained following IV administration. Radioactivity was undetectable after two weeks.
- The systemic plasma clearance (IV administration) ranged from 130 to 150 L/h and the apparent oral clearance (CL/F) was ~ 500 L/h for the 400 mg dose.
- Dronedarone half-life following IV administration was between 13 and 19 hours; following oral administration half-life appeared to be dose- and time- dependent ranging from 27 to 32 hours.

2. Pharmacodynamic effects of dronedarone

- Alters electrophysiological measures: generally increases QT-, PR- and RR- and QRS- intervals and decreases T-wave amplitude
- Decreases heart rate (bradycardic effect)
- Tends to decrease blood pressure (systolic and diastolic)
- Causes an increase in serum creatinine levels by inhibiting renal tubular secretion of creatinine; which leads to apparent decrease in renal function (CLcr decreased). However, this effect is reversible upon discontinuation of dronedarone therapy.

3. QT/QTc Information

A clear dose-response relationship was shown for QT prolongation in healthy subjects.

4. Special Populations

- ***Renal Insufficiency:*** The effect of impaired renal function was not evaluated in the dronedarone program

- ***Hepatic insufficiency:*** The effect of impaired hepatic function has not been evaluated, but there is an ongoing study to evaluate this patient population.
- ***Gender:*** Relative to elderly males, elderly females have exposures that are approximately 30 % higher.
- ***Age:*** Relative to healthy young males, healthy elderly males have exposures that are about 40 % higher
- ***Race:*** Relative to healthy male Caucasians, healthy Asian (Japanese) males have exposures that are about 100 % higher

5. Formulation

Dronedarone hydrochloride has been formulated into 400 mg tablets; the to-be-marketed tablets are similar to those used in the pivotal safety/effectiveness trials. It is to be noted that the placebo formulation is identical to the drug formulation, except for the active ingredient.

6. PK/PD drug-drug interaction information

Drug	Classification	Effect of co-administration		
		PD (either or both drugs)	Dronedarone	Other Drug
	Miscellaneous			
digoxin	PGP substrate	NA	NA	↑ 2.5 fold
pantoprazole	decrease gastric pH	NA	↔	NA
theophylline	CYP1A2 substrate	NA	↔	↓ 20 %
	CYP3A function			
rifampicin	inducer	None	↓ 80 %	NA
dilitiazem	weak inhibitor	↑ repolarization time	↑ 60 %	NA
nifedipine	weak inhibitor	Lowered blood pressure	↑ 20 %	NA
grapefruit juice	moderate inhibitor	NA	↑ 3-fold	NA
ketoconazole	strong inhibitor	↑ PR, no effect on QT	↑ ≥ 9-fold	NA
verapamil	Substrate, inhibitor	↑ repolarization time	↑ 40 %	↑ 40 %
nisoldipine	substrate	↔	↔	↑ 100 %
simvastatin	substrate	↔	↔	↑ 4-fold
ethinylestradiol	substrate	NA	NA	↑ 25 %
levonorgestrel	substrate	NA	NA	↑ 18 %
	CYP2C9 function			
losartan	substrate	↑ heart rate	↔	↔
S-warfarin/R-warfarin	substrate	↑ INR by 7 %	↔	↑ AUC 11 %
	CYP2D6 function			
metoprolol	Substrate	↓ cardiac contractility	NA	↑ 60 -150 %
propranolol	substrate	↓ HR, DBP, SBP	↔	↑ 16 to 33 %

7. Dissolution

The Agency's recommended dissolution specification differs from that of the applicant.

Applicant's Proposal

1. Dissolution Method: apparatus- paddle at 75 rpm; medium: 1000 ml of phosphate buffer, at pH 4.5 and 37° C
2. Dissolution Specification: 1) Not less than 20 % and not more than 60 % dissolved after 30 min 2) Q = 75 after 90 min

Reviewer's Recommendation

1. Dissolution Method: applicant's proposal is acceptable
2. Dissolution specification: 1) Not less than 25 % and not more than 50 % is dissolved within 30 minutes 2) Q = 80 at 90 minutes

Signatures

Reviewer: _____

Pharmacometrics Reviewer _____

Team Leader Concurrence _____

2 Question Based Review

2.1 What are the general attributes of dronedarone?

2.1.1 Regulatory Background

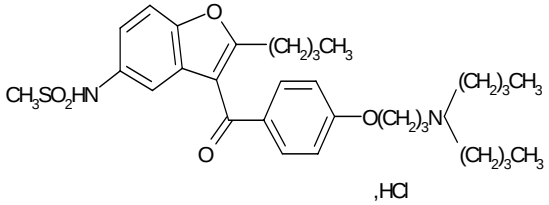
Several meetings were held between the Agency and the applicant to discuss the dronedarone development program (IND 49,484). Two major highlights of clinical pharmacology impact were:

- Meetings held on July 13, 2004 and January 3, 2005: Sponsor was asked to study effect of dronedarone in patients with congestive heart failure (CHF)
- End of Phase 2 meeting held on April 9, 2001: Sponsor was asked to study different doses of dronedarone in mortality trial and AF/AFL population to evaluate exposure-response relationships for dosage adjustments

2.1.2 Highlights of chemistry and physical-chemical properties of the drug substance and product

Dronedarone HCl is a benzofuran derivative that is formulated into 400 mg tablets for oral administration. Additional characteristics of dronedarone are as follows:

Chemical name	N-{2-butyl-3-[4-(3-dibutylaminopropoxy)benzoyl]benzofuran-5-yl}methanesulfonamide, hydrochloride
Molecular weight	593.2
Molecular formula	$C_{31}H_{44}N_2O_5$ S. HCl
Structural formula	



Appearance	white fine powder
Solubility	practically insoluble in water and freely soluble in methylene chloride and methanol.
Formulation	400 mg tablet (expressed as base)
Proposed Name	Multac contains 400 mg of dronedarone (free base)
Miscellaneous	analogue of amiodarone, an approved anti-arrhythmic agent; dronedarone is anticipated to have fewer safety concerns (e.g. thyroid, ophthalmologic and pulmonary) than amiodarone

<u>Miscellaneous Formulation Information</u>

Several formulations (tablets and capsules) were developed; the final formulation was one that minimized food effects, yet provided adequate exposure. Dronedarone was administered mainly as a tablet formulation, but dronedarone was also give as an intravenous oral solution in several studies. The final tablet formulation is referenced as 2E5. The composition of the to-be-marketed formulation is presented in Table 1. It

should be noted that he placebo formulation is identical to the drug formulation, except for the active ingredient.

Table 1: Composition of dronedarone HCl 400 mg (base) film coated tablets (reference 2E5)

Ingredients	Compendial grade	Function	Unit quantity (mg/tablet)	% (w/w)
CORE				
Drug substance				
Dronedarone hydrochloride (a)	In-house monograph	Active substance	426.00 (b)	65.54
Excipients				
Hypromellose (6 mPa)	Ph. Eur.-USP	Binder	26.00	4.00
Maize starch	Ph. Eur.-NF	Diluent-Disintegrant	45.50	7.00
Crospovidone (type A)	Ph. Eur.-NF	Disintegrant	65.00	10.00
Poloxamer 407	Ph. Eur.-NF	Solubilizing agent	40.00 (c)	6.15
Lactose monohydrate (d)	Ph. Eur.-NF	Diluent	41.65	6.41
Colloidal anhydrous silica	Ph. Eur.-NF	Flow aid	2.60	0.40
Magnesium stearate (e)	Ph. Eur.-NF	Lubricant/Anti-adherent	3.25	0.50
Purified water (f)	Ph. Eur.-USP	Granulation solvent	-	-
Core mass			***650***	***100***
COATING/POLISHING				
Hypromellose (6 mPa.s)	Ph. Eur.-USP	Film agent	7.25	72.50
Titanium dioxide	Ph. Eur.-USP	Opacifier	1.00	10.00
Macrogol 6000	Ph. Eur.-NF	Plasticizer	1.75	17.50
Purified water (f)	Ph. Eur.-USP	Coating solvent	-	-
Film-coating mass			***10***	***100***
Carnauba wax	Ph. Eur.-NF	Polishing agent	Traces	-
Film-coated tablet mass			***660***	

(a) The strength of the tablet is expressed as base (dronedarone)
(b) Corresponds to 400 mg of the base
(c) Corresponds to 10 % of the dronedarone quantity (400 mg)
(d) BSE free
(e) From vegetable origin
(f) Removed during manufacture

2.1.3 Proposed Mechanism of Action and Indication

The reported primary mechanisms of action of dronedarone are related to anti-arrhythmic activity with effects from all four classes of the Vaughan Williams' classification (VWC). Per VWC dronedarone is a multi-channel blocker inhibiting the potassium currents (including $I_{K(Ach)}$, I_{Kur}, I_{Kr}, I_{Ks}) and thus prolonging cardiac action potential and refractory periods (Class III), the sodium currents (Class Ib), the calcium currents (Class IV) and it non-competitively antagonizes adrenergic activities (Class II).

2.1.4 Proposed Administration Route and Dosage

Dronedarone hydrochloride (Multac®) is intended for oral administration via 400 mg tablets. The recommended dosage is 400 mg twice daily (800 mg daily). Per the applicant, treatment with Multac can be initiated in an outpatient setting. Multac should be taken as one tablet with or shortly after the morning meal and one tablet with or shortly after the evening meal. If the patient is switched to Multac from Class I or Class III anti-arrhythmic therapy the following paradigm should be adopted:

Treatment with Multac can be initiated as soon as amiodarone therapy is stopped. An ECG should be performed in these patients about four hours after drug administration. It is recommended that all other Class I and III anti-arrhythmic be withdrawn for at least five plasma half-lives before starting treatment with Multac.

2.2 What are the general clinical pharmacology characteristics of dronedarone?

2.2.1 Design features of clinical studies used to support dosing in AF/AFL patients

The key design features of the clinical pharmacology and clinical studies used to support dosing in the target population (AF/AFL) are summarized in Table 2.

Table 2: Key design features of the primarily clinical and clinical pharmacology studies supporting proposed indication

	Non-placebo controlled Trials in Healthy Male Subjects (Phase I)		Placebo Controlled Trials in Patients with AF/AFL			
			Phase II	Phase III		
Study	TDR2395	TDR3549	DRI3550/ DAFNE	ERATO EFC4508	EURIDIS EFC3153	ADONIS EFC4788
Descriptor/ Objective	Tolerability following single and multiple oral doses	Tolerability following BID repeated ascending oral doses	maintenance of sinus rhythm after cardioversion of AF- dose-ranging study	control of ventricular rate during AF	maintenance of normal sinus rhythm after conversion of AF/AFL in two "regions" (Europe for EURIDIS and (American Australian- African for ADONIS)	
Doses (mg)	400 to 1000 BID and 800 to 1600 QD	800 to 1600 BID	400, 600 and 800 BID	400 BID	400 BID	
Measures/ Endpoints	ECG parameters Vital Signs PK intensive sampling	MTD, ECG parameters Vital Signs PK intensive sampling	ECG measures Vital Signs PK trough and maximum levels only (defined by time window)	ECG measures Vital Signs PK (sparse sampling for Population PK)		
Indication	NA	NA	Supportive for sinus rhythm maintenance Supportive for ventricular rate control	Confirmatory for ventricular rate control	Confirmatory for sinus rhythm maintenance Supportive for ventricular rate control	

2.2.2 Clinical response (efficacy) endpoints

There were two primary clinical response endpoints in this application depending on the indication:

1. Time in days between randomization and the first AF/AFL recurrence, defined as an episode lasting 10 minutes or more, as indicated by two consecutive 12-lead ECGs or TTEM tracings recorded 10 minutes apart, and both showing AF/AFL confirmed by the ECG Corelab.
2. Change in mean ventricular rate (hr) measured by 24-hour Holter recording at rest on day 14 (steady state) compared to baseline.

2.2.3 Identification and measurement of dronedarone concentrations in plasma

Dronedarone appeared to be adequately identified and measured in most studies; similarly, dronedarone's main metabolite, SR35021 (active compound) was adequately measured and identified. Dronedarone and SR35021 were measured by an array of

validated assays. These assays employed LC/MS/MS and HPLC methodologies. Please refer to Analytical Section (2.6) for additional assay information.

2.2.4 Dronedarone Exposure-Response

The exposure-response evaluation revealed that:

- There was no clear dose-response relationship for effectiveness in the target patient population
- A trend towards a linear dose-response (ECG measures and heart rate) was observed in healthy subjects
- A dose-response relationship existed for safety (incidence and severity of diarrhea and decrease in CLcr).

Three studies provide the main exposure-response information: TDR2395 and TDR3549 (healthy subjects) and DRI3550 or DAFNE (AF/AFL patients). The study designs of these three trials were presented previously.

The Pharmacometrics Reviewer, Dr. Garnett conducted and in-depth review of the DAFNE trial to assess exposure-response with respect to efficacy and safety. Three main questions were addressed by the PM reviewer; each question is addressed in turn:

- Is there a concentration-response relationship for the effectiveness endpoints 1) time to AF recurrence and 2) ventricular rate?
- Is there a concentration-response (safety) relationship for treatment-emergent diarrhea?
- Does elevated serum creatinine return to baseline after dronedarone treatment is discontinued (safety-related)?

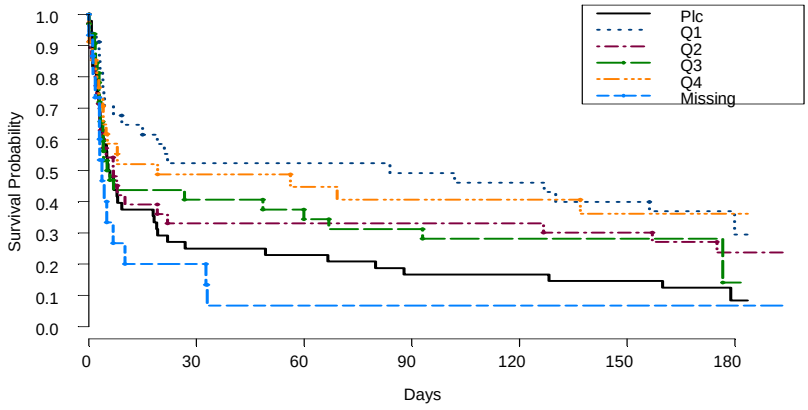
Reviewer Note

The PM Review did not conduct an exposure-response analysis for the data from the pivotal trials because only one dose was studied (400 mg).

2.2.4.1 *Exposure- Effectiveness Assessment*

Figure 1 depicts the Kaplan Meier survival curves for time to AF recurrence (days) by concentration quartile.

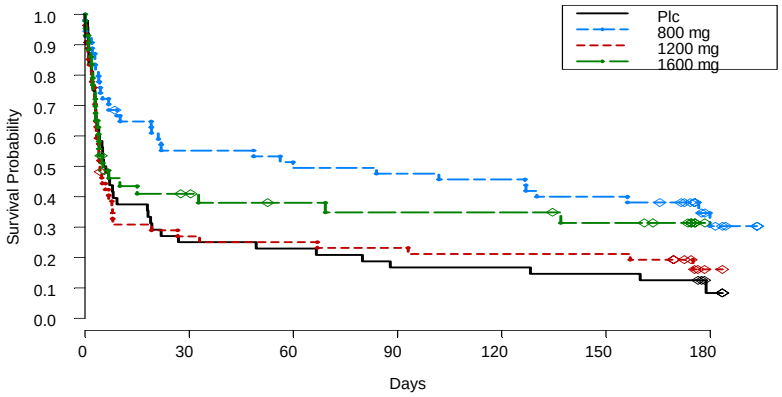
Figure 1: Kaplan-Meier Survival Curves by Concentration (ng/mL) Quartile (Q1 = 13.3-49.5, Q2 = >9.5-72.4, Q3 = >2.4-113.5, and Q4 = >113.5-559)



There was no trend for increasing or decreasing concentration-response relationships. The median time to recurrence was longest for the group of subjects with the lowest concentrations (Q1); median = 84 days. It should be noted that 14 of the 15 subjects (93.3%) with missing concentration experienced AF recurrence. The median (range) of event times for this group were 3.4 (.003 to 33) days. Therefore, the majority of subjects (12/14, 86%) in this group had an event prior to the scheduled pharmacokinetic sample on Day14.

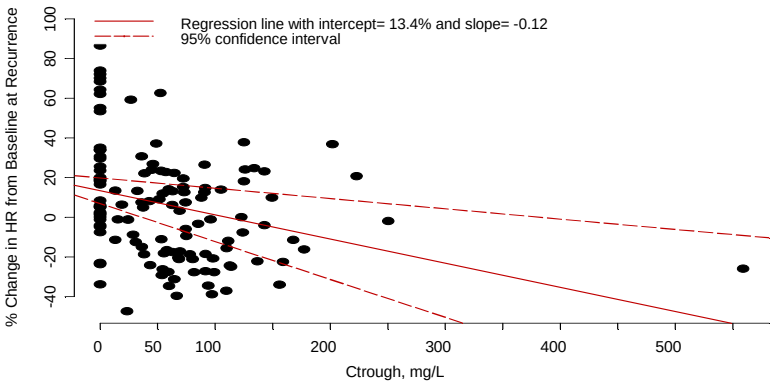
There was no clear dose response as depicted in Figure 2.

Figure 2: Kaplan-Meier Plot for Time to First Recurrence of AF from Conversion [reviewer's figure from independent analysis of data]



The change in heart rate from baseline vs. trough concentration is shown in Figure 3. For this plot, baseline was defined as the ventricular rate (measured by ECG) during the initial AF episode prior to dronedarone treatment.

Figure 3: Ventricular Rate Control vs. Trough Concentration



There was a trend for lower heart rate at AF recurrence with higher trough concentrations. It should be noted that subjects with missing trough concentrations were excluded from the analysis.

2.2.4.2 *Exposure-Safety Assessment*

- **Treatment emergent diarrhea**

In the DAFNE trial the incidence and severity of treatment-emergent diarrhea was dose related, with the highest dose group (800 mg BID) having the highest incidence and intensity of diarrhea (Table 3). However, diarrhea does not appear to be related to plasma concentrations of dronedarone.

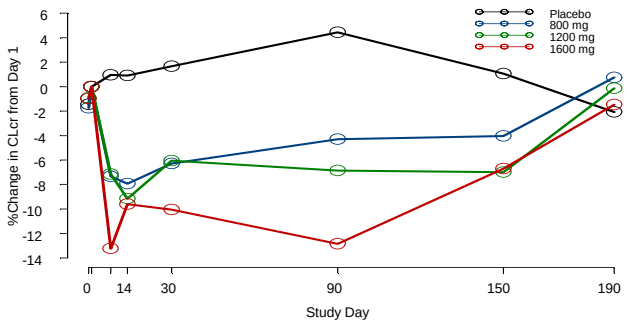
Table 3: Overview of Diarrhea Treatment emergent adverse events

Intensity	Placebo (N=66)	800 mg (N=76)	1200 mg (N=66)	1600 mg (N=62)	Total Drug (N=204)
Total	2 (3.0)	2 (2.6)	5 (7.6)	17 (27.4)	24 (11.8)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.8)	3 (1.5)
Moderate	0 (0.0)	1 (1.3)	1 (1.5)	5 (8.1)	7 (3.4)
Mild	2 (3.0)	1 (1.3)	4 (6.1)	9 (14.5)	14 (6.9)
SAE	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)

- **Dose-Response and other information related to changes in serum creatinine due to dronedarone administration (PM and Primary Reviewers)**

Treatment with dronedarone caused an elevation of serum creatinine that was reflected in an apparent decrease in creatinine clearance (CLcr). Figure 4 shows that CLcr is reduced throughout the study (Days 1-150) but returns to baseline after treatment is discontinued: CLcr returns to baseline at Day 190 which corresponds to the last patient visit at 10 days after stopping drug.

Figure 4: Mean percent change in CLcr by Study Visit (PM Review)



The impact of short term dronedarone administration on measures of renal function is summarized in Table 4 (PDY5487). In Study PDY5487 dronedarone 400 mg BID was given for seven days. The effect of dronedarone on CLcr was similar in the short term (PDY5487) and long term study (DAFNE): initial decline upon dronedarone administration followed by return to baseline after drug discontinuation (within 14 days).

Table 4: Impact of dronedarone administration on PD measures of renal function

Component	Estimates	Dronedarone vs. placebo	Comment
Renal Sinistrin	GFR	↔	No effect
CLcr	Renal function	↓	
CLcr/CL sinistrin	Renal tubular secretion of creatinine	↓	interferes
PAH	Renal Blood flow (RBF) and tubular organic anion transporter (OAT)	↔	No effect on RBF
NMN renal clearance	Tubular organic cation transporter (OCT)	↓	May impact organic cations eliminated renally
24-hr creatinine clearance	Overall renal function	↔	Findings are inconclusive due to study design
Electrolytes (UFR, Na, K ions)	Excretion and osmolality	↔	No effect on physiological processes

Evaluation of the PD findings (Table 4) suggests that dronedarone decreases apparent renal function (measured by CLcr) by interfering with tubular secretion of creatinine. However, this interference does not appear to significantly alter overall renal function as evidenced by the minimal impact on GFR, renal blood flow and other measures of renal function. Some investigators indicate that an apparent decrease in CLcr alone, does not necessarily signify a worsening of renal function. In light of the findings from study PDY5487, DAFNE and the observations reported by other investigators, it is reasonable to conclude that dronedarone's impact on renal function may not be clinically significant. However, the decrease in the function of OCT suggests that dronedarone may affect the elimination of organic cation that are renally excreted; thus, there is a potential for drug-drug interactions to occur between dronedarone and such compounds.

Primary Reviewer's Note on Potential Study Limitations Related to Trough Estimations and impact on exposure-response analyses

Trough concentrations were defined in a time window (0 to 2 hours post dose and 8 to 18 hours) and may not accurately reflect true trough concentrations. The lack of definitive trough times, typically taken at predose, may contribute to the variability and failure to observe a concentration-response relationship. Additionally, the poor power of the study, due to a limited number of subjects may have impacted the exposure-response analyses; for instance, subjects in the 800 mg BID had a much higher rate of discontinuation due to adverse events than other groups.

Per the PM review, analyses of the patient demographics indicated that all baseline characteristics were similar across treatment groups, apart from the duration of AF episodes (p=0.0133) Additionally, with respect to concomitant medications, more subjects in the placebo and 800 mg dose group were taking beta-blockers. There were similar percentages of patients taking anticoagulant therapy, digoxin, and calcium channel blockers. It is unclear if these differences in baseline characteristics, particularly concomitant medications, may have affected the dose-response relationship. With respect to concomitant medications, it should be noted that in the drug-drug interaction studies, unexpected or idiosyncratic PD effects were observed on occasion. For example in the diltiazem-dronedarone interaction study (INT4084), there was no clear dose response: the

400 mg dronedarone dose produced the greatest PR prolongation, followed by the 800 mg and finally 1200 mg dose. For QT prolongation, there was a dose-response relationship, but data were highly variable. The same study showed a decrease in QT for all dronedarone doses co-administered with nifedipine. These idiosyncratic effects may be due to a combination of synergistic, additive and or antagonistic interactions; ultimately leading to an apparent lack of dose-response.

2.2.4.3 ***QT and QTc interval and other electrophysiological measures***

Consistent with it's an anti-arrhythmic property, dronedarone, altered electrophysiological measures, such as QT-, QTc-, PR- and QRS-intervals and T-wave amplitude. A formal QT study was not conducted, however, results from several studies showed consistent trends or statistically significant findings, suggesting that dronedarone prolonged cardiac repolarization. On occasion, dronedarone's effect on EP parameters appeared dependent on concomitant medications.

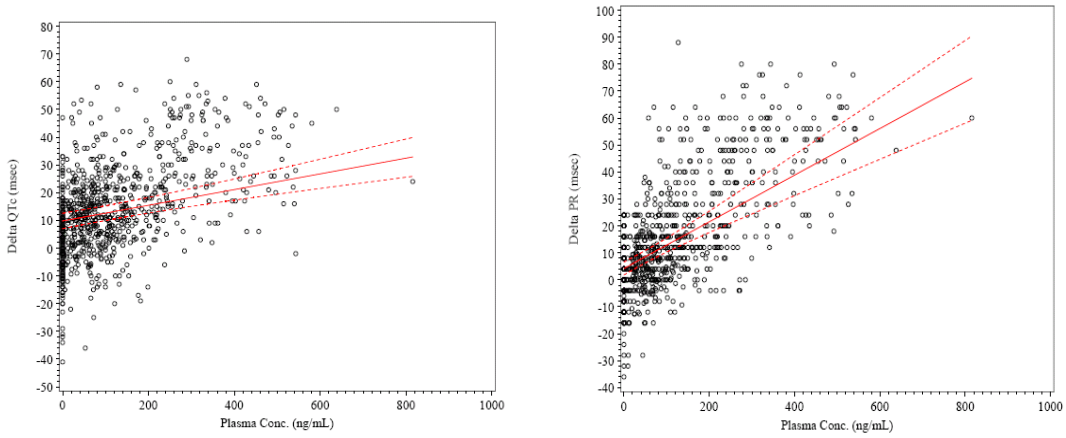
Exposure-Response Evaluation in Healthy Volunteers

In the healthy volunteer dose-response studies, TDR3549 and TDR2395, two salient trends were observed:

- Dronedarone significantly prolonged QT-, QTc- and PR- intervals in a dose-dependent manner (linear or showed trend) over the 800 – 1600 mg QD and 400 to 1600 mg BID dose range
- There was a trend showing that BID dosing had a greater effect than QD dosing on the EP parameters

The applicant summarized the findings on exposure-response (ECG parameters) graphically in Figure 5 using data from TDR2395, TDR3549 and INT4882 (verapamil drug interaction study).

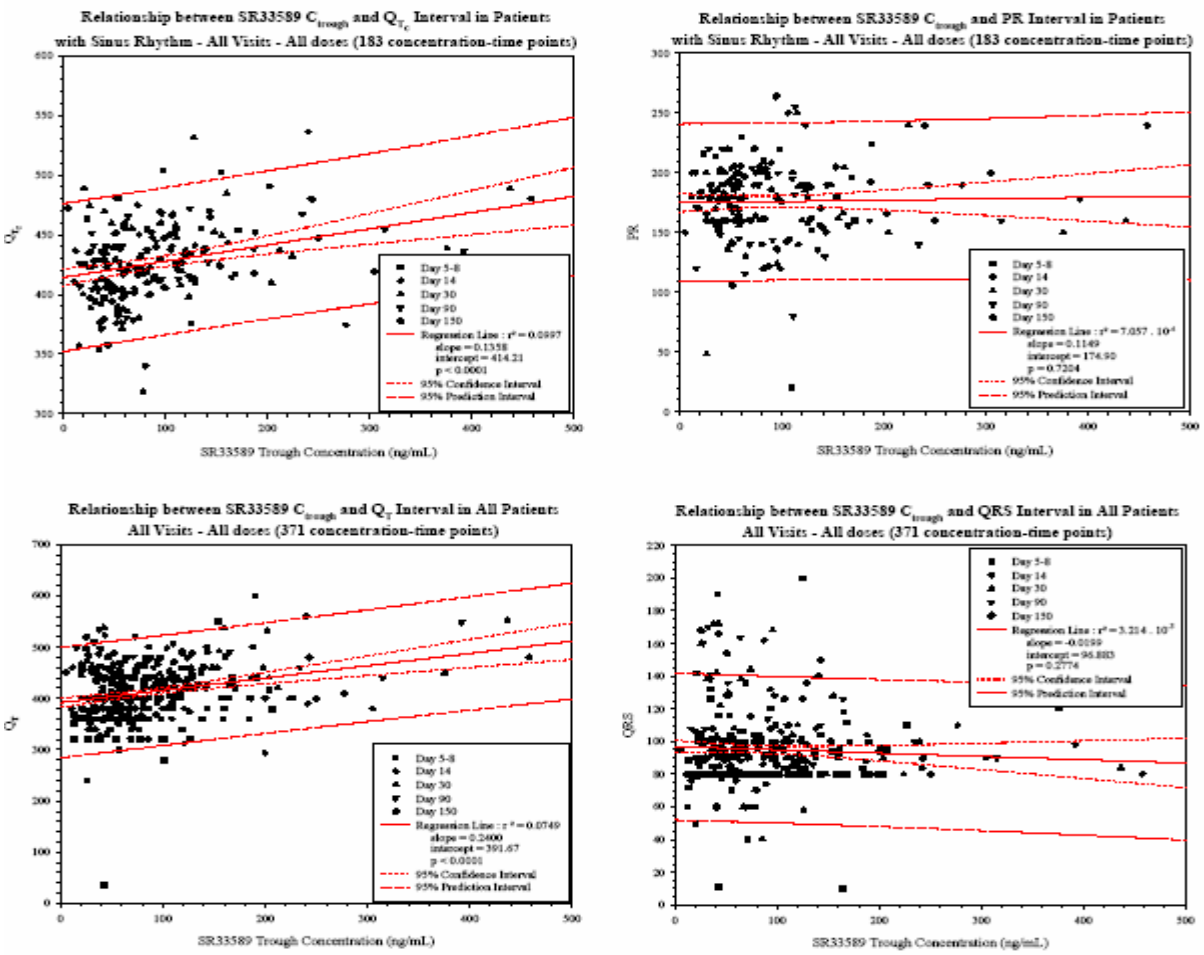
Figure 5: QTc (left panel) and PR (right panel) changes from baseline (ms) versus dronedarone plasma concentrations (ng/mL) with estimated mean linear model and two-sided 95% confidence limits - Pooled data from TDR2395, TDR3549 and INT4882



Exposure-Response Evaluation in Patients

The applicant summarized the exposure-response relationship in the DAFNE trial in Figure 6. There was a trend towards increasing QT and QTc with increasing concentration.

Figure 6: Individual dronedarone Ctrough Levels (ng/mL) as a Function of ECG Parameters



2.2.4.4 Heart Rate and other Vital signs

In the healthy volunteer dose-response studies, TDR3549 and TDR2395, the following two observations were made:

- Dronedarone decreased heart rate during exercise testing in a dose-dependent manner (Figure 7). At rest, the bradycardic effect was not as clear.
- There was no clearly dose-related effect in the BP changes; some active dose groups caused decreases in DBP or SBP but others had no effect Figure 8).

Figure 7: Change in Daily Heart Rate as a function of dronedarone dosage during exercise test

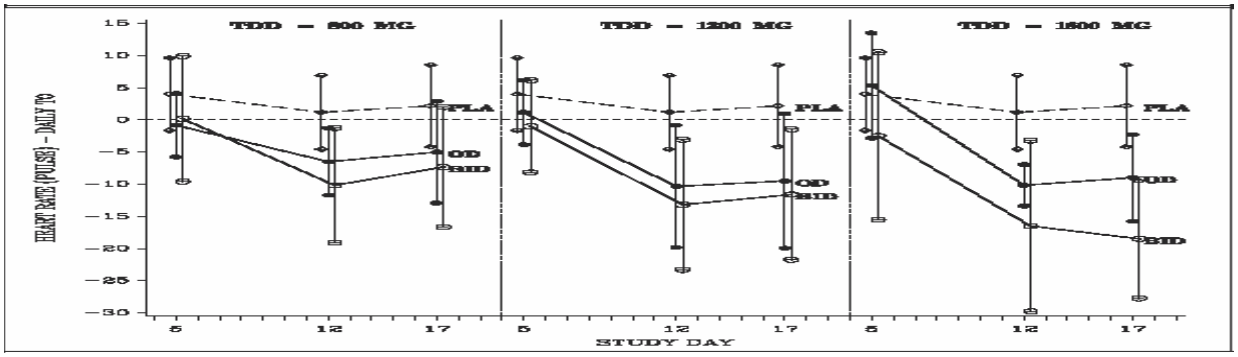
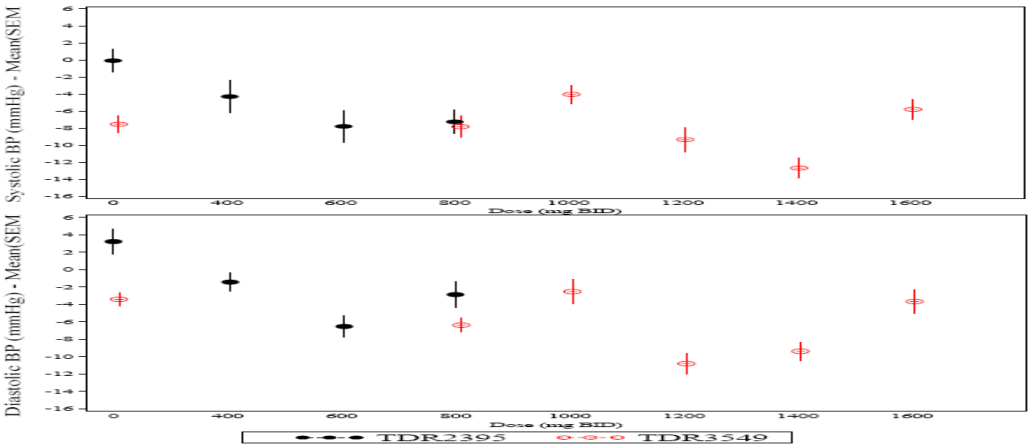


Figure 8: Mean (SEM) changes from baseline in SBP and DBP (mmHg) at 4 hours postdose over the last 5 days of treatment in studies TDR2395 and TDR3549 (per applicant)



Reviewer Note on Sections 2.2.4.3 and 2.2.4.4

Overall, dronedarone induced ECG changes consistent with the electrophysiological properties of the compound, in particular a dose-related anti-adrenergic effect (class II), a prolongation of the PR-interval (class II and/or class IV) but a moderate QT-prolongation (class III). Relative to higher dronedarone doses (>= 800 mg BID) slight changes in PD measures were observed at 400 mg BID.

2.2.4.5 ***Acceptability of applicant's proposed dosage regimen***

The proposed dosage, 400 mg BID, appears adequate based on the known relationship between dose-concentration-response; however, the dose-response relationship has not been adequately defined in patients. It is unclear if the selected dose is optimized with respect to safety and effectiveness because only one dose was studied in the pivotal trials (see Medical Review), and the DAFNE trial did not show a dose-response relationship.

The major unresolved issue is the inadequate characterization of the dronedarone dose-response relationship, specifically there is a:

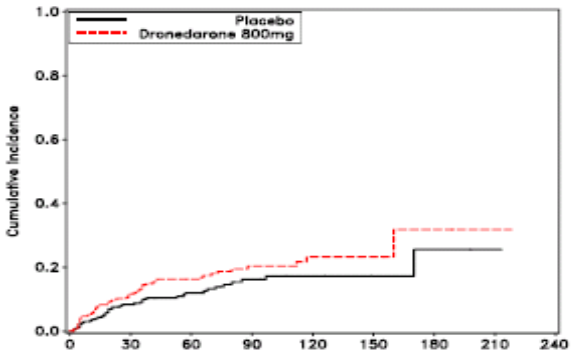
- Lack of response (particularly effectiveness) information at doses < 400 mg
- Minimal response (effectiveness and safety) information at doses > 400 mg
- Lack of dose-ranging information in patients with more advanced heart disease, such as patients with congestive heart failure (CHF), who are likely to use dronedarone
- Lack of dose titration (if needed) information for dronedarone, which is further limited by the availability of only one dosage strength.

Overall the lack of comprehensive dose-response information should limit dronedarone usage to situations were dronedarone exposure is comparable to that obtained at the 400 mg dose, only. In particular, the clinical risk-benefit profile is unknown in the following two situations:

- Concomitant medications that alter dronedarone exposure significantly
- Patient groups that may not respond favorably to a 400 mg dose

In ANDROMEDA, subjects on dronedarone treatment had a greater number of deaths or worsening heart failure than patients on placebo (Figure 9 and Table 5).

Figure 9: Kaplan-Meier cumulative incidence curves for the primary endpoint (death or hospitalization for worsening heart failure)



Nb Exposed at risk								
Placebo	317	234	159	87	41	16	6	1
Dronedarone 800mg	310	232	151	87	49	19	4	1

Table 5: Primary analysis (death or hospitalization for worsening heart failure up to 16 January 2003) of ANDROMEDA trial

	Placebo (N=317)	Dronedarone 800 mg (N=310)
Number of patients who died or were hospitalized for worsening heart failure	40	53
Relative risk[a]	1.38	
95% CI[a]	[0.918 ; 2.088]	
Log-rank's test result (p-value)	0.118	

a: Determined from Cox regression model

The issue of altered dronedarone exposure due to concomitant medications was addressed to some degree in the drug interaction studies and in the pivotal clinical trial that indicated co administration did not lead to significant adverse effects.

2.2.5 Pharmacokinetic characteristics of dronedarone and its major metabolites

Dronedarone pharmacokinetics were determined following oral and IV administration in healthy subjects and in patients with various forms of cardiac disease. The most relevant PK information was obtained from studies LIN2890, POP2769, BEX2770 and PPK2397.

2.2.5.1 *Dronedarone pharmacokinetic measures*

Dronedarone and SR35021 PK measures following single (Day 1) and multiple dose (Day 14) administration are presented in Table 6.

Table 6: Dronedarone and SR35021 PK Measures in Healthy Males Following Single and Multiple Dose Administration (200, 400 and 800 mg BID)

PK Parameters		Dronedarone			SR35021		
		200 mg n = 17	400 mg n = 16 [b]	800 mg n = 17 [c]	200 mg n = 17	400 mg n = 16 [b]	800 mg n = 17 [c]
C_{max} (ng/mL)	Day 1	23.1 (38)	67.2 (36)	162 (40)	20.8 (21)	49.5 (25)	109 (29)
	Day 14	40.3 (30)	111 (17)	298 (13)	41.2 (27)	107 (22)	282 (21)
t_{max} [a] (h)	Day 1	3 [2; 5]	3 [2; 5]	3 [2; 6]	5 [2; 5]	5 [3; 6]	5 [3; 6]
	Day 14	5 [2; 5]	5 [3; 6]	5 [2; 6]	5 [2; 6]	5 [3; 8]	5 [3; 4 8]
AUC_{0-12} (ng.h/mL)	Day 1	111 (24)	310 (28)	846 (27)	123 (19)	275 (23)	668 (24)
	Day 14	276 (23)	798 (19)	2510 (12)	325 (21)	882 (17)	2680 (20)
$t_{1/2z}$ (h)	Day 1	9.81 (33)	17.6 (56)	19.6 (33)	16.2 (28)	19.2 (24)	21.9 (22)
	Day 14	26.9 (32)	30.0 (29)	31.2 (32)	23.5 (14)	21.1 (16)	20.4 (8)
AUC (ng.h/mL)	Day 1	160 (27)	474 (33)	1310 (26)	237 (23)	545 (22)	1360 (20)
CL/F [d] (L/h)	Day 1	1350 (29)	937 (35)	669 (38)	-	-	-
	Day 14	765 (25)	517 (18)	324 (13)	-	-	-
Vz/F [d] (L)	Day 1	18000 (24)	21000 (31)	17900 (33)	-	-	-
	Day 14	29400 (34)	22800 (41)	14500 (31)	-	-	-

Numbers rounded at 3 significant figures.
[a] median value [Min–Max]
[b] n = 14 at Day 14
[c] n = 16 at Day 14
[d] CL_{0-12}/F and Vz_{0-12}/F at Day 14

2.2.5.2 *Pharmacokinetic Comparisons: Normal Volunteers vs. Patients*

Overall the PK in patients with AF/AFL appeared comparable to that in healthy subjects; this was shown in the Cmax and Ctrough estimations from ANDROMEDA (Table 7), where intensive sampling was carried out, as well as in the population PK analyses (Table 8).

Table 7: Steady State Dronedarone following 400 mg BID dosing

PK Measure	ANDROMEDA		LIN2890
	400 mg Dose [intensive sampling (n = 11)]	400 mg [all samples (n = 125]	400 mg Dose (n = 16)
AUC (ng h/mL)	886 (55%)	NR	798 (19)
Cmax (ng/mL)	113 (59)	101 (54)	111 (17)
Ctrough (ng/mL)	NR	64.7 (66)	40 - 50

Table 8: Table (2.7.2.3.4) 1 - Mean (CV%) dronedarone and SR35021 plasma concentrations in patients (DRI3550/DAFNE*, EFC3153/EURIDIS, EFC4788/ADONIS, EFC4966/ANDROMEDA, and EFC4508/ERATO)

	DRI3550			EFC3153	EFC4788	EFC4966	EFC4508
	400 mg BID	600 mg BID	800 mg BID	400 mg BID	400 mg BID	400 mg BID	400 mg BID
Dronedarone							
$C_{trough,av}$ (ng/mL)	42.7-58.0 [a]	81.2-109 [a]	124-176 [a]	65.7 (56)	60.0 (58)	64.7 (66)	56.4 (56)
$C_{max,av}$ (ng/mL)	-	-	-	106 (50)	97.9 (64)	101 (54)	92.0 (107)
SR35021							
$C_{trough,av}$ (ng/mL)	32.6-40.0 [a]	55.7-67.8 [a]	77.2-91.3 [a]	40.0 (44)	38.3 (46)	35.8 (62)	38.2 (33)
$C_{max,av}$ (ng/mL)	-	-	-	59.2 (45)	52.8 (51)	60.6 (50)	50.0 (56)

[a]: range of mean C_{trough} or C_{max} at steady state across visits

2.2.5.3 *Characteristics of drug absorption*

Based on the Tmax and absolute bioavailability information, overall dronedarone was moderately to poorly absorbed. Peak concentrations were reached between three and six

hours post dose. Food also increased dronedarone exposure by approximately 2- to 5-fold but had a minimal impact on Tmax.

Absolute Bioavailability (Study PPK2397)

The absolute BA study was conducted in healthy subjects who received a dronedarone capsule formulation and IV dronedarone in both fasted and fed states. Results from the fasted state are not reliable due to the small number of subjects and difficulties with assay; the absolute BA in the fasted state was ~ 4 %. The absolute BA in the fed state is ~ 15 % (Table 9); the use of data from the fed state is acceptable because PK data are less variable and dronedarone is recommended to be taken with food.

Table 9: Dronedarone PK Measures following 60 mg dronedarone IV infusion and 800 mg dronedarone oral (fed and fasted) to determine absolute bioavailability

Parameter (units)	Intravenous Fasted	Oral Fasted	Oral Fed	90% CI (Oral Fed / Oral Fasted)	p-value
C_{max} (mg/l)	0.189 (0.034)	0.020 (0.012)	0.120 (0.043)	442 - 900	0.0001
t_{max} (h)	0.67 (0.12)	2.7 (1.3)	4.3 (1.1)	NPT	0.001
AUC_{0-t} (mg/l*h)	0.288 (0.051)	0.108 (0.097)	0.644 (0.282)	481-1169	0.0001
AUC (mg/l*h)	0.350 (0.054)	0.219 (0.209)†	0.721 (0.327)‡	----------	----------
$t_{½}$ (h)	7.5 (3.4)	9.3 (9.5)†	8.9 (6.1)	NPT	0.31
$Vd\lambda_z$ (l)	1837 (713)	----------	----------	----------	----------
Cl_t (l/h)	176 (34)	----------	----------	----------	----------
F (%)	----------	4 (4)†	15 (6)‡	----------	----------

†n=6, ‡n=11
NPT - non-parametric test

However there are two main limitations with the absolute bioavailability information with respect to its applicability to the to-be-marketed (TBM) formulation:

- Study conducted at 800 mg dose level and dronedarone exhibits non-linear PK
- Study conduced with capsule formulation that has different food effect than TBM tablet

Consequently, the utility of the absolute BA findings is unclear and the quantitative absolute BA information obtained with the capsule at the 800 mg dose should not be extrapolated to the TBM tablets that will be administered at 400 mg.

Food Effect

The plasma concentration-time profiles in (Figure 10) and data in Table 11 demonstrate that food increases dronedarone exposure (bioavailability or BA) relative to the fasted state:

1. Food (low fat meal and high fat meal) increases dronedarone BA on average by approximately 2- to 5-fold at the 800 mg dronedarone dose level.
2. The high fat meal had only a slightly greater effect on (~ 40 % increase) than the low fat meal, suggesting that dronedarone may be administered with low or high fat meals.
3. Food did not significantly prolong drug absorption; the median Tmax was 5 hr under fasted and fed conditions.

It is noted that two subjects had far greater food effects than the other subjects. The reason for this finding is unclear; without these two subjects the difference in food effect

between the high fat meal and low fat meal may not have reached statistical significance and the food effect data would be less variable.

Figure 10: Mean dronedarone plasma concentration-time profile under fasted and fed conditions

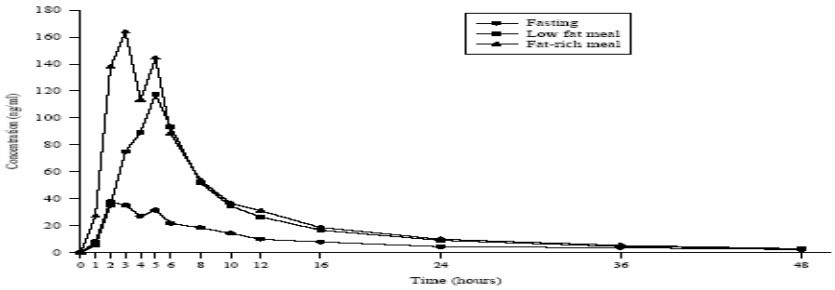


Table 10: Dronedarone PK measures in healthy males following single dose administration under fasted and fed conditions

Parameters (units)	Statistics	Administration		
		Fasted	Low fat meal	Fat-rich meal
C_{max} (ng/ml)	Mean	42.92	128.29	192.40
	Median	40.00	120.80	173.40
	SD	21.50	50.26	90.88
	CV%	50	39	47
t_{max} (h)	Mean	3.67	4.67	3.89
	Median	5.00	5.00	5.00
	SD	1.58	1.00	1.36
	CV%	43	21	35
AUC_{last} (ng.h/ml)	Mean	416.35	975.61	1274.37
	Median	416.00	964.59	1179.63
	SD	106.59	252.08	329.89
	CV%	26	26	26

n = 9

Table 11: Dronedarone geometric mean ratios and associated 90 % confidence intervals* under fed and fasted conditions

Parameters (units)	Low fat meal / fasted	Fat-rich meal / fasted	Fat-rich meal / low fat meal
C_{max} (ng/ml)	3.15 [2.28 - 4.36]	4.59 [3.32 - 6.35]	1.46 [1.05 - 2.01]
AUC_{last} (ng.h/ml)	2.34 [1.99 - 2.75]	3.06 [2.60 - 3.61]	1.31 [1.11 - 1.54]

n = 9

Role of PGP

Relative to vincristine or digoxin, which are model PGP efflux pump substrates (relative permeability > 25); dronedarone (relative permeability 2.5) has limited efflux potential. This finding suggests that dronedarone exposure is unlikely to be affected by coadministration with a PGP inhibitor or inducer via a PGP-based mechanism.

2.2.5.4 Distribution of dronedarone

Following IV administration of dronedarone (40 to 80 mg single dose) the volume of distribution (Vz) associated with the terminal phase was approximately 2500 to 3500 L).

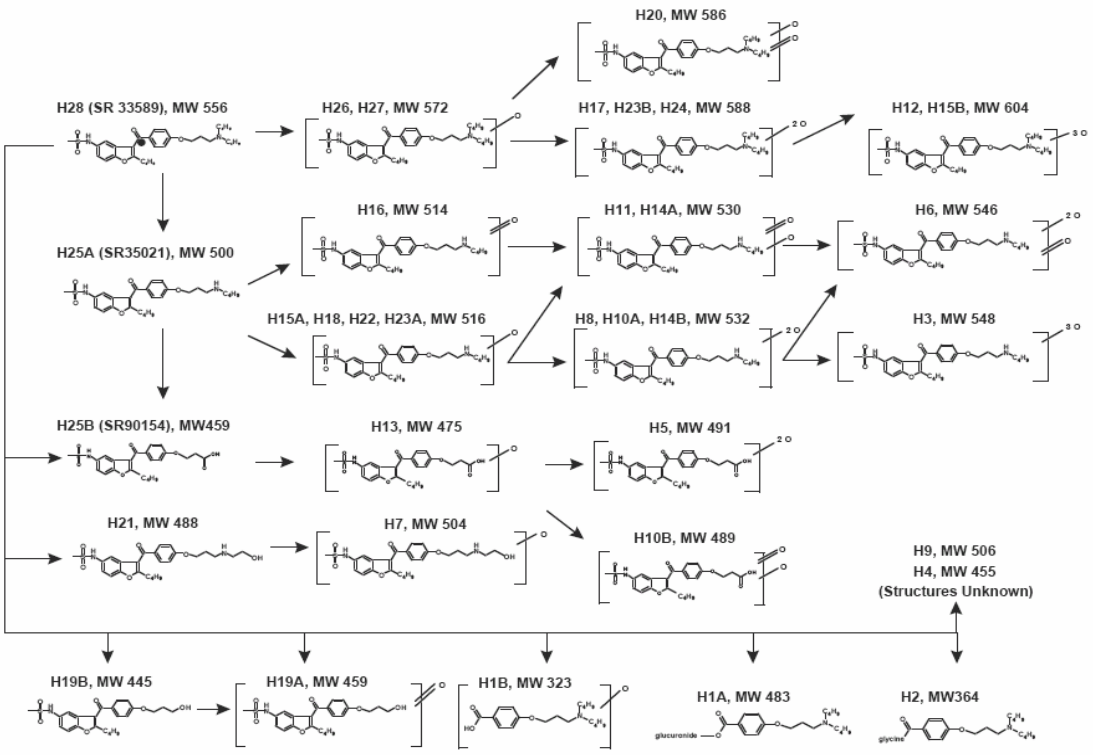
Dronedarone was greater than 99 % bound to plasma proteins and binding was not concentration-dependent over a dronedarone concentration range of 25 to 50000 ng/mL. HSA is the major binding protein, with approximately three times more drug bound to HSA than AAG. These two proteins appear to account for the majority of the plasma protein binding of dronedarone (LPH0006).

SR35021 was also highly bound to plasma proteins: binding was greater than 98 % and not concentration-dependent over the SR35021 concentration range of 25 to 50000 ng/mL. HSA is the major binding protein, with approximately six times more drug bound to HSA than AAG. These two proteins appear to account for the majority of the plasma protein binding of SR35021 (LPH0021).

2.2.5.5 ***Mass Balance Information***

Overall, the mass balance results suggest that the primary route of drug elimination is hepatic via metabolism; the metabolized drug is subsequently removed from the body primarily via feces.

Figure 11: Metabolic pathways of dronedarone via mass balance



(• Denotes the site of the radiolabel)

Healthy adult volunteers received two oral dronedarone doses (0.1 and 0.48 µg/kg) of radiolabeled dronedarone. Total recovery of radioactivity was 90 %: approximately 6% was excreted in the urine and 84% was excreted in the feces. Dronedarone was extensively metabolized; only low amounts of dronedarone were detected in feces and dronedarone was non-existent in urine. Over 30 metabolites were observed. The metabolites formed in feces, urine and plasma were similar. In general, individual metabolites accounted for < 5 % of the radioactive dose, only the metabolite H13 had an amount > 18 % in both urine and feces. In plasma the most abundant metabolites were SR35021 and SR90154 (appeared together as unresolved peak).

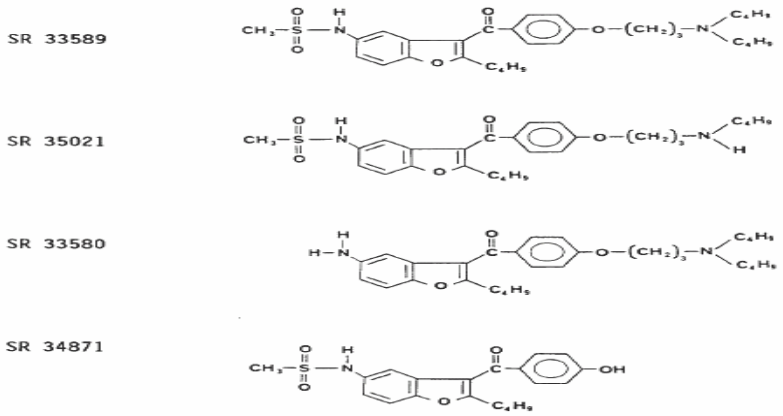
Three major pathways of dronedarone metabolism were identified (Figure 11):
1) N-debutylation, followed by oxidation (CYP3A pathway)
2) N- dealkylation to form the propanoic acid metabolite, followed by oxidation
3) Direct oxidation of dronedarone
Additionally, mono- and multiple-hydroxylated metabolites were observed, along with metabolites containing a ketone moiety.

2.2.5.6 ***Metabolism***

In vitro system
In vitro studies with microsomes and human hepatocyte system (MIV0158 and MIV0159) indicated that dronedarone is primarily metabolized by CYP3A to an N-dealkylated moiety, SR35021; this metabolite and dronedarone can undergo further metabolism. These studies also demonstrated that dronedarone is neither a CYP2D6 nor CYP1A2 substrate. However, these studies did not determine if dronedarone is metabolized by other potential CYP pathways such as, CYP2C8, CYP2C9, CYP2C19, CYP2A6 or CYP2E1. The applicant will be asked to reevaluate dronedarone metabolism using current techniques to provide comprehensive labeling information. The metabolism studies included in the NDA were conducted before 1993.

Dronedarone forms several metabolites when incubated with a human hepatocyte or microsome system (Figure 12) The metabolites formed *in vitro* are also formed *in vivo* as demonstrated in the previously described mass balance study.

Figure 12: Dronedarone metabolites identified by HPLC during in vitro studies



In Vivo Systems
In vivo, SR35021 is the major metabolite, with plasma exposure approximately half that of dronedarone following administration of dronedarone. Generally, SR25021 is formed to a minimal extent following IV administration, suggesting that it is formed primarily during first pass metabolism, rather than in the systemic circulation. Additionally, SR35021 metabolism appears to be formation rate limited. According to the applicant, SR35021 has approximately 1/3rd to 1/10th the anti-arrhythmic activity of dronedarone. Based on the relative activity and exposure, SR35021 is unlikely to contribute significantly to dronedarone activity. The other dronedarone metabolites (minor) have

exposure that is less than 5 % that of dronedarone, therefore their impact on dronedarone overall activity is likely to be negligible unless each individual metabolite or the metabolites collectively possess activity that is comparable to or surpasses that of dronedarone.

Metabolic Ratio

The metabolic ratio, SR35021/Dronedarone for AUC and Cmax on Days 1 and 14 are presented in Table 12.

Table 12: Mean (CV %) metabolic ratio of Cmax and AUC (Study LIN2890)

Dose		200 mg n = 17	400 mg n = 16 [b]	800 mg n = 17 [c]
R_{met} C_{max}	Day 1	0.996 (34)	0.795 (32)	0.724 (31)
	Day 14	1.08 (28)	0.973 (20)	0.944 (15)
R_{met} AUC[a]	Day 1	1.55 (25)	1.22 (26)	1.08 (19)
	Day 14	1.22 (24)	1.12 (17)	1.07 (17)

[a] AUC on Day 1 and AUC_{0-12} on Day 14
[b] n = 14 at Day 14
[c] n = 16 at Day 14

Based on Day 1 AUC and Cmax data, more metabolite was formed at lower doses than at higher doses, suggesting saturation in metabolism may occur (non-linear PK). On Day 14, numerically the same trend was observed, but differences in metabolite formation were not as great as on Day 1.

2.2.5.7 ***Excretion and Elimination***

As reported previously in the mass balance findings, following oral administration of dronedarone ~ 84 % of the total radioactivity was found in feces and ~ 6 % in urine. Limited amounts of dronedarone were found in the feces, with no dronedarone in the urine. The recovery was maximal within approximately 180 hours for oral administration.

Following single IV administration, the terminal elimination half-life was between 13 and 18 hours; for oral administration, the elimination half-life appeared both time- and dose-dependent. At the proposed oral dose of 400 mg BID, the half-life after single dose administration was ~ 18 hours and the half-life for multiple dose administration was ~ 30 hours. Overall, dronedarone concentrations appeared to decline in a biphasic manner after achieving Cmax (oral and IV routes).

2.2.5.8 ***Degree of Linearity/Nonlinearity in dose-concentration relationship***

Based on a dose-proportionality assessment and evaluation of dronedarone's PK profile across doses), dronedarone exhibits a slightly non-linear dose-concentration relationship (Table 13) and dose-dependent PK.

Table 13: Dose-proportionality Estimations Following Single and Multiple Dose Administration of Dronedarone 200, 400 and 800 mg Doses

Ratio estimates for dose proportionality at Days 1 and 14

PK Parameters		Ratio Estimate	90% CI
Dronedarone			
C_{max} (ng/mL)	Day 1	2.62	[2.39 – 2.88]
	Day 14	2.77	[2.62 – 2.93]
AUC[a] (ng.h/mL)	Day 1	2.86	[2.67 – 3.06]
	Day 14	3.06	[2.92 – 3.20]
SR35021			
C_{max} (ng/mL)	Day 1	2.24	[2.10 – 2.38]
	Day 14	2.59	[2.46 – 2.73]
AUC[a] (ng.h/mL)	Day 1	2.37	[2.27 – 2.48]
	Day 14	2.82	[2.71 – 2.93]

a: AUC_{0-12} at Day 14.

There was a slightly greater than proportional increase in plasma exposure on Day 1 and Day 14 with increasing dose (pooled data from three dronedarone doses):

- Day 1: 2-fold increase in dose resulted in > 2.6 increase in dronedarone exposure
- Day 14: 2-fold increase in dose resulted in > 2.6 increase in dronedarone exposure

SR350121 exhibited a similar dose-concentration relationship as dronedarone.

CL/F on Day 1 for 400 mg dose was approximately 30 % higher than that of the 800 mg dose; a similar trend was observed on Day 14 for these two doses. The source(s) of the dose dependency is unclear, but is likely due to competing metabolic processes. However saturable elimination does not appear to be a predominant source of non-linearity because apparent terminal half-life was comparable for all dronedarone regimens (~ 30 hours on Day 14). It is noted that for IV administration dose-dependent (PK) were not observed following single doses.

2.2.5.9 ***Time Dependency of dronedarone PK***

Dronedarone PK appeared to be time-dependent as shown in Table 6. Considering the proposed therapeutic dose, 400 mg BID, dronedarone CL/F on Day 1 was ~ 40 % higher than that on Day 14. This finding suggests that dronedarone exhibits non-linear PK following oral administration. The source of the non-linearity is not known.

Steady-state dronedarone and SR35021 concentrations were generally reached within seven days; this finding was observed consistently across several studies. Single dose PK were not predictive of multiple dose PK; this was probably due to the observed non-linear PK.

The accumulation ratio (based on linear scale AUCs) for the 400 mg BID dronedarone regimen is ~ 2.6 .

Dronedarone exhibited diurnal variation in plasma concentrations (based on Cmax values): daytime concentrations were about 15 to 30 % greater than night-time concentrations over the 800 to 1600 mg BID dose range (Table 14). No diurnal variation information was available for the proposed dosage regimen.

Table 14: Dronedarone PK measures following administration of dronedarone at different doses (Study TDR3549)

C_{max} (ng/mL)	Dose administered				
	800 mg b.i.d.	1000 mg b.i.d.	1200 mg b.i.d.	1400 mg b.i.d.	1600 mg b.i.d.
C_{max}- Single administration					
Mean	86.7	132	135	147	223
SD	16.8	55.7	56.6	90.0	51.5
CV%	19	42	42	61	23
C_{max} - 10-days repeated administration (daytime)					
Mean	177	337	400	363	552
SD	57.7	92.8	131	118	139
CV%	33	28	33	33	25
C_{max} - 10-days repeated administration (night-time)					
Mean	136	264	343	242	476
SD	29.1	122	130	90.1	141
CV%	21	46	38	37	30

2.2.5.10 ***Inter and intra-subject variability in dronedarone PK***

There was moderate to high inter-subject variability in dronedarone PK (Table 14) following oral administration as evidenced by the CV (%). The potential sources of variability can be ascribed to the different metabolizing capacity of individuals, varying rates of absorption and limited drug solubility.

2.3 What Intrinsic Factors Affect Dronedarone Exposure-Response?

Dronedarone exposure appeared to be affected by the following intrinsic factors: age, gender, race and body weight. The findings related to age and gender were primarily from Study POP2769 and the finding on race was obtained from Study TDU4899. The weight finding is primarily based on population pharmacokinetic analyses using data from the pivotal clinical trials. It is noted that the population PK analyses also offer supportive evidence on age and gender effects. The applicant has proposed labeling on gender and age only. The potential effects of some intrinsic factors on dronedarone exposure-response follow.

Renal Insufficiency

The effect of impaired renal function was not assessed in this application. Renal impairment is unlikely to modify dronedarone PK; this conclusion is based on the mass balance study results that indicate dronedarone is not excreted in the urine and only 6 % of the total dose is excreted in urine (metabolites only). No dosage adjustment should be required for patients with impaired renal function.

Hepatic Insufficiency

The effect of impaired hepatic function has not been assessed in this NDA; however, the applicant indicates that there is an ongoing study, POP5820, to address this issue. According to the Medical Reviewer, subjects with impaired hepatic function were excluded from the pivotal trials, therefore there are no data for these subjects.

Reviewer Comment on Hepatic Insufficiency

The findings from the hepatic insufficiency study are critical as dronedarone is primarily metabolized hepatically. Most likely a dosage adjustment will be required for subjects

with impaired hepatic function, as dronedarone is extensively eliminated by the liver. The applicant has indicated (proposed labeling) that dronedarone should be used with caution in patients with moderate and severe hepatic impairment. Per the Hepatic Impairment guidance, drugs should be contraindicated in subjects with severe hepatic impairment, if PK information is not available in this group and the drug is hepatically cleared. Thus, the labeling should be modified to reflect the recommendation in the Guidance. Also, extreme caution should be applied in subjects with any form of hepatic insufficiency, since the exposure-response curve is unknown for exposures exceeding that achieved by 400 mg dronedarone.

Age (Geriatric Patients vs. Young Adults)

Relative to healthy young males, elderly males and females tended to have AUCs and Cmaxs that were approximately 30 to 50 % higher (Table 15, Table 16, and Table 17); however, data were highly variable (POP2769). These differences persisted even after correcting for body weight. The reason for the age differences is unclear as dronedarone is not extensively renally cleared. Typically drugs that are renally cleared show age effects due to the natural decline in renal function as one ages. It is unclear if the clearance differences are due to differential enzyme activity in young vs. old subjects. The population PK analyses indicated that elderly subjects had lower clearance than younger subjects.

Overall the magnitude of change in exposure does not appear large enough to require a dose adjustment based on age.

Table 15: Dronedarone PK measures in healthy males and elderly adults and females following single and multiple dose administration (800 mg QD)

Parameter	Statistic	Young Male		Elderly Male		Elderly Female	
		Day 1	Day 17	Day 1	Day 17	Day 1	Day 17
C_{max} (ng/ml)	Mean	76	130	89	168	142	241
	SD	29	37	27	55	38	62
	CV%	38%	28%	30%	33%	27%	26%
t_{max} (h)	Mean	3.00	4.67	4.67	3.83	4.75	4.83
	SD	1.28	1.15	2.06	1.19	1.42	0.83
	CV%	43%	25%	44%	31%	30%	17%
AUC_{0-24h} (ng.h/ml)	Mean	511	1139	679	1520	1035	2393
	SD	171	318	228	508	303	702
	CV%	33%	28%	34%	33%	29%	29%
R_{ac}	Mean	N/A	2.35	N/A	2.31	N/A	2.35
	SD		0.66		0.72		0.46
	CV%		28%		31%		19%
C_{min} (ng/ml)	Mean	N/A	14.6	N/A	23.2	N/A	39
	SD		6.4		10.4		12.3
	CV%		44%		45%		32%
AUC_{last} (ng.h/ml)	Mean	609	N/A	874	N/A	1335	N/A
	SD	200		308		350	
	CV%	33%		35%		26%	
AUC (ng.h/ml)	Mean	628	N/A	936	N/A	1473	N/A
	SD	205		323		383	
	CV%	33%		35%		26%	
$t_{½}$ (h)	Mean	17.9	24.1	24.3	38.1	28.8	44.6
	SD	4.2	7.2	5.4	10.1	9.8	13.9
	CV%	23%	30%	22%	26%	34%	31%

N/A: Not applicable

Gender

Elderly females tended to have ~ 23 % higher exposure than elderly male subjects after correcting for body weight differences (Table 15, Table 16, Table 17). However, data

were highly variable as evidenced by the wide confidence intervals associated with the point estimates. From this study it is unclear if the gender effect will exist for young subjects because young female subjects were not included in this study. Data from patients (Population PK analyses) suggest that female subjects have a lower clearance than male subjects.

Overall the magnitude of change in exposure does not appear large enough to require a dose adjustment based on gender.

Table 16: Comparison of Cmax and Cmin between elderly subjects and young male subjects

Parameter	Elderly Male vs. Young Male			Elderly Female vs. Elderly Male		
	Ratio	95 % CI	90 % CI	Ratio	95 % CI	90 % CI
C_{max}	1.23	[0.99 , 1.52]	[1.02 , 1.47]	1.54	[1.24 , 1.92]	[1.29 , 1.85]
C_{max} N	1.26	[0.98 , 1.63]	[1.02 , 1.56]	1.23	[0.95 , 1.58]	[0.99 , 1.51]
C_{min} (RD)	1.61	[1.13 , 2.28]	[1.20 , 2.15]	1.75	[1.23 , 2.47]	[1.31 , 2.33]

N: Normalized to 70 kg body weight
RD: Repeated Dose

Table 17: Comparison of AUC between elderly subjects and young male subjects

Parameter	Elderly Male vs. Young Male			Elderly Female vs. Elderly Male		
	Ratio	95% CI	90% CI	Ratio	95% CI	90% CI
AUC_{0-24h}	1.33	[1.04 , 1.69]	[1.08 , 1.62]	1.56	[1.22 , 1.99]	[1.28 , 1.91]
$AUC_{0-24h}N$	1.37	[1.05 , 1.79]	[1.09 , 1.71]	1.24	[0.95 , 1.62]	[0.99 , 1.55]
AUC_{last} (Day 1)	1.44	[1.10 , 1.88]	[1.16 , 1.80]	1.55	[1.18 , 2.02]	[1.24 , 1.93]
AUC (Day 1)	1.50	[1.15 , 1.95]	[1.20 , 1.87]	1.59	[1.22 , 2.08]	[1.28 , 1.99]

N: Normalized to 70 kg body weight
Day 1: Single Dose

Reviewer Note on Population PK Analyses in relation to Gender and Age

The PM reviewer indicated that the applicant's population model was acceptable, but viewed the model as providing supportive evidence only, because neither dosing regimens nor labeling statements were solely based on the results of the model. Overall the population PK analyses are consistent with the results obtained in POP2769 with regard to age and gender effects. Highlights of the population analyses findings follow.

<u>Population PK Analyses: Findings with respect to Intrinsic Factors</u>

Based on the applicant's analyses, the covariates explaining dronedarone PK variability in patients were gender, weight and age . A two compartmental Population PK model was developed and validated. In brief, the Population PK analyses indicated:

- Mean dronedarone exposure was 30% higher in female patients.
- Mean dronedarone exposure was 23% higher in patients $\geq$ 65 years compared with patients <65 years.
- For patients with a body weight <50 kg, mean dronedarone exposure was 40% higher compared with patients with a body weight between 50 and 100 kg.

Table 18: Mean (CV%) steady-state dronedarone exposures in patients and according to gender, age, and body weight (population pharmacokinetic analysis from EFC3153/EURIDIS, EFC4788/ADONIS, and EFC4966/ANDROMEDA)

Parameter	All patients (n=839)	Males (n=604)	Females (n=235)	Age (years)		Body Weight (Kg)		
				< 65 (n=390)	≥ 65 (n=449)	< 50 (n=6)	50 – 100 (n=700)	≥ 100 (n=133)
C_{maxSS} [a] (ng/mL)	121 (33)	112 (29)	144 (32)	109 (27)	131 (34)	159 (20)	125 (33)	99.9 (23)
C_{minSS} (ng/mL)	77.1 (42)	69.7 (38)	95.8 (38)	67.1 (37)	85.7 (41)	122 (22)	80.1 (40)	58.8 (37)
AUCss (ng.h/mL)	1230 (34)	1131 (30)	1483 (32)	1096 (28)	1345 (34)	1749 (20)	1271 (33)	988 (25)

[a]: min-max individual Cmax: 51–442 ng/mL

Race

- Japanese

Japanese males appeared to have lower clearance than their Caucasian counterparts receiving a single 400 mg dronedarone dose; this resulted in ~ 100 % exposure increase in Japanese males relative to Caucasian males (Table 19).

Table 19: Mean (CV %) Dronedarone PK Measures in Caucasian and Japanese males

	Caucasian	Asian
PK Measure	Single 400 mg Dose (LIN2890)	Single 400 mg Dose (TDU4899)
AUC (ng h/mL)	310 (24)	701 (55)
Cmax (ng/mL)	67.2 (36)	123 (58)
Half-life (h)	17.6 (56)	11.9 (17)
Tmax (h)^	3 (2 to 5)	3

^ Tmax reported as median and (range)

The reason for the apparent differences in clearances between the two studied races is unclear, because dronedarone is primarily metabolized by the CYP3A enzyme, which does not exhibit genetic polymorphism.

- Blacks

No PK information is available in Blacks, who are likely to use dronedarone treatment.

2.4 What Extrinsic Factors Affect Dronedarone Exposure Response?

2.4.1 Drug-drug Interactions

The main extrinsic factor that may influence the dronedarone exposure-response is concomitantly administered drugs. Drugs used in AF/AFL are summarized in Table 20 (per applicant).

Drug-drug interaction studies were carried with some of the compounds listed in Table 20; it is noted that certain classes of compounds are not likely to be coadministered due to safety concerns. For example, dronedarone would not be coadministered with amiodarone.

Table 20: Drugs used in AF/AFL treatment

	Rhythm control	Rate control
Anti-arrhythmic		
Class Ia	Disopyramide Procainamide Quinidine	-- -- --
Class Ic	Flecainide Propafenone	-- --
Class II	--	betablockers (eg metoprolol, carvedilol)
Pure Class III	Dofetilide Ibutilide	-- --
Class IV	-- --	diltiazem verapamil
Multifactorial	Sotalol Amiodarone	sotalol amiodarone
Digitalis	-- --	digoxin digitoxin

2.4.1.1 ***CYP Substrate Status***

As indicated in the metabolism section, dronedarone is primarily metabolized by CYP3A; the contribution to dronedarone metabolism, if any, of CYP2C8, CYP2C9, CYP2C19, CYP2A6 or CYP2E1 is unknown. However, dronedarone is not a substrate of CYP2D6 or CYP1A2. Based on the provided *in vitro* information, dronedarone PK is expected to be primarily altered by CYP3A inducers and inhibitors.

2.4.1.2 ***PGP substrate status***

Dronedarone has limited PGP substrate characteristics, thus it is unlikely that dronedarone exposure will be altered by PGP inhibitors or inducers.

2.4.1.3 ***CYP Induction and Inhibition Potential***

Dronedarone does not induce common CYP enzymes (MIV0144). This conclusion was based on *in vitro* assessment of enzymatic activity measured in cultured hepatocytes and Western blot analyses. Specifically, dronedarone does not induce the enzymatic activity of CYP1A2, CYP2A6 or CYP3A. Based on the finding that CYP3A activity is not induced, dronedarone will not induce the enzymatic activity of CYP2C8, 2C9, or 2C19, as these enzymes are typically coexpressed with CYP3A.

Dronedarone does not significantly inhibit the activity of CYP1A2, CYP2C9, CYP2C19 and CYP2E1 in human liver microsomes (MIH0007). Therefore clinically, dronedarone is not expected to inhibit the metabolism of compounds metabolized by these enzymes Dronedarone showed the most inhibition potential towards the CYP3A and CYP2D6 enzymes. Assuming *in vivo* dronedarone concentration of 0.2 µM, I/Ki values for CYP3A4 and CYP2D6 inhibition were ~ 0.01 and 0.06 suggesting a low inhibition potential, per Draft Drug Interaction Guidance.

2.4.1.4 ***PGP Inhibition Potential (Role of PGP Transporters)***

Dronedarone appears to be as potent an inhibitor as cyclosporine A, with respect to the ability to inhibit the efflux of two PGP probe substrates, digoxin and vincristine. The order of increasing numerical IC_{50} values for the two substrates, vincristine and digoxin, were:

- For vincristine- dronedarone < cyclosporine A < verapamil < quinidine
- For digoxin- cyclosporine A < dronedarone

Consequently, dronedarone may inhibit the efflux of PGP substrates, thereby increasing the plasma exposure of these compounds.

2.4.1.5 *In vivo studies with medications that are likely to be administered in AF/AFL patients and that serve as metabolic or transporter probes (substrates/inhibitors/ inducers)*

In several clinical PK/PD studies, administration of dronedarone at dosages equivalent to or greater than the proposed clinical dosage showed interactions that were generally not clinically significant. Results from these studies are summarized in Table 21; most studies were conducted in healthy male subjects.

Table 21: Summary of Drug Interaction Findings

PK/PD Effects of Dronedarone on Concomitant Medications	**Metabolic (other)**
Drugs not Affected by Dronedarone	
Losartan	CYP2C9 substrate
Drugs Affected by Dronedarone	
Digoxin	PGP substrate
Metoprolol, Propranolol	CYP2D6 substrates
Levonorgestrel, ethinylestradiol, nisoldipine, simvastatin, verapamil	CYP3A substrates
Warfarin	CYP2C9 substrate
Theophylline	CYP1A2 substrate
PK/PD Effect of Drugs on Dronedarone	
Drugs Affecting Dronedarone	
Rifampin	CYP3A inducer
Grapefruit juice, ketoconazole, verapamil, diltiazem, nifedipine	CYP3A inhibitors
Drugs not Affecting Dronedarone	
Pantoprazole	Decreases gastric pH
Simvastatin, nisoldipine	CYP3A substrates
Losartan, warfarin	CYP2C9 substrates

Dosage Adjustment for Dronedarone

No definitive dosage adjustments can be recommended for dronedarone because alternative dosage schedules have not been evaluated with respect to exposure-response. It should also be noted that dronedarone is available in only one tablet strength and the tablet is not scored therefore the only way to adjust dosage is by interval adjustment.

In the pivotal clinical trials most comedications used in AF/AFL therapy were allowed; these medications included diuretics, beta-blockers, digitalis, calcium antagonists, ACE inhibitors, angiotensin-II receptor antagonists, statins, coronary vasodilators, and oral anti-coagulants. Overall, there did not appear to be evidence of clinically significant adverse events due to comedication, suggesting that dronedarone can be given with most comedications, if appropriate caution is observed.

Based on the study results, the only proposed contraindication is with potent CYP3A inhibitors, such as ketoconazole. This proposal is reasonable based on the observed

results (> 5-fold increase in dronedarone exposure). Based on the drug interaction results some drugs are not recommended for coadministration with dronedarone due to the following:

- unacceptable lowering of dronedarone exposures (strong CYP inducers, such as rifampin, St John's Wort)
- potential development of proarrhythmia (Class I or class III anti-arrhythmic) and drugs that prolong the QT interval (inducing torsades de pointes).

Additionally, caution should be exercised for most drugs (e.g. beta blockers, calcium antagonists) to be used in combination with dronedarone for the treatment of AF/AFL due to potential PD interactions.

Dosage Adjustment for Concomitant Medications

The majority of drugs evaluated in the drug interaction studies and drugs likely to be used with dronedarone follow schedules that allow for titration, therefore, dosage can be modified accordingly when given with dronedarone. Additionally, appropriate caution should be exercised due to the potential PD interactions.

Reviewer Note on Dosage Adjustments during dronedarone therapy

Overall, the proposed drug interaction guidelines are acceptable with minor modifications which will be addressed in labeling (see Labeling Section of Review).

2.4.1.6 **Mechanistic basis for PD drug-drug interactions between dronedarone and comedications**

There is a potential for additive to synergistic pharmacodynamic effects between dronedarone, an anti-arrhythmic agent, and other drugs used in patients with cardiac disease. For dronedarone this interaction is enhanced due to its putative effects on all four classes of Vaughan Williams' classification. Therefore, caution should be exercised when dronedarone is combined with several agents, even if a clinically significant PK or PD interaction was not observed in the reported drug-drug interaction studies.

2.4.2 Unaddressed Potential Drug Interactions (Drugs that may be affected in inhibition of renal tubular secretion)

In a renal function study seeking to elucidate the effect of dronedarone on serum creatinine, dronedarone inhibited renal tubular secretion (Study PDY5487). This finding suggests that drugs predominantly eliminated by renal tubular secretion may have increased exposure when given with dronedarone. Dronedarone also inhibits the organic cation transporter and may affect drugs eliminated by this pathway. It is noted that the applicant cautioned against the concomitant use of ACE inhibitors with dronedarone in ANDROMEDA because of a concern for decreased renal function. This caution was issued prior to completion of PDY5487 that demonstrated the apparent decline in renal function was transient and not likely to alter the exposure of ACEs. As was shown in the PM analyses of DAFNE and PDY5487, serum creatinine rises initially when dronedarone therapy is initiated but decreases upon discontinuation of dronedarone. Appropriate precautionary language should be included in the label to address the potential interaction between dronedarone and the previously mentioned drugs.

2.5 What are the General Biopharmaceutics Characteristics of Dronedarone Formulations?

2.5.1 BCS Information

The applicant reports that dronedarone is a member of BCS 2, which are drugs with low solubility and high permeability. Solubility information was provided to support the claim of low solubility (see Dissolution), but limited to no permeability information was included in the application. The absolute bioavailability information (F < 20 %) suggests that dronedarone is a not a high permeability drug; it is unclear if the relatively high recovery of radioactivity as metabolites (90 %) in the mass balance study confers high permeability on dronedarone. Overall, the data do not suggest that dronedarone is a high permeability compound; additional *in vitro* or *in vivo* information is needed to accurately identify dronedarone BCS type (BCS 2 vs. BCS 4). The BCS type does not have a significant impact on the current application, apart from dissolution.

2.5.2 Relative bioavailability information

The relative bioavailability information provided for the TBM (prototype) formulation was adequate. The prototype formulation, 2E3, was used in the pivotal clinical trials and this formulation had comparable bioavailability to the 2E2 formulation used in the Phase 2 dose ranging study and other critical clinical pharmacology studies (Table 22). Two additional formulations were developed: 2E4 for stability studies and 2E5 the market formulation; neither of these two formulations was administered to humans but dissolution information is available on the formulation.

Table 22: Dronedarone geometric mean ratios (based on $^{12}C/^{13}C$ ratio) and associated 90 % confidence intervals under fasted conditions (2E3 vs. 2E2)

Mean (CV%) $^{12}C/^{13}C$ Ratio	Phase III tablet +^{13}C-dronedarone	Phase II tablet +^{13}C-dronedarone	Ratio [90% CI]	Within-subject SD
C_{max} (ng/mL)	0.77 (37)	0.69 (29)	1.09 [0.95 – 1.26]	0.19
AUC_{last} (ng.h/mL)	0.78 (17)	0.82 (8)	0.94 [0.88 – 1.00]	0.08
AUC (ng.h/mL)	0.82 (15)*	0.85 (8)	0.95 [0.88 – 1.02]*	0.09

Phase III (1x400mg tablet) + ^{13}C-dronedarone (4x100mg capsules): treatment A
Phase II (2x200mg tablets) + ^{13}C-dronedarone (4x100mg capsules): treatment B a: n=11

The 2E5 intended for marketing formulation has the same qualitative and quantitative compositions as the reference 2E3 formulation; the only difference between the two formulations is minor punch marking on 2E5. This minor difference does not appear likely to alter the *in vivo* performance of the formulations, and *in vitro* dissolution information suggests the formulations have comparable quality.

Food Effect Information

As indicated previously, food increases dronedarone exposure by approximately 2- to 5-fold (Table 23); overall, there was a small difference between dronedarone exposures obtained with a high fat meal vs. low fat meal.

Table 23: Dronedarone geometric mean ratios and associated 90 % confidence intervals under fed and fasted conditions

Parameters (units)	Low fat meal / fasted	Fat-rich meal / fasted	Fat-rich meal / low fat meal
C_{max} (ng/ml)	3.15 [2.28 - 4.36]	4.59 [3.32 - 6.35]	1.46 [1.05 - 2.01]
AUC_{last} (ng.h/ml)	2.34 [1.99 - 2.75]	3.06 [2.60 - 3.61]	1.31 [1.11 - 1.54]

n = 9

In the pivotal clinical studies and clinical pharmacology studies, dronedarone was typically given in the fed state (shortly before or after a meal) at breakfast and dinner for BID administration. Meal types were not standardized in the pivotal trial suggesting that patients received meals of different fat content. Since the clinical effectiveness and safety data were obtained in the fed state and there is limited information in the fasted state (low exposure) to support safety and effectiveness, dronedarone should be given in the fed state.

In sum, dronedarone should be given in the fed state, either shortly before or after a meal; the fat content of the meal is not critical.

Reviewer Note on Food Effect with different dronedarone formulations
Several different dronedarone formulations were developed by the applicant in an attempt to optimize bioavailability while minimizing the effect of food. Initial formulations were greatly affected by food; in some instances (early capsule formulations), when food was present, dronedarone exposure was increased more than 10-fold relative to the fasted state. Ultimately, a tablet formulation containing 10 % pluronic acid, was found to have an acceptable bioavailability profile.

2.5.4 Dissolution
The applicant developed an acceptable dissolution methodology for dronedarone tablets to ensure *in vivo* performance and quality of Multac tablets. The proposed dissolution method and specification are as follows.

Applicant's Proposal
Dissolution methodology
Apparatus: paddle at 75 rpm; Medium: 1000 ml of pH 4.5 phosphate buffer

Dissolution specification
- Not less than 20 % and not more than 60 % dissolved after 30 min
- Q = 75 after 90 min

Applicant's Rationale for setting Q specifications
The applicant indicates that during the development of the dissolution method they could not routinely obtain 85 % dissolution of the drug substance after 60 minutes; this was mainly due to the poor solubility of the drug substance.

Reviewer's Recommendation
Dissolution methodology
Applicant's proposal is acceptable.

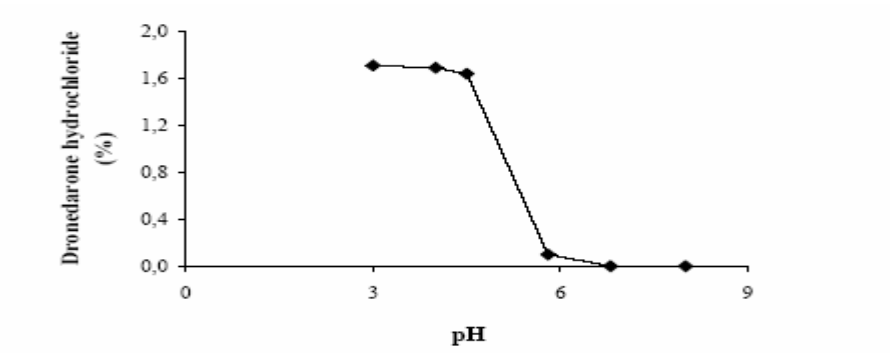
Dissolution specification

- Not less than 25 % and not more than 50 % dissolved within 30 minutes
- Q = 80 % in 90 minutes

Reviewer Notes on Methodology

As shown in Figure 13, dronedarone is most soluble at pHs between 3 and 5; subsequent studies indicated that solubility is optimal (maintenance of sink conditions) at pH 4.5.

Figure 13: Dronedarone solubility in aqueous solution at 25° C in phosphate buffer systems



Testing in various buffer systems at pH 4.5 demonstrated that the phosphate buffer was acceptable for dissolution. Upon addition of surfactant, the overall dissolution rate did not improve, however there was an indication that inter-individual variability was decreased (Table 24). It should be noted that there was a limit as to how much surfactant could be added before precipitation occurred. The applicant elected not to include surfactant in subsequent dissolution testing.

Table 24: Dissolution of 400 mg dronedarone tablets in pH ~ 4.5 media containing surfactant

Media	pH	Dissolution (%) after 60 min Mean (3 individual values)
Acetate buffer	4.6	85 (77 ; 93 ; 84)
Acetate buffer + SDS 0.2 %	4.6	85 (71 ; 91 ; 91)
Acetate buffer + SDS 0.5 %	4.6	81 (81 ; 73 ; 87)
Phosphate buffer	4.5	83 (89 ; 78 ; 81)
Phosphate buffer + polysorbate 80 at 0.2 %	4.4	83 (86 ; 82 ; 82)
Phosphate buffer + polysorbate 80 at 0.5 %	4.4	76 (79 ; 77 ; 74)

The applicant also adequately evaluated the effect of different dissolution apparatus and rotation speeds on dronedarone dissolution.

Reviewer Comments on Methodology

Based on the information provided, the proposed methodology is acceptable; the method may be limited by the overall poor dissolution profile of dronedarone that is related to dronedarone solubility. However, the applicant has not adequately evaluated the discriminatory ability of the dissolution method when different manufacturing conditions, such as varying temperature and pressure conditions are employed.

Reviewer Comment on Specification

Based on the poor solubility profile of dronedarone and its putative BCS 2 designation, the setting of a two-point dissolution specification is reasonable, per Dissolution

Guidance. As mentioned previously, dronedarone may belong to BCS 4 rather than BCS 2, based on its apparently low *in vivo* permeability. The Dissolution Guidance dose not offer specific recommendations regarding the setting of dissolution specifications for low solubility/low permeability compounds, BCS 4. However, an approach similar to that for BCS 2 appears reasonable, because the drug solubility characteristics have the greatest impact on drug dissolution. Irrespective of BCS designation, the data do not support the applicant's specification proposal. The proposed specifications, particularly Q = 75 after 90 minutes, are not rigid enough to ensure product quality. Per the Dissolution Guidance, the following criteria should be considered for slowly dissolving or poorly water soluble drugs such as dronedarone to characterize product quality:

- Two point specification: specification at 15 minutes including a dissolution range or window and specification at later time point such as 30, 45, or 60 minutes
- Dissolution profile

Using the two point approach, the data suggest the following specification is appropriate:

- Not less than 25 % and not more than 50 % is dissolved within 30 minutes
- Q = 80 % in 90 minutes

2.6 What Analytical Methods were used in the Dronedarone Development Program?

Overall, the performance of the bioanalytical methods used to identify and measure dronedarone levels was acceptable, per Bioanalytical Guidance. The analytical methods used in the clinical pharmacology and efficacy/safety studies are summarized in Table 25.

The assays satisfy the criteria (per Bioanalytical Guidance) for accuracy precision, and specificity. Sample stability was also demonstrated under various conditions including long-term storage, freeze-thaw, sample-handling, sample transport and with autosampler. Generally low, mid and high QC samples were present and these QC samples were adequate with respect to their relevant values to points on the standard curve.

Table 25:- Summary of bioanalytical studies associated with clinical pharmacology studies and efficacy/safety clinical studies (per Applicant)

Methods Report (Report Location)	Analytes	Type of Method	Calibration Range[a] (ng/mL)	Precision CV%		Accuracy A%[b]		Matrix (Anticoagulant)	Clinical Studies
				Within run	Between run	Within run	Between run		
DOS0124 (Sec. 5.3.1.4)	dronedarone	LC-UV	5 to 1000	Better than 8.5%	Better than 10.3%	92 to 95%	90 to 97%	Plasma (lithium heparinate)	TDU2164
	SR35021	LC-UV	5 to 1000	Better than 10%	Better than 9%	93 to 99%	94 to 98%		
DOH0020 (Sec. 5.3.1.4)	dronedarone	LC-UV	5 to 1000	3.9 to 5%	5.9 to 9.4%	98 to 104%	95 to 101%	Plasma (CDP)	INT2631, INT2634, INT2931, TDR2394, TDU2164
	SR35021	LC-UV	5 to 1000	3.1 to 5.5%	5.7 to 8%	97 to 106%	96 to 104%		
DOH0072 (Sec. 5.3.1.4)	dronedarone	LC-UV	5 to 1000	-	Better than 7.1%	-	106 to 111%	Plasma (CDP)	TDR2395, PDY2399, PDY2400, PDY2402, PDY2945, ACT2771, ACT2401, BEX2770, INT2636
	SR35021	LC-UV	5 to 1000	-	Better than 9.2%	-	96 to 108%		
DOH0048 (Sec. 5.3.1.4)	dronedarone	LC-UV	10 to 1000	Better than 14.7%	Better than 6.6%	86 to 107%	89 to 100 %	Blood (CDP)	ACT2771
DOH0036 (Sec. 5.3.1.4)	dronedarone	LC-MS/MS	0.5 to 50	1.3 to 4.8%	1.9 to 6.4%	-9.3 to -2%	-9.9 to -3.6%	Plasma (CDP)	INT3353, POP2769, TDU3007, PDY2399, PDY2400
	SR35021	LC-MS/MS	0.5 to 50	1.5 to 4.1%	1.7 to 4.3%	5.7 to 8.1%	3.9 to 9.6%		
DOH0151 (Sec. 5.3.1.4)	dronedarone	LC-MS/MS	0.5 to 50	3.8 to 11.2%	4.7 to 10.8%	-2.91 to 8.0%	-2.1 to 0.8%	Plasma (CDP)	INT3561, INT3683, INT4074, INT4442, TDR3549, PDY3828, DRI3550
	SR35021			5.5 to 13.3%	4.8 to 14.3%	-6.3 to –0.3%	-2.6 to 0.5%		
DOH0203 (Sec. 5.3.1.4)	dronedarone	LC-MS/MS	0.5 to 50	Better than 5.9%[c]		Better than 7.4%[c]		Plasma (CDP)	
	SR35021			Better than 16.8%[c]		Better than 9.5%[c]			
	SR35021			Better than 6.96%[c]		Better than 9.48%[c]			
	^{13}C-SR33589			Better than 5.97%[c]		Better than –4.19%[c]			
	^{13}C-SR35021			Better than 5.59%[c]		Better than –14.5%[c]			

Methods Report (Report Location)	Analytes	Type of Method	Calibration Range[a] (ng/mL)	Precision CV%		Accuracy A%[b]		Matrix (Anticoagulant)	Clinical Studies
				Within run	Between run	Within run	Between run		
DOH0239 (Sec. 5.3.1.4)	dronedarone	LC-MS/MS	0.5 to 300	Better than 8.37%[c]		Better than 9.49%[c]		Plasma (lithium heparinate)	INT4695, INT4880, INT4881, INT4886, LTS3841, EFC4788/ADONIS, DRI3151, INT4882, TDU4899
	SR35021			Better than 6.70%[c]		Better than –10.7%[c]			
DOH0292 (Sec. 5.3.1.4)	dronedarone	LC-MS/MS	0.5 to 300	Better than 9.08%[c]		Better than 3.04%[c]		Plasma (lithium heparinate)	INT4880, INT5189, EFC4788/ADONIS EFC4508/ERATO, EFC4966/ANDROMEDA
	SR35021			Better than 7.99%[c]		Better than 6.30%[c]			
DOH0309 (Sec. 5.3.1.4)	dronedarone	LC-MS/MS	0.5 to 300	Better than 4.07%[c]		Better than 6.38%[c]		Plasma (lithium heparinate)	LIN2890, INT3560, INT4884, POP2896, EFC3153/EURIDIS
	SR35021			Better than 4.15%[c]		Better than –11.4%[c]			

CV=coefficient of variation

[a] expressed as non salified compound

[b] A% = (Mean found / theoretical value)*100 for DOH0020 and DOH0072 and A% = ((Observed conc. – Expected conc)/Expected conc.)*100 for DOH0036 and DOH0238

[c] Total

3 Detailed Labeling Recommendations

Based on the Clinical Pharmacology and Biopharmaceutics Review, the following changes were made to the applicant's original labeling proposal. These changes apply to the Clinical Pharmacology and Dosage and Administration sections of the label.

The applicant's proposed labeling is acceptable with the noted recommendations (please refer to the sections of attached label.

4 Appendices

4.2 Individual Study Reviews

List of Studies in NDA 21-913

Study Report ID	Study Title or Description	Reviewed?
	Bioavailability	
PPK2397	Assessment of food effect on pharmacokinetic parameters of a single dose (800 mg) of SR33589B and assessment of absolute bioavailability	No
ALI3179	Effect of Fat Content on the Bioavailability of an Oral Administration of Two 400 mg Tablets of SR33589B Containing 5% of Pluronic F127.	No
ALI3180	Effect of fat content on the bioavailability of an oral administration of two 400 mg tablets of SR33589B containing 10% of Pluronic F127.	Yes
BDR2889	Relative bioavailability of four different formulations after a single oral dose of 800 mg of SR33589B under fasting and non- fasting conditions in healthy male subjects.	No
GAR3144	Relative bioavailability of three different formulations after a single oral dose of 800 mg of SR33589B under fasting and non fasting conditions in healthy male subjects.	No
GAR3585	Relative bioavailability of four different formulations after a single oral dose of 800 mg of SR33589B under fasted and fed conditions in healthy male subjects.	No
BDR4680	Relative bioavailability between the dronedarone tablets used in phase II studies and those prepared for phase III studies after single oral administration to young healthy subjects. Open, randomized, crossover and single center study.	Yes
	Healthy Subject Pharmacokinetic and Initial Tolerability Study Reports	
TDU2163	Single ascending dose tolerability study of SR33589B administered orally to healthy volunteers.	No
TDU2164	Single ascending dose tolerability study of SR33589B administered intravenously to healthy volunteers.	No
BEX2770	Excretion balance, pharmacokinetics, metabolite profile, and identification after a single PO and i.v. (by infusion) dose of SR33589B using 14C and 13C- labeled compounds in healthy male subjects.	Yes
TDU3007	Study on the tolerability of SR33589B given as a single ascending dose administered intravenously in healthy male subjects.	Yes
TDU4899	Study of the safety and pharmacokinetics or (SR33589B) in single oral administration in Japanese young male healthy subjects.	Yes
TDR2395	Study on the tolerability of SR33589B given as single and multiple oral doses in healthy male subjects under non fasted conditions.	Yes
LIN2890	Dose proportionality study after oral single and twice daily (BID) repeated (for 10 days) administrations of 200 mg, 400 mg, 800 mg dronedarone in healthy young male subjects - Randomized, open- labeled, non placebo-controlled, three- treatment, three- period crossover study.	Yes
TDR3549	Study on the tolerability of SR33589B given twice daily as repeated ascending oral doses in healthy male subjects.	Yes
	Patient Pharmacokinetic and Initial Tolerability Study Reports	
TDR2394	Repeated ascending dose tolerability study of SR33589B administered orally to patients with premature ventricular beats.	No
	Intrinsic Factor Pharmacokinetic Study Reports	
POP2769	Pharmacokinetic profile of SR33589 and its metabolite SR35021 after single and repeated oral administration of 800 mg SR33589B in healthy young male and elderly male and female subjects.	Yes
POP2896	Pharmacokinetics and safety of dronedarone after repeated oral doses for 10 days in patients with moderate hepatic impairment in comparison with healthy matched subjects- non- randomized, non- placebo-controlled, open-labeled, 2 parallel- groups study.	No
	Drug-Drug Interaction Study Reports	
INT2631	Assessment of plasma levels of single dose of warfarin administered alone or following administration of a repeated dose of SR33589B in healthy male volunteers.	No
INT2634	Evaluation of the effect of repeated oral doses of SR33589B on steady-state plasma digoxin concentrations in healthy volunteers.	No
INT2636	Pharmacokinetic and pharmacodynamic effects of single and repeated oral	Yes

	doses of SR33589B and of propranolol given alone or coadministered in healthy male subjects.	
INT2931	Tolerability of ascending oral doses of SR33589B Co-administered with a stable dose of 80 mg of propranolol in healthy male subjects.	No
INT3353	Study on the interaction between a single oral dose of warfarin and repeated oral doses of SR33589B in healthy male subjects.	Yes
INT3560	Pharmacokinetic interaction of repeated oral 40 mg o.d. pantoprazole on repeated oral 400 mg bid dronedarone in healthy young male subjects - Open- labeled, non placebo-controlled, randomized, 2- treatment, 2- period crossover study.	Yes
INT3561	Influence of repeated oral doses of ketoconazole [inhibitor of cytochrome P450 3A4 (CYP3A4)] on the pharmacokinetic profile of dronedarone in healthy male subjects.	Yes
INT3683	Influence of repeated oral doses of Rifampicine (inducer of Cytochrome P450 3A4) on the pharmacokinetic profile of Dronedarone in healthy male subjects.	Yes
PDY3828	Dose escalation study tolerability and pharmacokinetic effects of Dronedarone on top of Metoprolol in healthy male volunteers.	Yes
INT4074	Influence of repeated oral doses of nifedipine and of repeated oral doses of diltiazem (inhibitors of cytochrome P450 3A4) on the pharmacokinetic profile of dronedarone in healthy male subjects. Preliminary study.	Yes
INT4442	Interaction between repeated oral doses of dronedarone and a single oral dose of simvastatin in healthy male subjects.	Yes
INT4695	Effect of repeated oral doses of 800 mg b.i.d. dronedarone on the pharmacokinetic profile of oral contraceptive in healthy female subjects - randomized, double- blind, placebo- controlled study.	Yes
INT4880	Interaction study between repeated oral doses of dronedarone and repeated oral doses of simvastatin in healthy male subjects - randomized, open-labeled, 3- treatment, cross- over study.	Yes
INT4881	Interaction study between repeated oral doses of dronedarone and repeated oral doses of nisoldipine in healthy male subjects - randomized, open-labeled, 3 treatments, crossover study.	Yes
INT4882	Interaction study between repeated oral doses of dronedarone and repeated ascending oral doses of verapamil in healthy young male subjects - Three-group, randomized, open- labeled, three- treatment, crossover study	Yes
INT4884	Interaction study between repeated oral doses of dronedarone and repeated oral doses of losartan in healthy young male subjects - Randomized, open-labeled, non-placebo- controlled, three- treatment, crossover study.	Yes
INT4886	An interaction study to investigate a potential effect of repeated oral ingestion of grapefruit juice on the pharmacokinetic profile of single and repeated oral doses of dronedarone in young healthy male subjects.	Yes
INT5189	Pharmacokinetic interaction of repeated oral 400 mg BID dronedarone for 10 days on repeated oral 0.25 mg OD Digoxin in healthy young male subjects - Randomized, double- blind, placebo- controlled, two- sequence, two-treatment, crossover study.	Yes
INT	Theophylline	Yes
	Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Study Reports	
POH0051	Population Pharmacokinetic Analysis on the pool of EURIDIS & ADONIS (European and American- Australian trials in atrial fibrillation or flutter patients for the maintenance of sinus rhythm) and ANDROMEDA (Antiarrhythmic trial in congestive heart failure and left ventricular dysfunction) studies.	Yes
PDY5487	Effect of dronedarone on renal functions in healthy male subjects - Randomized, double- blind, placebo- controlled, two- by- two crossover in sequential groups study.	Yes
	Renal function	No
PDY2399	Hemodynamic study of patients with normal left ventricular function following I.V. infusion of 3 doses of SR33589B or I. V. amiodarone.	No
PDY2400	Study of the electrophysiological and hemodynamic characteristics of	No

	SR33589B administered intravenously to patients with impaired left ventricular function.	
ACT2401	Study of the safety and the pharmacodynamic effects of SR33589B administered orally for one month to patients with left ventricular dysfunction.	No
PDY2402	Study of the electrophysiological and hemodynamic characteristics of SR33589B administered orally for one month at the doses 400mg and 800mg versus Amiodarone (400mg) to patients with normal or impaired left ventricular function.	No
SPH, LPH and DOH studies	**Reports of Bioanalytical and Analytical Methods for Human Studies (n = 15)**	Yes (partially)
	Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials	
LPH0006	In Vitro Characterisation of the Binding of [14C]- SR33589 to Human Plasma Proteins.	Yes
LPH0021	In Vitro Characterisation of the Binding of [14C]- SR35021 to Human Plasma Proteins.	Yes
MIH0006	Assessing the potential for Co- administered drugs to inhibit the N-debutylation of SR33589B using human liver microsomes in vitro.	No
MIH0007	Assessing the potential for SR33589B or amiodarone to inhibit cytochrome P450 (CYP) enzymes using human liver microsomes in vitro.	Yes
MIH0037	Investigating the Potential for SR35021 to Inhibit Cytochrome P450 (CYP) Enzymes Using Human Liver Microsomes in vitro.	Yes
MIV0144	Regulation of the expression of cytochrome P450 gene subfamilies IA, IIA and IIIA by SR33589B in primary cultures of human hepatocytes.	Yes
MIV0158	SR33589B metabolism using human hepatic models.	Yes
MIV0159	Identification of main cytochrome P450 isozymes involved in SR33589B metabolism by human liver microsomal fractions.	Yes
MIV0281	Role for CYP3A4 in the hepatic metabolic clearance of SR33589B, using primary cultures of human hepatocytes.	No
AIV0062	In vitro investigation of SR33589B trans- epithelial transport polarisation and inhibitory potency towards the active efflux of vincristine and digoxine using Caco- 2/TC-7 cells monolayers.	Yes
	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication	
DRI3550	Dose-ranging study of the efficacy and safety of Dronedarone for the maintenance of sinus rhythm in patients undergoing cardioversion for atrial fibrillation.	Yes (PM consult)
EFC4508	Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation (ERATO).	No
EFC3153	EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maIntenance of Sinus rhythm (EURIDIS).	No
EFC4788	American- Australian- African trial with DronedarONe In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm (ADONIS).	No
	Other Study Reports	
ACT2771	Efficacy of the intravenous formulation of SR33589B (dronedarone) in patients with a sustained episode of atrial fibrillation at the dose 80 mg versus placebo.	No
PDY2945	Study of the efficacy of Dronedarone (SR33589B) in the suppression of inducible ventricular tachycardia.	No
DRI3151	Placebo- controlled dose- finding safety and tolerability study in patients with an implantable cardioverter defibrillator (ICD).	No
LTS3841	Long- term tolerability and efficacy estimation study in patients with an implantable cardioverter defibrillator (ICD).	No
EFC4966	ANtiarrhythmic trial with DROnedarone in Moderate to severe CHF Evaluating morbidity DecreAse (ANDROMEDA).	No

4.2.1 Dose proportionality study after oral single and twice daily (BID) repeated (for 10 days) administrations of 200 mg, 400 mg, 800 mg dronedarone in healthy young male subjects - Randomized, open- labeled, non placebo- controlled, three-treatment, three-period crossover study (LIN2890)

PROTOCOL #	LIN2890
INVESTIGATOR	Dr Nicolas Fauchoux
STUDY SITE	Biotrial Rue Jean- Louis Bertrand Technopole Atalante Villejean 35000 Rennes, France
STUDY PERIOD	06 May 2004 to 15 Sep 2004

Objectives (per applicant):

- To assess the deviation from dose proportionality of dronedarone and of its N-debutyl metabolite SR35021 pharmacokinetics after 200 mg, 400 mg, and 800 mg single and BID repeated oral doses of dronedarone for 10 days.
- To assess the clinical and biological tolerability [including blood pressure (BP), heart rate (HR), and electrocardiogram (ECG)] of 200 mg, 400 mg, and 800 mg single and repeated oral doses of dronedarone for 10 days.

Study Design

This was a randomized, open-labeled, non placebo-controlled, three-treatment, three-period crossover study. There was a washout of 14 days between periods. Healthy male subjects, aged between 18 to 40 years were enrolled. Doses were as follows: 200 mg (2 x 100 mg tablets), 400 mg (1 x 400 mg tablet) and 800 mg (2 x 400 mg tablets). All doses were given as a single dose on Day 1, BID from Day 5 to Day 13, and only in the morning on Day 14. Dronedarone was given orally in fed conditions (standard meal). Details of the standard meal were not provided.

Subject Demographics

Subject demographics are presented in Table 26.

Formulation (2E3 Formulation)

- Dronedarone 100 mg tablets, batch number CL-04600
- Dronedarone 400 mg tablets, batch number CL-04530

Pharmacokinetics

The following pharmacokinetic measures were determined:

- Day 1: Cmax, tmax, AUC_{0-12h}, AUClast, AUC, $t_{1/2z}$, CL/F, Vz/F (for dronedarone only), and metabolic ratio, Rmet, (SR35021 AUC_{0-12}/dronedarone AUC_{0-12}).
- Day 14: Cmax, tmax, AUC_{0-12h}, $t_{1/2}z$, CL/F, Vz/F (for dronedarone only), and Rmet; accumulation ratio, Rac, calculated from AUC_{0-12h} and Cmax.

Pharmacokinetic sampling times

PK samples for assays of dronedarone and its metabolite SR35021 were collected as follows:

- before dosing (T0) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72 and 96 hours after dosing on Day 1 and Day 14
- before morning dosing (T0) for trough determinations on Days 6, 7, 8, 9, 10, and 12.

Table 26: Subject Demographic Data

Parameter (Unit)	Statistics / Category	Overall Subjects (N = 21)
Age (years)	N Mean (SD) Min-Max	21 28.3 (6.4) 19-40
Weight (kg)	N Mean (SD) Min-Max	21 71.67 (9.34) 54.0-89.0
Height (cm)	N Mean (SD) Min-Max	21 178.2 (6.5) 168-192
BMI (kg/m^2)	N Mean (SD) Min-Max	21 22.56 (2.88) 19.0-28.7
Gender	Male (N,%)	21 (100)
Race	Caucasian (N,%) Black (N,%) Other (N,%)	18 (85.7) 2 (9.5) 1 (4.8)

Bioanalytical methods

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as illustrated in Table 27.

Table 27: Performance of Dronedarone and SR35021 Assays (DOH0309)

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day precision	CV data were not provided	Cannot be assessed
Between day accuracy	The majority of QC samples were within 15 % of the nominal concentrations	Acceptable
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day precision	CV data were not provided	Cannot be assessed
Between day accuracy	The majority of QC samples were within 15 % of the nominal concentrations	Acceptable
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

*The validation report for the assay included precision measurements (CV < 5 %) and chromatograms that suggest that the assay was precise and specific

Results

Subject Disposition (Patients contributing PK data)

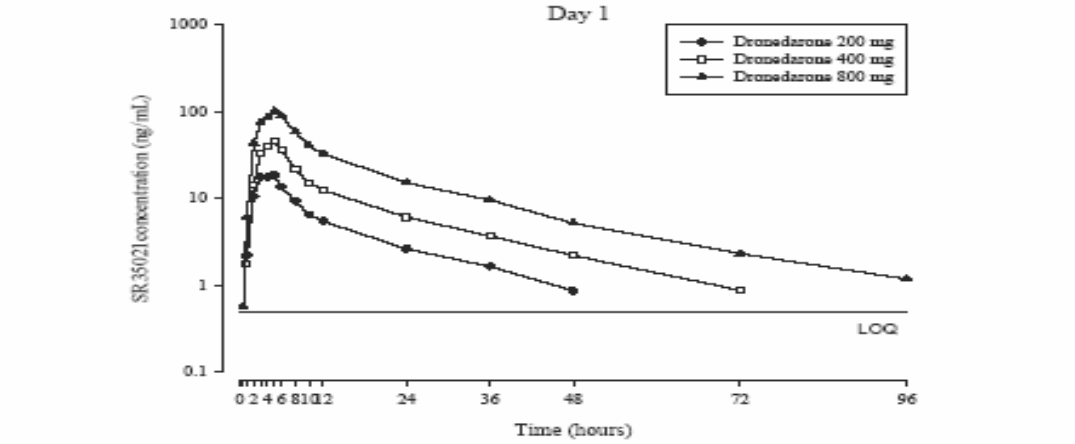
Data from several subjects were excluded from the PK analyses for various reasons; the main reasons for exclusions were absence of PK assessments and incomplete PK assessments. Exclusion of these data appears reasonable. Despite these exclusions there were a sufficient number of subjects to facilitate statistical analysis of PK data ($n \geq 16$ for each condition).

Reviewer Note on Figures and Tables
It should be noted that Study Day 5 and Day 14 correspond to the first and tenth days of BID dosing respectively.

Plasma Concentrations

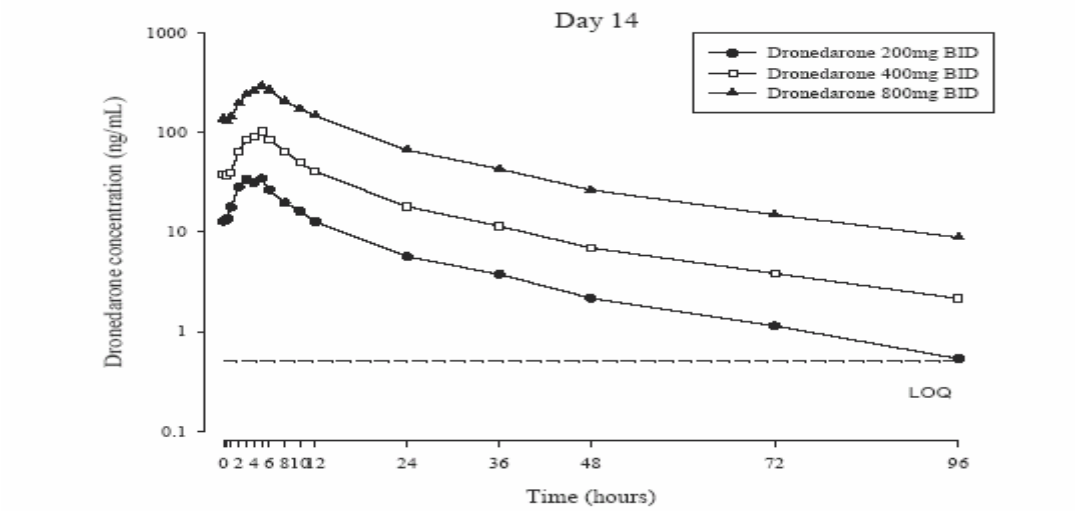
The dronedarone plasma concentration-time profile on Day 1 is depicted in Figure 14.

Figure 14: Mean dronedarone plasma concentration-time profile on Day 1



The dronedarone plasma concentration-time profile on Day 14 is depicted in Figure 15.

Figure 15: Mean dronedarone plasma concentration-time profile on Day 14



Both Day 1 and day 14 profiles depict a biphasic elimination of dronedarone after Cmax is reached. The Day 1 and 14 plasma concentration-time profiles of the dronedarone metabolite are depicted in Figure 16 and Figure 17, respectively.

Figure 16: Mean SR35021 plasma concentration-time profile on Day 1 following dronedarone administration

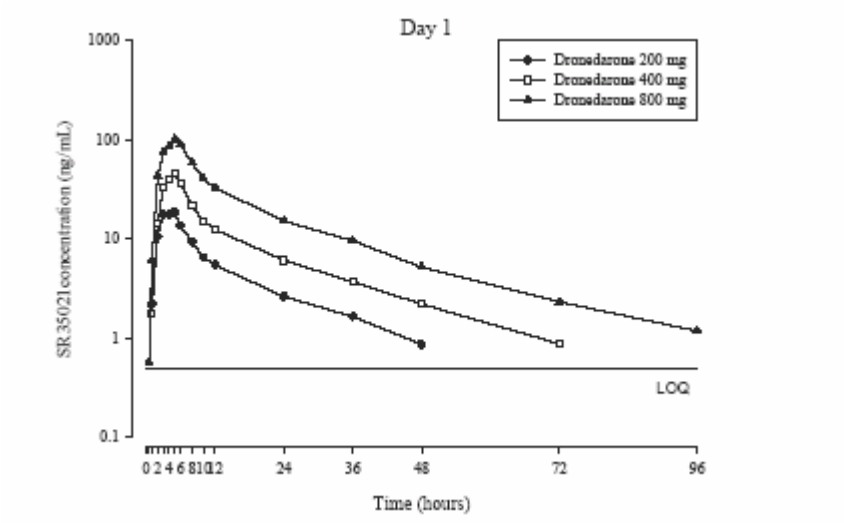
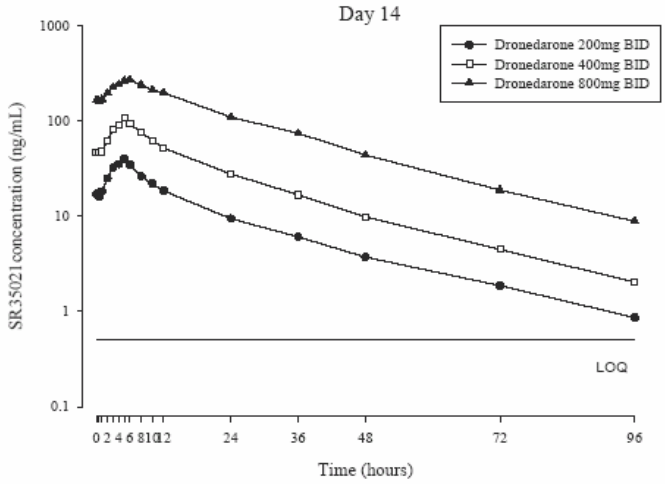


Figure 17: Mean SR35021 plasma concentration-time profile on Day 14 following dronedarone administration



Dronedarone and SR35021 PK measures on Day 1 and Day 14 are presented in Table 28.

General Observations

- Dronedarone and SR35021 plasma concentrations increased with dose in a greater than dose proportional manner over the 200 to 800 mg dosage
- Day 14 concentrations were greater than Day 1 concentrations, indicating accumulation occurred
- Tmax was independent of Day or dronedarone dose
- Day 1 $t_{1/2}$ (< 20 hr) appeared shorter than Day 14 $t_{1/2}$ (> 29 hr), and Day 1 $t_{1/2}$ was dose-dependent

Table 28: Dronedarone and SR35021 PK Measures in Healthy Males Following Single and Multiple Dose Administration (200, 400 and 800 mg BID)

PK Parameters		Dronedarone			SR35021		
		200 mg n = 17	400 mg n = 16 [b]	800 mg n = 17 [c]	200 mg n = 17	400 mg n = 16 [b]	800 mg n = 17 [c]
C_{max} (ng/mL)	Day 1	23.1 (38)	67.2 (36)	162 (40)	20.8 (21)	49.5 (25)	109 (29)
	Day 14	40.3 (30)	111 (17)	298 (13)	41.2 (27)	107 (22)	282 (21)
t_{max} [a] (h)	Day 1	3 [2; 5]	3 [2; 5]	3 [2; 6]	5 [2; 5]	5 [3; 6]	5 [3; 6]
	Day 14	5 [2; 5]	5 [3; 6]	5 [2; 6]	5 [2; 6]	5 [3; 8]	5 [3; 4 8]
AUC_{0-12} (ng.h/mL)	Day 1	111 (24)	310 (28)	846 (27)	123 (19)	275 (23)	668 (24)
	Day 14	276 (23)	798 (19)	2510 (12)	325 (21)	882 (17)	2680 (20)
$t_{1/2z}$ (h)	Day 1	9.81 (33)	17.6 (56)	19.6 (33)	16.2 (28)	19.2 (24)	21.9 (22)
	Day 14	26.9 (32)	30.0 (29)	31.2 (32)	23.5 (14)	21.1 (16)	20.4 (8)
AUC (ng.h/mL)	Day 1	160 (27)	474 (33)	1310 (26)	237 (23)	545 (22)	1360 (20)
CL/F [d] (L/h)	Day 1	1350 (29)	937 (35)	669 (38)	-	-	-
	Day 14	765 (25)	517 (18)	324 (13)	-	-	-
Vz/F [d] (L)	Day 1	18000 (24)	21000 (31)	17900 (33)	-	-	-
	Day 14	29400 (34)	22800 (41)	14500 (31)	-	-	-

Numbers rounded at 3 significant figures.
[a] median value [Min–Max]
[b] n = 14 at Day 14
[c] n = 16 at Day 14
[d] CL_{0-12}/F and Vz_{0-12}/F at Day 14

Dose Proportionality Assessment

As shown in Table 13 there was a slightly greater than proportional increase in plasma exposure on Day 1 and Day 14 with increasing dose (pooled data from three dronedarone doses):

- Day 1: for a two-fold in increase in dose exposure increased more than 2.6-fold
- Day 14: for a two-fold in increase in dose exposure increased more than 2.7-fold

This finding suggests that dronedarone may exhibit non-linear PK. The source of the non-linearity is not known; however, non-linearity does not appear due to saturable elimination because half-life was comparable for all dronedarone regimens (~ 30 hours on Day 14).

Table 29: Dose-proportionality Estimations Following Single and Multiple Dose Administration of Dronedarone 200, 400 and 800 mg Doses

Ratio estimates for dose proportionality at Days 1 and 14

PK Parameters		Ratio Estimate	90% CI
Dronedarone			
C_{max} (ng/mL)	Day 1	2.62	[2.39 – 2.88]
	Day 14	2.77	[2.62 – 2.93]
AUC[a] (ng.h/mL)	Day 1	2.86	[2.67 – 3.06]
	Day 14	3.06	[2.92 – 3.20]
SR35021			
C_{max} (ng/mL)	Day 1	2.24	[2.10 – 2.38]
	Day 14	2.59	[2.46 – 2.73]
AUC[a] (ng.h/mL)	Day 1	2.37	[2.27 – 2.48]
	Day 14	2.82	[2.71 – 2.93]

a: AUC_{0-12} at Day 14.

Accumulation Assessment

The accumulation ratios for the various dronedarone regimens are summarized in Table 30.

Table 30: Accumulation Ratio Summary for BID Dosing

Accumulation ratio summary

PK Parameters		R_{ac} Estimate	95% CI
Dronedarone			
C_{max} (ng/mL)		1.84	[1.65, 2.04]
AUC_{0-12} (ng.h/mL)		2.72	[2.52, 2.94]
SR35021			
C_{max} (ng/mL)	200 mg	1.96	[1.72, 2.23]
	400 mg	2.15	[1.87, 2.47]
	800 mg	2.66	[2.33, 3.03]
AUC_{0-12} (ng.h/mL)	200 mg	2.62	[2.36, 2.91]
	400 mg	3.21	[2.87, 3.60]
	800 mg	4.07	[3.65, 4.53]

The applicant pooled accumulation ratio (R_{ac}) data for the three dronedarone doses, rather than calculating R_{ac} for separate doses. The approximate ratios (based on linear scale AUCs) for each dose were 200 mg ~ 2.49, 400 mg ~ 2.57 and 800 mg ~ 2.97. Thus, numerically, there appears to be an increasing degree of accumulation with increasing dose; this trend was also observed for the metabolite.

Metabolic Ratio

The metabolic ratio, SR35021/Dronedarone for AUC and Cmax on Days 1 and 14 are presented in Table 12

Table 31: Mean (CV %) metabolic ratio of Cmax and AUC

Dose		200 mg n = 17	400 mg n = 16 [b]	800 mg n = 17 [c]
R_{met} C_{max}	Day 1	0.996 (34)	0.795 (32)	0.724 (31)
	Day 14	1.08 (28)	0.973 (20)	0.944 (15)
R_{met} AUC[a]	Day 1	1.55 (25)	1.22 (26)	1.08 (19)
	Day 14	1.22 (24)	1.12 (17)	1.07 (17)

[a] AUC on Day 1 and AUC_{0-12} on Day 14
[b] n = 14 at Day 14
[c] n = 16 at Day 14

Based on Day 1 AUC and Cmax data, more metabolite was formed at lower doses than at higher doses, suggesting saturation in metabolism may occur (non-linear PK). On Day 14, numerically the same trend was observed, but differences were not as great as on Day 1.

Steady State Assessment

Based on a visual inspection of the data (Figure 18 and Figure 19) following the 400 mg BID dose, dronedarone and SR35021 steady-state is achieved by Day 9, which corresponds to 4 days of BID dosing. There appeared to be a dose effect with respect to time to reach steady state. The applicant's statistical analyses revealed that dronedarone steady-state is achieved within 3 to 4 days and SR35021 steady-state is achieved within 4 to 5 days. Overall the findings suggest that steady state is reached within 6 days of dosing (~ 1 week).

Figure 18: Dronedarone Ctrough vs. Time

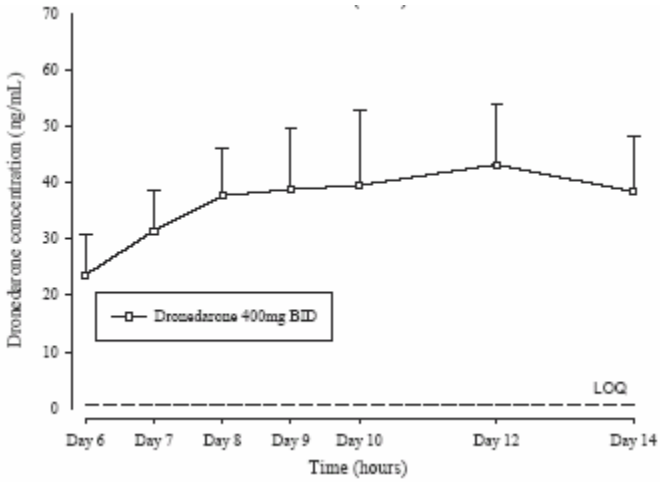
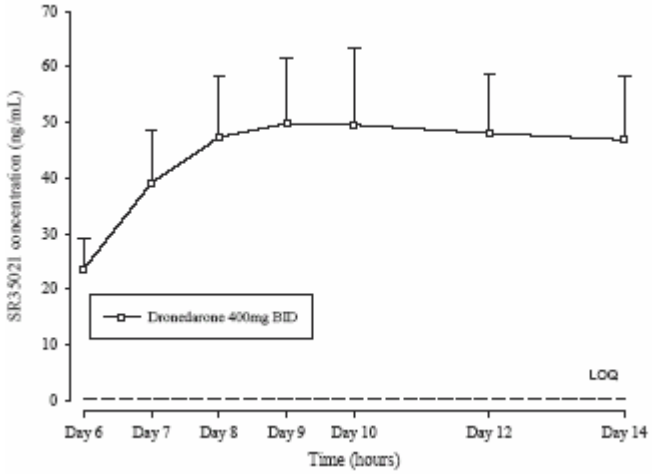


Figure 19: SR35021 Ctrough vs. Time



Applicant's Safety Summary

No deaths or serious adverse events (SAEs) occurred during the study. The most common treatment emergent adverse event in all dronedarone dose groups was asthenia (23.5%). Two subjects were withdrawn from treatment because of AEs: one due to a moderate urticaria occurred 4 days after completing the period 1 treatment with dronedarone 800 mg; and one due to a severe myalgia on Day 10 of period 3 treatment with dronedarone 800 mg. Both events resolved after drug discontinuations. Regarding ECG parameters, no prolongation of QTc > 500 ms was recorded. Two subjects in the 800 mg treatment period experienced both prolonged QTc intervals > 450 ms and changes from baseline in delta QTc > 60 ms. The overall clinical and laboratory tolerability of dronedarone 200 mg, 400 mg, and 800 mg single and BID administrations in this study was good.

Recommendations/Conclusions

The following PK information generated in Study LIN2890 is acceptable for labeling purposes, as appropriate. It should be noted that PK were not determined in the fasted state

1. Steady-state dronedarone and SR35021 concentrations were reached within 6 days.
2. Dronedarone appears to exhibit non-linear PK as shown by:

- Cmax and AUC_{0-12} of dronedarone and SR35021 increased more than dose-proportionally, for a two fold increase in dose, plasma exposure increased > 2.6 times
- The amount of metabolite formed appeared to be dose dependent: the lower the dose, the more metabolite formed. This finding suggests that there is a saturable first pass effect.

3. The accumulation ratio (based on AUC ratios) was approximately 2.7 across the 200 mg to 800 mg dose range; the accumulation ratio for the 400 mg dose was ~ 2.6
4. Dronedarone $t_{1/2}z$ increased significantly from 200 mg to 800 mg and from Day 1 to 10.

Mean (CV %) Dronedarone PK Measures following 400 mg Dronedarone Dose in Healthy Subjects

PK Measure	Single 400 mg Dose	Day 10 Multiple 400 mg BID Dose (steady state)
AUC (ng h/mL)	310 (24)	798 (19)
Cmax (ng/mL)	67.2 (36)	111 (17)
Half-life (h)	17.6 (56)	30 (29)
Tmax (h)^	3 (2 to 5)	5 (3 to 6)

^ Tmax reported as median and (range)

4.2.2 Excretion balance, pharmacokinetics, metabolite profile, and identification after a single p.o. and i.v. (by infusion) dose of SR33589B using 14 C And 13 C- labeled compounds in healthy male subjects (BEX2770)

PROTOCOL #	BEX2770
INVESTIGATOR	Philip T. Leese, M. D.
STUDY SITE	Innovex Inc., 11250 Corporate Avenue, Lenexa, Kansas 66219.
STUDY PERIOD	October to December 1996

Objectives (per applicant)

- To determine the pharmacokinetics of ^{14}C relative to unchanged SR33589B (dronedarone) in blood and plasma; the balance excretion (mass balance) of ^{14}C in urine, feces and expired air; the metabolite profile in urine, feces and plasma; and the identification of metabolites in selected samples after single oral (p.o.) or single intravenous (i.v.) doses.
- To assess clinical and biological safety and tolerability of dronedarone.

Study Design

This was an open-label, single dose, parallel group study in healthy male volunteers. Twelve subjects enrolled: n = 6, single oral dose six and n = 6, single intravenous dose. A single 800 mg dronedarone dose was given orally: 400 mg as ^{13}C- dronedarone and 400 mg as ^{14}C-dronedarone. A single 40 mg dronedarone dose was given intravenously: 20 mg of dose was ^{13}C-dronedarone and 20 mg ^{14}C- dronedarone. The IV dose was given as a 60-minute infusion. The study proceeded for seven days post-dose or until urinary and excretion radioactivity criteria were met (< 0.1 % of dose and < 0.5 % of dose for urine and feces, respectively).

Subject Demographics

The subject demographics are summarized in Table 32.

Table 32: Demographic Characteristics of Subjects in BEX2770

Demographic characteristic	Oral SR33589B (n=6)	Intravenous SR33589B (n=6)
Age (years)		
Mean (SD)	60.5 (6.2)	56.2 (7.4)
Range	50.0 - 69.0	51.0 - 68.0
Weight (kg)		
Mean (SD)	79.1 (9.5)	87.2 (10.1)
Range	70.7 - 95.6	75.2 - 100.1
Height (cm)		
Mean (SD)	174.2 (5.1)	177.6 (5.6)
Range	165.8 - 181.0	167.6 - 183.0

It should be noted that all subjects were > 50 years, which may affect drug disposition, if an age effect exists for dronedarone.

Formulation

- Dronedarone capsules, 200 mg, ^{13}C- labeled dronedarone; batch No. DPJ 134
- Dronedarone capsules, 200 mg, ^{14}C- labeled dronedarone with 179.01 m Ci (6.63 MBq); batch No. DPJ 134
- Dronedarone solution, 0.33 mg/mL; batch No. DPJ 137.
- Dronedarone solution, 0.33 mg/mL with 60.6 m Ci (2.24 MBq) of ^{14}C-labeled dronedarone; batch No. DPJ 137.

Bioanalytical Assay

Liquid scintillation counting was used to determine radioactivity in the different matrices. Blood concentrations of dronedarone and its N-debutyl metabolite, SR35021, in plasma was determined by a validated electrospray LC-MS/MS. Metabolite profiling and quantification was conducted by HPLC with fraction collection, followed by liquid scintillation counting. The metabolite structures were elucidated using tandem mass spectrometry with electrospray ionization following HPLC. All assays performed in an acceptable manner.

Pharmacokinetic Methods

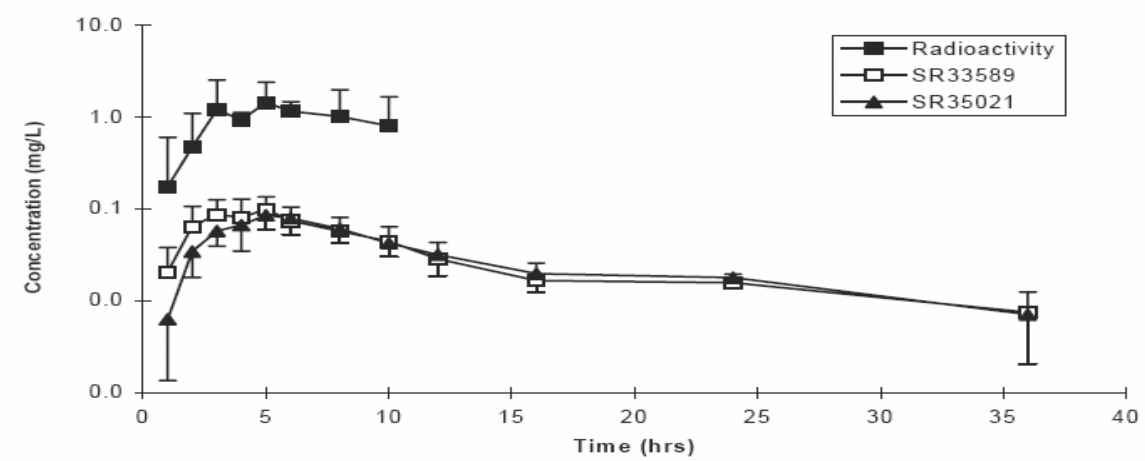
The pharmacokinetics (PK) of total radioactivity, dronedarone and SR35021 and metabolites in plasma, urine, feces and expired air were determined, as appropriate. No formal statistics were performed on the PK measures.

Results

Oral and IV Plasma Pharmacokinetics

The mean (± SD) plasma concentration-time profiles of radioactivity, SR33589 (dronedarone) and SR35021 following oral administration of 800 mg dronedarone are shown Figure 20.

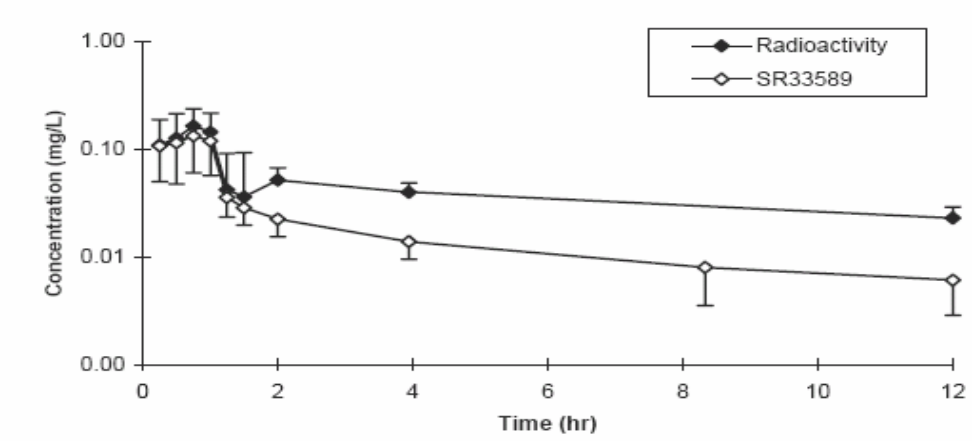
Figure 20: Plasma concentration-time profiles of total radioactivity, dronedarone and SR35021 following oral administration of radiolabeled dronedarone



The profiles suggest that dronedarone is extensively metabolized, as the total radioactivity exceeds that of non-labeled dronedarone and its known metabolite, SR35021.

The mean (± SD) plasma concentrations of radioactivity and dronedarone following intravenous administration of 40 mg dronedarone is shown in Figure 21.

Figure 21: Plasma concentration-time profiles of total radioactivity and dronedarone following intravenous administration of radiolabeled dronedarone



The profile obtained after IV administration indicates:

- dronedarone is extensively metabolized
- the primary metabolite, SR35021 is not formed, suggesting SR35021 is formed mainly during first pass metabolism after oral administration

The mean (SD) plasma PK measures of total radioactivity, dronedarone and SR35021 following oral administration of 800 mg (6.63 MBq) of ^{14}C-droendarone are shown in Table 33.

Table 33: PK measures for dronedarone, SR35021 and total radioactivity following oral dronedarone administration

Parameter (units)	Oral Group		
	Radioactivity [a,b]	SR33589 [a]	SR35021 [a]
C_{max} (mg/L)	1.75 (1.06)	0.10 (0.04)	0.09 (0.02)
t_{max} (h)	4.5 [c] (3 to 6) [d]	4.5 [c] (3 to 6) [d]	5.5 [c] (5 to 6) [d]
$t_{½}$ (h)	ND [e]	18.84 (4.01)	18.49 (2.57)
AUC_{0-t} (mg*h/L)	19.86 (29.85)	1.11 (0.41)	1.08 (0.34)
t (h)	11.0 (2.0)	36.0 (7.6)	40.8 (6.6)
AUC (mg*h/L)	ND	1.58 (0.39)	1.46 (0.34)
%(Extrapolated AUC /AUC)	ND	18.35 (6.54)	18.46 (4.43)

[a] Mean (±SD)
[b] Radioactivity is expressed as mg-equivalents where appropriate
[c] Median of all subjects
[d] Range for t_{max} from all subjects
[e] Not determined

The applicant notes that a terminal elimination half-life for plasma radioactivity could not be determined due to the rapid decline of plasma concentrations of radioactivity.

The mean (SD) plasma pharmacokinetic parameters of radioactivity and dronedarone following IV administration of 40 mg radiolabeled dronedarone are shown in Table 34.

Table 34: PK Measures for dronedarone and total plasma radioactivity following IV administration of radiolabeled dronedarone

Parameter (units)	Intravenous Group	
	Radioactivity [a,b]	SR33589 [a]
C_{max} (mg/L)	0.17 (0.07)	0.14 (0.07)
t_{max} (h)	0.83 [c] (0.75 to 1.0) [d]	1.0 [c] (0.75 to 1.25) [d]
$t_{½}$ (h)	11.76 (5.78)	10.97 (5.21)
AUC_{0-t} (mg*h/L)	0.65 (0.32)	0.35 (0.15)
t (h)	17.33 (8.26)	17.33 (6.02)
AUC (mg*h/L)	0.95 (0.44)	0.49 (0.19)
%(Extrapolated AUC/AUC)	34.01 (8.56)	25.65 (11.48)

[a] Mean (±SD)
[b] Radioactivity is expressed as mg-equivalents where appropriate
[c] Median of all subjects
[d] Range for t_{max} from all subjects

Total Recovery of Radioactivity

The mean recovery of radioactivity in urine, feces and expired air following IV and oral administration are summarized in Table 35 and Table 36. The data indicate that recovery was relatively high (> 80 %) following both administration routes.

Table 35: Mean recovery of radioactivity in urine, feces and expired air following oral administration

Excretion (% of dose)			
Urine	Feces	Expired air	Total
5.8 ± 1.2	83.9 ± 5.1	0.0 ± 0.0	89.7 ± 4.7

Table 36: Mean recovery of radioactivity in urine, feces and expired air following IV administration

Excretion (% of dose)			
Urine	Feces	Expired air	Total
8.3 ± 1.9	74.5 ±7.8	0.0 ± 0.0	82.8 ± 8.4

The recovery was maximal within 180 hours for oral administration and 300 hours for IV administration.

Metabolites and metabolite profiling

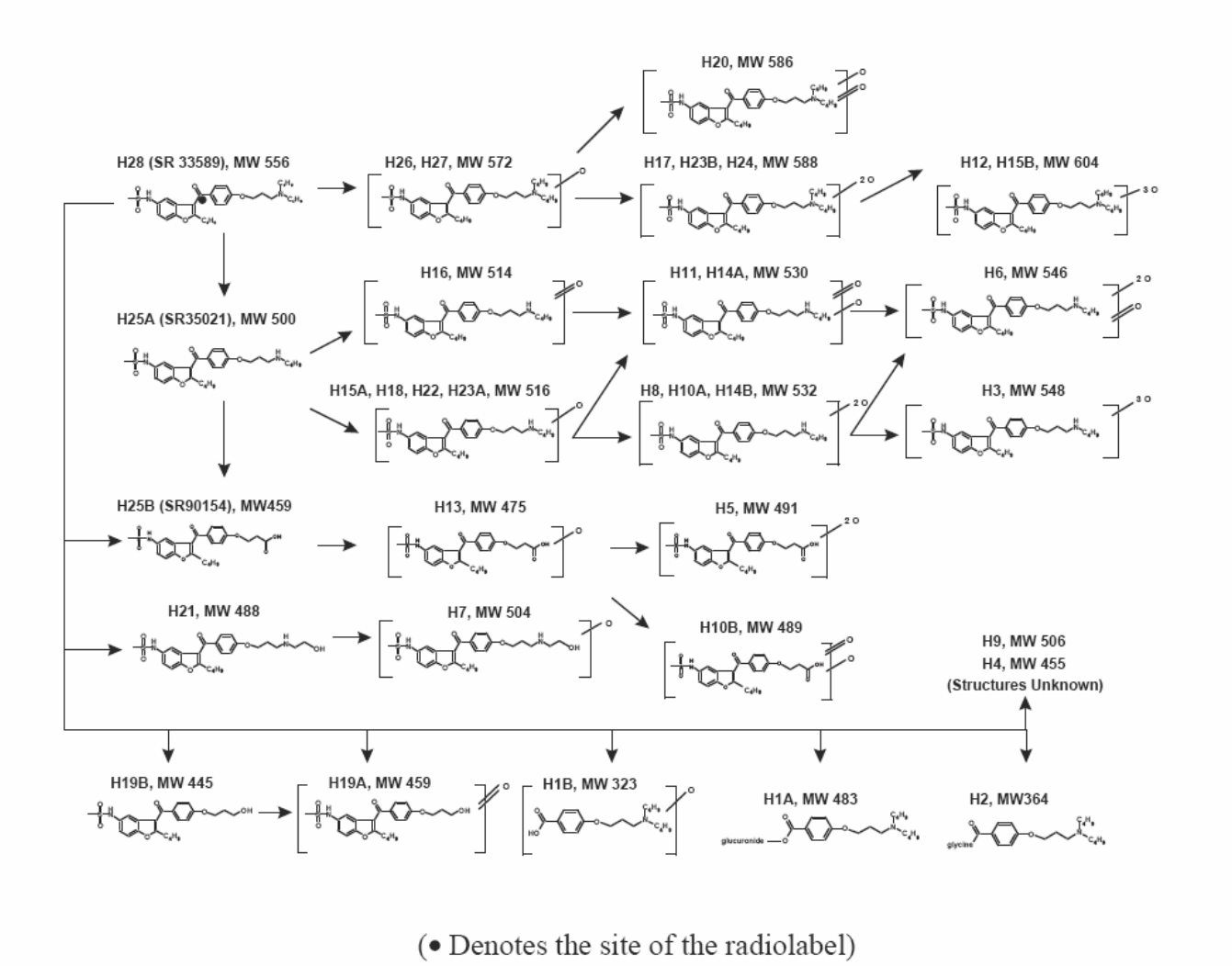
Thirty-four putative metabolites were noted in urine or feces. Structural information was obtained on 32 of these metabolites. Most of the metabolites excreted in urine and feces could be organized into one of three major groups based on structure. These groups included the:

- N-debutylated metabolite and oxygenated metabolites
- Propanoic acid metabolite and oxygenated metabolites of this metabolite
- Metabolites resulting from the direct oxygenation of dronedarone.

Many of the excreted metabolites, from each of the major metabolite groups, were also observed in plasma through 12 hours after dosing.

The characterized pathways of dronedarone metabolism are shown in Figure 11.

Figure 22: Metabolic pathways of dronedarone



Metabolites accounted for the majority (> 70 %) of the radioactivity recovered in the urine and feces following both oral and IV administration. The applicant indicates that plasma from subjects receiving the intravenous dose of dronedarone was not analyzed for metabolites due to the low amounts of radioactivity at all time points. Metabolites were not detected in blood samples.

<u>Relative Amounts of Metabolites in Urine, Feces and Plasma after Oral Administration</u>

The relative amounts of dronedarone metabolites in the different matrices are summarized in Table 37, (HU is for urine) and Table 38, (HF is for feces) and Figure 23 (HP is for plasma). In general, individual metabolites accounted for < 5 % of the radioactive dose.

Reviewer Note on Metabolite Identification

The applicant reported that some of the chromatographic peaks could not be resolved. In other instances some metabolites were not detected in extracted urine samples by radio chromatography, but were observed with LC-MS detection. The peaks that could not be resolved

were primarily the N- debutylated metabolite (SR35021) and the propanoic acid metabolite (SR90154); these peaks were identified as HP25A and HP25B (in plasma), respectively. Consequently, these metabolites were quantified together because they were not resolved from each other by radio chromatography. This approach is acceptable as quantitative assessment is not critical in this mass balance study.

Table 37: Dronedarone metabolites in urine

HU1 (A,B)	HU2, 3	HU4	HU5	HU6	HU7	HU8	HU9	HU10 (A,B)	HU11
7.3 (0.8)	5.7 (0.8)	3.6 (0.6)	3.5 (0.5)	2.0 (0.6)	0.9 (0.4)	1.1 (0.3)	1.1 (0.5)	2.1 (0.6)	10.7 (1.5)
HU12	**HU13**	**HU14 (A,B)**	**HU15 (A,B)**	**HU16**	**HU17**	**HU18**	**HU19 (A,B)**	**HU20**	**HU21**
NQ	21.7 (2.0)	1.9 (0.4)	4.1 (0.8)	1.3 (0.3)	2.6 (0.6)	1.4 (0.4)	3.8 (0.7)	NQ	1.2 (0.6)
HU22	**HU23 (A,B)**	**HU24**	**HU25 (A,B)**	**HU26**	**HU27**	**HU28**	**Total**		
NQ	2.0 (0.7)	NQ	1.9 (0.8)	0.8 (0.3)	NQ	NQ	**80.8 (3.6)**		

[a] Expressed as a percent of urinary radioactivity (0 - 168 hours)
NQ - Not quantifiable, but detected by LC-MS/MS

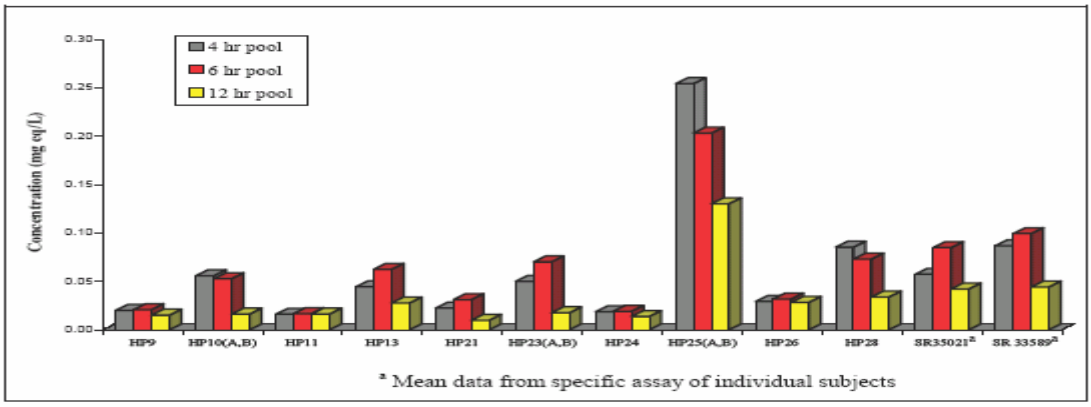
Table 38: Dronedarone metabolites in feces

HF1 (A,B)	HF2, 3	HF4	HF5	HF6	HF7	HF8	HF9	HF10 (A,B)	HF11
ND	ND	ND	ND	ND	0.7 (0.1)	1.0 (0.1)	ND	10.5 (0.5)	5.4 (1.1)
HF12	**HF13**	**HF14 (A,B)**	**HF15 (A,B)**	**HF16**	**HF17**	**HF18**	**HF19 (A,B)**	**HF20**	**HF21**
2.8 (0.4)	18.5 (1.1)	3.1 (0.8)	3.7 (0.9)	0.3 (0.1)	0.9 (0.1)	0.6 (0.1)	NQ	0.7 (0.1)	1.9 (0.5)
HF22	**HF23 (A,B)**	**HF24**	**HF25 (A,B)**	**HF26**	**HF27**	**HF28**	**Total**		
0.4 (0.1)	6.5 (2.1)	1.4 (0.5)	4.4 (0.7)	0.4 (0.2)	0.4 (0.05)	6.3 (2.3)	**70.2 (4.6)**		

[a] Expressed as a percent of fecal radioactivity (0 - 216 hours)
ND, Not detectable
NQ - Not quantifiable, but detected by LC-MS

The applicant notes that the numbering of metabolites in urine and feces is the same; for example, HU2 corresponds to HF2.

Figure 23: Mean plasma concentrations of dronedarone, SR35021 and metabolites at 4, 6 and 12 hours post dose



Applicant's safety summary
All subjects completed the study. There were no discontinuations for any reason. The most frequent adverse events were headache and increases in hepatic enzymes. The elevations of AST and GGT of up to 2.5 times the upper limit of the reference range, observed in three subjects, were considered clinically relevant by the investigator. Cardiac monitoring suggested no arrhythmogenic effects of dronedarone, and there were no significant findings in vital signs monitoring or in physical examinations.

Recommendations/Conclusions
The following information from Study BEX2770 is acceptable for labeling, as needed

- The total recovery of radioactivity was 90 % after oral administration. Approximately 6% and 84% of the administered oral dose of ^{14}C- dronedarone was excreted in urine and feces, respectively. In urine, unnamed metabolites HU11 (~ 11 %) and HU13 (~ 22 %) contributed the most to total radioactivity; whereas in feces, unnamed metabolites HF10 (11 %) and HF13 (19 %) contributed the most to total radioactivity. In plasma, SR35021 and SR95014 (existed as unresolved peak) contributed the most to total radioactivity. Generally all other individual metabolites contributed < 5 % to total radioactivity.
- The total recovery of radioactivity was ~ 83 % following IV administration; ~ 8% and 75% of the administered intravenous dose was excreted in urine and feces, respectively.
- Dronedarone was extensively metabolized to a variety of different metabolites that were excreted in urine and feces; dronedarone was only observed in low amount in feces and non-existent in urine.
- The metabolites formed in feces, urine and plasma were similar
- Major pathways of dronedarone metabolism included: 1) N-debutylation, followed by oxidation, 2) N- dealkylation to form the propanoic acid metabolite, followed by oxidation, and 3) direct oxidation of dronedarone. Mono- and multiple hydroxylated metabolites were also observed, along with metabolites containing a ketone moiety.

4.2.3 Pharmacokinetic profile of SR33589 and its metabolite SR35021 after single and repeated oral administration of 800 mg SR33589B in healthy young male and elderly male and female subjects (POP2769)

PROTOCOL #	POP2769
INVESTIGATOR	Dr. Wolfgang Tetzloff
STUDY SITE	IPHAR - Institut für Klinische Pharmakologie GmbH - Arnikastrasse 4 - D - 85635 Höhenkirchen-Siegertsbrunn - Germany
STUDY PERIOD	August 1997 to January 1998

Objectives (per applicant):

- Provide estimates of pharmacokinetic parameters of SR33589 (dronedarone), and its N-debutyl metabolite, SR35021, after single and repeated doses in healthy subject population subgroups (elderly males, elderly females and young males), and to test for a gender effect in elderly healthy subjects.
- To assess the tolerability of dronedarone in healthy elderly subjects in comparison to healthy young male subjects, after single and repeated doses in fed conditions.

Study Design

This was a double-blind, randomized and placebo-controlled study that enrolled elderly male, elderly female and young male subjects. On Day 1 each subject received an oral dose of dronedarone 800 mg or placebo. Following a two day wash-out period, a once daily dose of 800 mg dronedarone or placebo was given for 14 days from Day 4 to Day 17 inclusive, under fed conditions.

Subject Demographics

Subject demographics are summarized in Table 39.

Table 39: Subject Demographic Data (Study POP2769)

Age Group	Statistic	Placebo Group			SR33589B Group		
		Age (years)	Height (cm)	Weight (kg)	Age (years)	Height (cm)	Weight (kg)
Elderly female (n = 17)	n	4	4	4	13	13	13
	Mean	72	160	59	69	161	61
	SD	6.5	5	7.5	3.3	5.3	8.5
	Minimum	66	153	48.8	65	150	47
	Maximum	80	165	66.1	74	167	73.7
Elderly male (n = 19)	n	5	5	5	14	14	14
	Mean	70	176	79	69	175	76
	SD	5.1	5.0	7.0	3.3	6.5	9.3
	Minimum	65	169	71.6	65	163	60.7
	Maximum	77	182	89.8	74	186	94
Young male (n = 18)	n	5	5	5	13	13	13
	Mean	29	186	82	28	181	74
	SD	4.8	3.6	11.3	4.8	5.9	7.8
	Minimum	23	182	66.2	21	173	61.8
	Maximum	36	192	91	38	195	85.7

Formulation

- Dronedarone capsules: 200 mg strength, batch number 96-00365
- Placebo capsules: batch number 96-00247

Pharmacokinetic (PK) sampling times

PK blood samples were collected according to the following schedule:

- Study Day 1 and Day 17: blood samples were taken before drug administration and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours after drug administration.
- Predose blood samples were obtained on Days 7, 9, 11, 13, 15.

Pharmacokinetics

The following dronedarone and SR35021 pharmacokinetic measures were determined: Cmax, $AUC_{0\text{-}24h}$ AUC_{last} and AUC after single dose; Cmin after repeated dose; and accumulation ratio (Rac) after 14-day dosing. ANOVA was used to test for age, gender, and time effects on the PK measures.

Bioanalytical Assay

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as illustrated in Table 40.

Table 40: Performance of Dronedarone and SR35021 Assays (DOH0036)

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day Precision	CV were < 8 % for all quality control samples	Satisfactory
Accuracy	QC samples were between -7 and – 3 of the nominal concentrations	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity*	Chromatograms were not provided	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day Precision	CV were < 8 % for all quality control samples	Satisfactory
Between day Accuracy	QC samples were between -4 and -2 % of the nominal concentrations	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity*	Chromatograms were not provided	Cannot be assessed

* Chromatograms were not provided, however, assay validation report includes chromatograms that indicate assay is specific

Results

Dronedarone Pharmacokinetics

Dronedarone plasma concentration-time profiles in young males and elderly subjects following single (Day 1) and 14 days of repeated dose administration (Study Day 17) are depicted in Figure 24. SR35021 plasma concentration-time profile in young males and elderly volunteers following single (Day 1) and repeated administration (Day 17) are depicted in Figure 25.

The key comparisons for this study are as follows:

1. Elderly male vs. young male adults to evaluate the age effect (in males)
2. Elderly female vs. elderly males to evaluate the gender effect (in elderly subjects)

The absence of a young healthy female group does not allow one to determine if a gender effect occurs in young adults.

Figure 24: Mean dronedarone plasma concentration-time profile in elderly males and females and young males on Day 1 and Study Day 17 following 800 mg dronedarone once daily administration

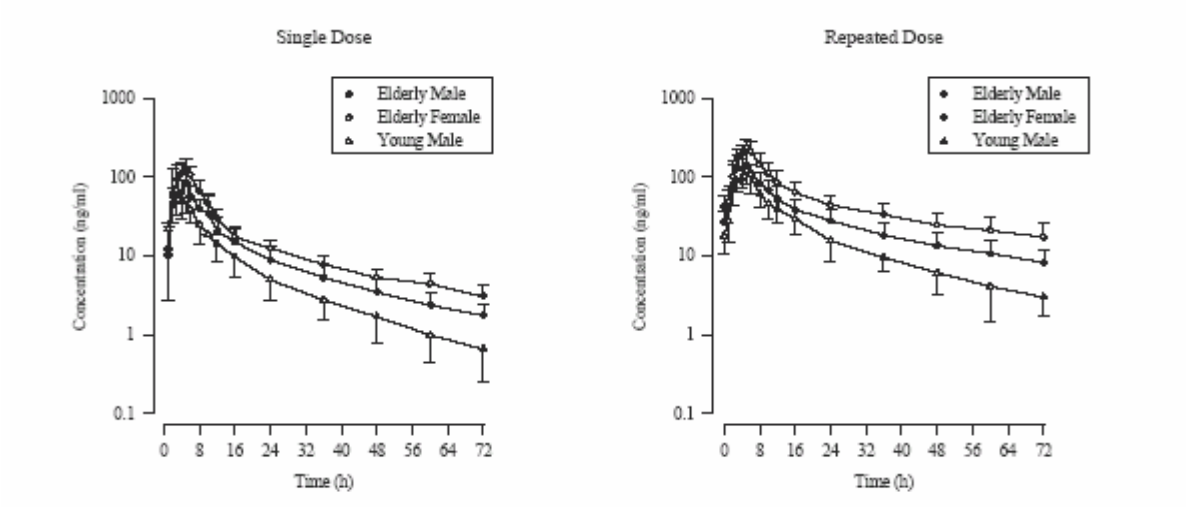
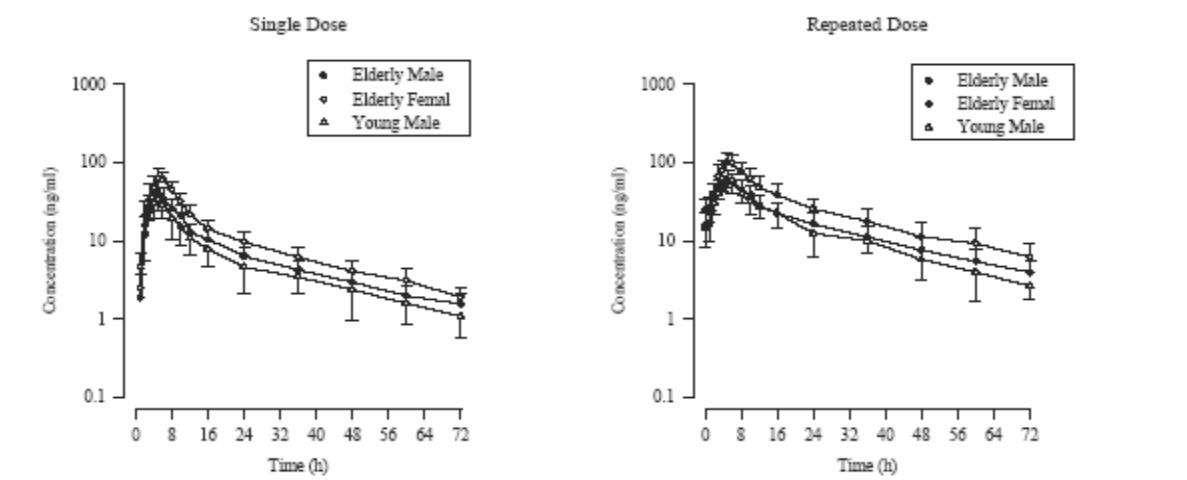


Figure 25: Mean SR35021 plasma concentration-time profile in elderly males and females and young males on Day 1 and Study Day 17 following 800 mg dronedarone once daily administration



Dronedarone PK measures in young males and elderly subjects are summarized in Table 15.

General PK Observations

- Tmax was comparable among the three study groups and was comparable on Day 1 (following single dose) and Study Day 17 (following 14 days of multiple dosing).
- Approximately 2.3-fold accumulation occurred on multiple dosing in all subject groups
- Half-life on Day 1 was shorter than on Day 17; additionally, elderly subjects had significantly longer half-life than younger subjects

Table 41: Dronedarone PK measures in healthy males and elderly adults and females following single and multiple dose administration (800 mg QD)

Parameter	Statistic	Young Male		Elderly Male		Elderly Female	
		Day 1	Day 17	Day 1	Day 17	Day 1	Day 17
C_{max} (ng/ml)	Mean	76	130	89	168	142	241
	SD	29	37	27	55	38	62
	CV%	38%	28%	30%	33%	27%	26%
t_{max} (h)	Mean	3.00	4.67	4.67	3.83	4.75	4.83
	SD	1.28	1.15	2.06	1.19	1.42	0.83
	CV%	43%	25%	44%	31%	30%	17%
AUC_{0-24h} (ng.h/ml)	Mean	511	1139	679	1520	1035	2393
	SD	171	318	228	508	303	702
	CV%	33%	28%	34%	33%	29%	29%
R_{ac}	Mean	N/A	2.35	N/A	2.31	N/A	2.35
	SD		0.66		0.72		0.46
	CV%		28%		31%		19%
C_{min} (ng/ml)	Mean	N/A	14.6	N/A	23.2	N/A	39
	SD		6.4		10.4		12.3
	CV%		44%		45%		32%
AUC_{last} (ng.h/ml)	Mean	609	N/A	874	N/A	1335	N/A
	SD	200		308		350	
	CV%	33%		35%		26%	
AUC (ng.h/ml)	Mean	628	N/A	936	N/A	1473	N/A
	SD	205		323		383	
	CV%	33%		35%		26%	
$t_{½}$ (h)	Mean	17.9	24.1	24.3	38.1	28.8	44.6
	SD	4.2	7.2	5.4	10.1	9.8	13.9
	CV%	23%	30%	22%	26%	34%	31%

N/A: Not applicable

Exposure comparisons (Cmax, Cmin and AUC) between elderly subjects and between elderly subjects and young males are summarized in Table 16 and Table 17.

Table 42: Comparison of Cmax and Cmin between elderly subjects and young male subjects

Parameter	Elderly Male vs. Young Male			Elderly Female vs. Elderly Male		
	Ratio	95 % CI	90 % CI	Ratio	95 % CI	90 % CI
C_{max}	1.23	[0.99 , 1.52]	[1.02 , 1.47]	1.54	[1.24 , 1.92]	[1.29 , 1.85]
C_{max} N	1.26	[0.98 , 1.63]	[1.02 , 1.56]	1.23	[0.95 , 1.58]	[0.99 , 1.51]
C_{min} (RD)	1.61	[1.13 , 2.28]	[1.20 , 2.15]	1.75	[1.23 , 2.47]	[1.31 , 2.33]

N: Normalized to 70 kg body weight
RD: Repeated Dose

Table 43: Comparison of AUC between elderly subjects and young male subjects

Parameter	Elderly Male vs. Young Male			Elderly Female vs. Elderly Male		
	Ratio	95% CI	90% CI	Ratio	95% CI	90% CI
AUC_{0-24h}	1.33	[1.04 , 1.69]	[1.08 , 1.62]	1.56	[1.22 , 1.99]	[1.28 , 1.91]
AUC_{0-24h}N	1.37	[1.05 , 1.79]	[1.09 , 1.71]	1.24	[0.95 , 1.62]	[0.99 , 1.55]
AUC_{last} (Day 1)	1.44	[1.10 , 1.88]	[1.16 , 1.80]	1.55	[1.18 , 2.02]	[1.24 , 1.93]
AUC (Day 1)	1.50	[1.15 , 1.95]	[1.20 , 1.87]	1.59	[1.22 , 2.08]	[1.28 , 1.99]

N: Normalized to 70 kg body weight
Day 1: Single Dose

Age and Gender Effect (Table 16 and Table 17)

1. Elderly Male vs. Young Male

- Based on the point estimate and associated 90 % confidence interval (CI), Cmax, weight normalized Cmax and Cmin are ~ 25 % higher in elderly males than young males
- The weight normalized data suggest that the difference in Cmax is not only due to weight differences between the two groups
- AUC data show a similar trend as observed with Cmax data

2. Elderly Female vs. Elderly Male

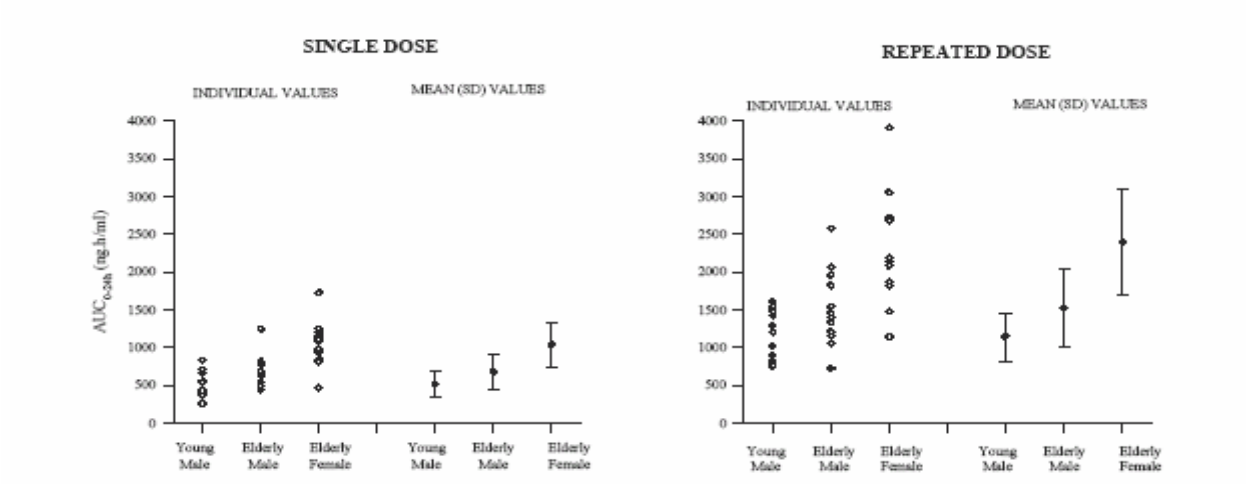
- Based on the point estimate and associated 90 % CI, Cmax and AUC of elderly females is ~ 50 % higher than elderly males.
- Weight normalization eliminates the statistical difference in exposure between the two groups; however, elderly females still tend to have higher (~ 25 %) numerical dronedarone exposure than elderly males

3. Elderly Female vs. Young Male

Assuming that the observed age (males) and gender (elderly subjects) are additive, female subjects will have exposures that are ≥ 50 % that of young males.

The individual and mean dronedarone PK measures following single and multiple dose administration in young males and elderly volunteers is shown in Figure 26.

Figure 26: Individual and Mean dronedarone AUC in young males and elderly volunteers following administration of 800 mg dronedarone



The preceding plots indicate that the female subjects exhibited the highest degree of inter-patient variability. Additionally, the figures and preceding table demonstrate that single dose PK differ from multiple dose PK; time dependent dronedarone PK have been observed in other PK studies and may be due to time-dependent metabolic processes.

The reason for the observed age and gender effects is unclear. Dronedarone is cleared primarily by metabolism, rather than by the renal pathway; thus, typical decline in renal function with age does not account for the differences.

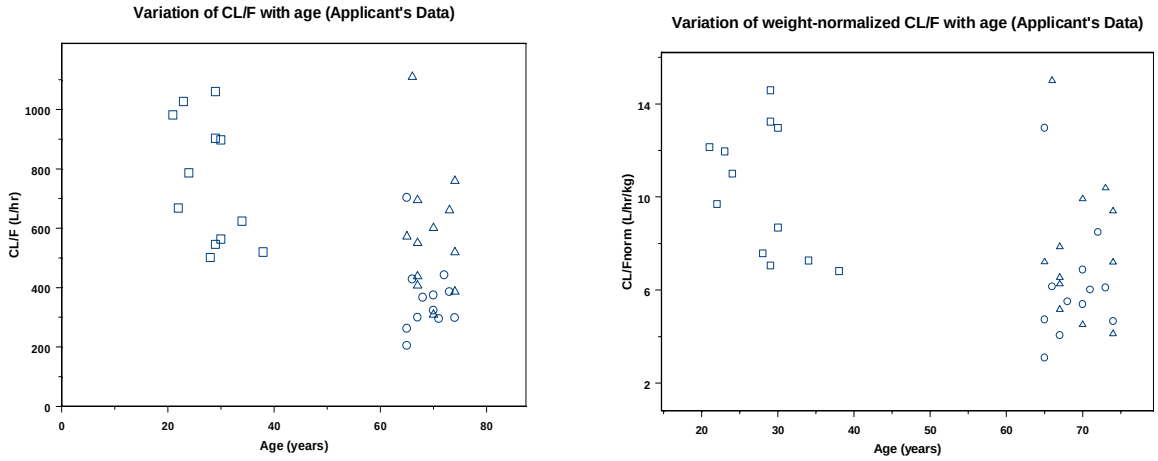
Reviewer Note: Clearance Data Generated to Facilitate Group Comparisons
This reviewer generated weight normalized and non-normalized apparent oral clearance (CL/F) data to facilitate group comparisons and evaluate the effect of weight on CL/F. All subjects received the same dose, thus the AUC values are reflective of CL/F since CL/F= Dose/AUC. CL/F data (Day 17) are summarized in Table 44.

Table 44: Mean steady state apparent oral clearance in young males and elderly subjects

	Young Males	Elderly Males	Elderly Females
	Applicant	Applicant	Applicant
CL/F (L/hr)	755 ± 210	586 ± 213	365 ± 127

Clearance Information (Reviewer Generated)
In the following plots (Figure 27) squares represent young adult males, triangle represent elderly males and oblong symbols represent elderly females.

Figure 27: Variation of non-normalized and body weight normalized clearance with age



The preceding plots demonstrate that:

- overall, the individual CL/Fs of young males are greater than that of elderly subjects, suggesting that an age effect exists
- the individual CL/Fs of elderly males and females overlap to a great extent, suggesting that the apparent gender effect in the elderly, may not be clinically significant

Reviewer's Note on Activity (Applicant's Findings)
The study report included limited information on dronedarone activity. According to the applicant, despite a significant difference in plasma concentration between strata, no obvious difference in PK/PD linear relationship was detected for QTc among population strata.

Applicant's Safety Summary
Single dose administration of dronedarone did not lead to study discontinuation. All adverse events were of either mild or moderate intensity, and the subjects recovered without sequelae. During the multiple dose phase, six (four on dronedarone and two on placebo) subjects were withdrawn from the study as a direct result of the adverse event. Some of the AEs were cardiac (e.g. asymptomatic non-sustained ventricular tachycardia, atrial fibrillation and sinus bradycardia

and accelerated idioventricular rhythm. However, occurrence of cardiac events occurred in an equal number of elderly females, elderly males, and young males following repeated doses.

Recommendations/Conclusion

The following findings from Study POP2769 are acceptable for labeling:

- Dronedarone PK are affected by age: elderly males have approximately 30 % higher dronedarone exposure than young males receiving 800 mg dronedarone after correcting for weight differences. The CL/F of elderly males is ~ 20 % lower than that of young males.
- Dronedarone PK are affected by gender: elderly females have approximately 23 % higher dronedarone exposure than elderly males receiving 800 mg dronedarone after correcting for weight differences. The CL/F of elderly females is ~ 40 % lower than that of elderly males.
- Potentially elderly female subjects may have dronedarone exposure that is ≥ 50 % of that in young male subjects
- From this study it is unclear if the gender effect will exist for young subjects because young female subjects were not included in this study.

Due to nonlinear PK, the quantitative values obtained in this study (800 mg) may differ from that at the proposed clinical dose (400 mg); however, the results can be expected to be qualitatively similar at both doses.

Labeling Comments

The gender differences (elderly female vs. elderly male) observed in this study do not appear to warrant dosing adjustments, as the difference in exposure is relatively small (~ 25 %) and statistically insignificant after correcting for body weight. The highest potential difference occurs between healthy males and elderly females, however, the maximal difference is approximately 50 %, which does not appear to warrant dose adjustments based on the limited dronedarone exposure-response information.

In sum, neither age nor gender differences will require dosage adjustment.

4.2.4 Effect of fat content on the bioavailability of an oral administration of two 400 mg tablets of SR33589B containing 10% pluronic F12 (ALI3180).

PROTOCOL #	ALI3180
INVESTIGATOR	Dr. Wolfgang Tetzloff
STUDY SITE	iphar, Institut für Klinische Pharmakologie GmbH, Arnikastrasse 4, 85635 Höhenkirchen- Siegertsbrunn, Germany.
STUDY PERIOD	April 1997 to June 1997

Objectives (per applicant):

- To assess the effect of fat content of a morning meal on the bioavailability of two 400 mg tablets of SR33589B containing 10% pluronic F127, compared to results obtained when the tablets were given under fasted conditions.
- To assess clinical and biological tolerability.

Study Design

This was an open-label, non-placebo controlled, single-group, cross-over study. Each subject received three different treatments. Dronedarone was given under each of the following treatment conditions: fasted, immediately after a low fat meal, and immediately after a fat-rich meal. There was a wash-out period of at least seven days between treatments. The meal compositions are in the Appendix. The high fat meal was acceptable as it is consistent with the FDA-recommended high-fat meal composition.

Subject Demographics

Subject demographics are presented in Table 45.

Table 45: Subject Demographic Data

Characteristics	Parameters	Values
Age (years)	Mean	31.1
	SD	6.5
	Minimum	24.0
	Maximum	39.0
Height (cm)	Mean	181.9
	SD	3.6
	Minimum	177.0
	Maximum	188.0
Weight (kg)	Mean	77.5
	SD	6.7
	Minimum	68.5
	Maximum	88.5

n = 9

Pharmacokinetic sampling times

PK samples for assays of dronedarone and its metabolite SR35021 were collected at 0h (before administration), 1h, 2h, 3h, 4h, 5h, 6h, 8h, 10h, 12h, 16h, 24h, 36h, and 48h after each drug administration.

Formulation

Dronedarone 400 mg tablets containing 10% pluronic F127, batch No. D005680/96-00494.

Bioanalytical methods

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as illustrated in Table 27.

Table 46: Performance of Dronedarone and SR35021 Assays (DOH0036)

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.991$	Satisfactory
Between day Precision	CV was < 8.0 %	Satisfactory
Accuracy	QC samples were between +0.6 and -2.2 of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.991$	Satisfactory
Between day Precision	CV was < 6.0 %	Satisfactory
Accuracy	QC samples were between +0.7 and -0.4 of nominal concentration	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

*The validation report for the assay included chromatograms that suggest the assay was specific

Pharmacokinetics

The following dronedarone pharmacokinetic measures were determined after each treatment: Cmax, tmax, and AUClast.

Statistical methods

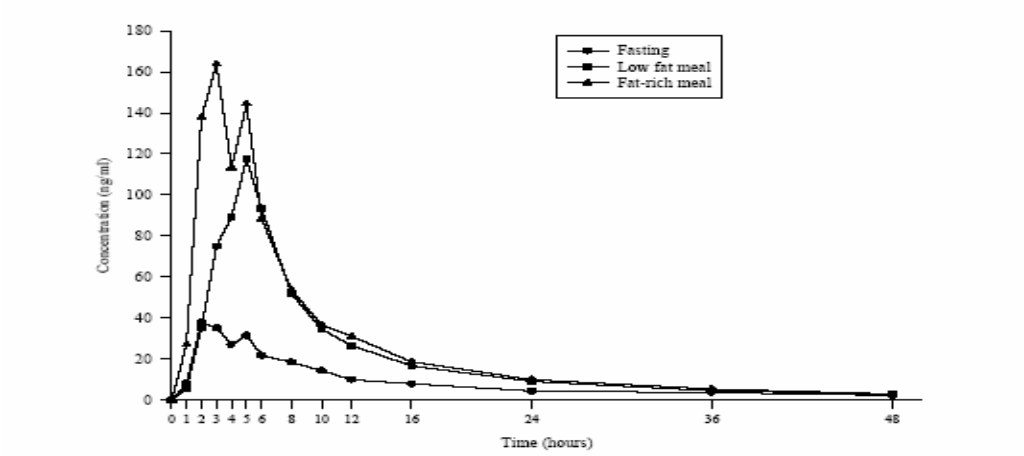
Standard pharmaco-statistical methods were used to evaluate the food effect. The fasted treatment was the reference treatment and test treatments were the high fat and low fat meals.

Results

Dronedarone Pharmacokinetics

The mean dronedarone plasma concentration-time profiles in the fasted and fed conditions (low fat and high fat meals) are shown in Figure 28.

Figure 28: Mean dronedarone plasma concentration-time profile under fasted and fed conditions



Dronedarone PK measures under the three treatment conditions are presented in Table 47.

Table 47: Dronedarone PK measures in healthy males following single dose administration under fasted and fed conditions

Parameters (units)	Statistics	Administration		
		Fasted	Low fat meal	Fat-rich meal
C_{max} (ng/ml)	Mean	42.92	128.29	192.40
	Median	40.00	120.80	173.40
	SD	21.50	50.26	90.88
	CV%	50	39	47
t_{max} (h)	Mean	3.67	4.67	3.89
	Median	5.00	5.00	5.00
	SD	1.58	1.00	1.36
	CV%	43	21	35
AUC_{last} (ng.h/ml)	Mean	416.35	975.61	1274.37
	Median	416.00	964.59	1179.63
	SD	106.59	252.08	329.89
	CV%	26	26	26

n = 9

Geometric mean ratios and associated 95% CI of the main dronedarone PK measures are presented in Table 11.

Table 48: Dronedarone geometric mean ratios and associated 90 % confidence intervals* under fed and fasted conditions

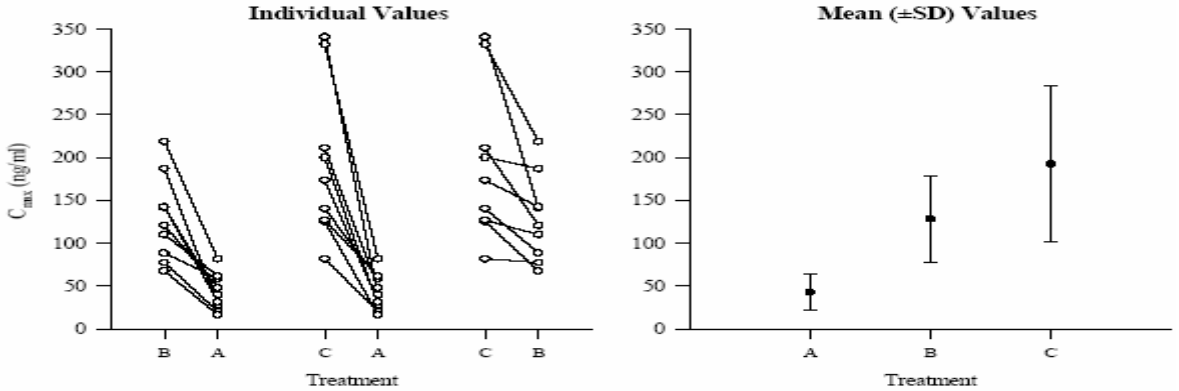
Parameters (units)	Low fat meal / fasted	Fat-rich meal / fasted	Fat-rich meal / low fat meal
C_{max} (ng/ml)	3.15 [2.28 - 4.36]	4.59 [3.32 - 6.35]	1.46 [1.05 - 2.01]
AUC_{last} (ng.h/ml)	2.34 [1.99 - 2.75]	3.06 [2.60 - 3.61]	1.31 [1.11 - 1.54]

n = 9

* Typically, 90 % confidence intervals are preferred over 95 % confidence intervals for regulatory evaluations.

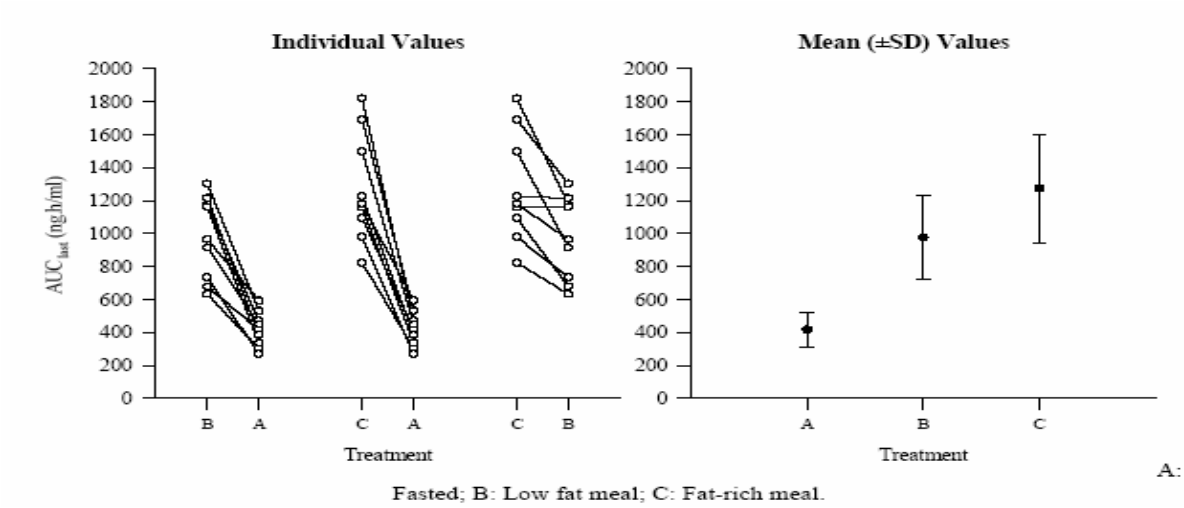
The data in Table 11 demonstrate that food increases dronedarone BA relative to the fasted state; additionally, increasing fat content increases bioavailability. It is noted that two subjects had far greater food effects than the other subjects (Figure 29 and Figure 30). The reason for this finding is unclear; without these two subjects the difference in food effect between the high fat meal and low fat meal may not have reached statistical significance and the food effect data would be less variable.

Figure 29: Individual and mean Cmax values under fasted and fed conditions



Fasted; B: Low fat meal; C: Fat-rich meal.

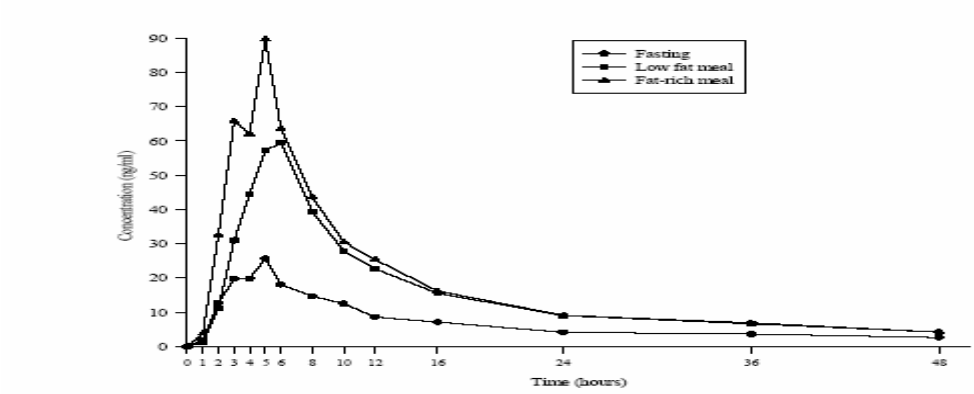
Figure 30: Individual and mean AUC values under fasted and fed conditions



SR35021 Pharmacokinetics

The mean SR35021 plasma concentration time profile under fasted and fed conditions is depicted in Figure 31.

Figure 31: Mean SR35021 plasma concentration-time profile under fed and fasted conditions



SR35021 PK measures in the study are shown in Table 49.

Table 49: SR30521 PK measures in healthy males following single dose administration of dronedarone under fasted and fed conditions

Parameters (units)	Statistics	Administration		
		Fasted	Low fat meal	Fat-rich meal
C_{max} (ng/ml)	Mean	26.43	62.99	98.71
	Median	27.30	69.40	81.60
	SD	9.49	17.33	39.74
	CV%	36	28	40
t_{max} (h)	Mean	4.56	5.56	4.56
	Median	5.00	6.00	5.00
	SD	0.88	0.53	0.88
	CV%	19	9	19
AUC_{last} (ng.h/ml)	Mean	329.44	724.34	868.94
	Median	344.95	732.69	811.80
	SD	83.87	170.65	221.37
	CV%	25	24	25

n = 9

Geometric mean ratios and associated 95% CI of the main dronedarone PK measures are presented in Table 50.

Table 50: SR30621 Geometric mean ratios and associated confidence intervals under fasted and fed conditions

Parameters (units)	Low fat meal / fasted	Fat-rich meal / fasted	Fat-rich meal / low fat meal
C_{max} (ng/ml)	2.44 [1.96 - 3.05]	3.70 [2.97 - 4.62]	1.51 [1.21 - 1.89]
AUC_{last} (ng.h/ml)	2.22 [2.00 - 2.45]	2.65 [2.39 - 2.93]	1.20 [1.08 - 1.32]

n = 9

The SR35021 PK data indicate that food increases SR35021 bioavailability to a similar degree as observed with dronedarone.

Applicant's Safety Summary

Three subjects reported adverse events:

- Subject A had a serious adverse event (calcaneus fracture), due to an accident, not related to the study drug
- Subject B had a short lasting episode of diarrhea
- Subject C had two short lasting episodes of non-sustained asymptomatic ventricular tachycardia.

The serious adverse event required hospitalization and conservative therapy whereas the other events resolved spontaneously.

Laboratory tests, vital signs, electrocardiograms, and telemetric evaluations showed no clinically relevant changes from baseline.

Recommendations/Conclusions

The following PK information generated in Study ALI3180 is acceptable for labeling purposes, as appropriate.

1. Food (low fat meal and high fat meal) increases dronedarone bioavailability on average by approximately 4-fold (3.15 to 4.59) at the 800 mg dronedarone dose level.
2. The high fat meal had only a slightly greater effect on bioavailability (~ 40 % increase) than the low fat meal, suggesting that dronedarone may be administered with low or high fat meals.
3. Food did not significantly prolong drug absorption; the median Tmax was 5 hr under fasted and fed conditions.

APPENDIX to Study ALI3180

Composition of Meals

Standard rich fat meal.

Food item	Calories	Fat (g)	Carbohydrates (g)	Protein (g)
2 eggs (scrambled)	203	16.2	1.2	12.2
2 slices white bread toasted	128	1.8	23.4	4.2
1 teaspoonful butter	36	4.1	Trace	0.0
1 tablepoonful jelly	55	Trace	14.1	Trace
2 strips of bacon	70	6.2	0.2	3.2
4 oz hash brown potatoes	72	0.1	16.4	1.8
8 oz of whole milk	157	8.9	11.4	8.0
TOTAL		**37.3**	**66.7**	**29.4**
TOTAL CALORIES	**718,10**	**335,70**	**266,80**	**117,60**

Standard low fat meal.

Food item	Protein [g]	Fat [g]	Carbohydrate [g]	
120 g yoghurt (0.3%)	5.28	0.12	5.04	
2 rolls (100g)	7.6	1.2	47.8	
40 g honey	0.1	-	30.04	
25 g jam	0.15	-	16.5	
5 g margarine	0.2 g	4 g	-	
2 cups decaffeinated coffee				
TOTAL	**13.33**	**5.32 (4.5%)**	**99.38**	
TOTAL CALORIES	**54.65**	**49.48 (9.7%)**	**407.49**	**∑511.62**

4.2.5 Relative bioavailability between the dronedarone tablets used in phase II studies and those prepared for phase III studies after single oral administration to young healthy subjects (BDR4680)

PROTOCOL #	BDR4680
INVESTIGATOR	Emmanuel Krupka, M.D.
STUDY SITE	LARIME, Z.A. des Greffières, Rue Auguste Perret, 17140 Lagord, France
STUDY PERIOD	July to August 2001

Objectives (per applicant):

- to evaluate, after single oral administration, in fasted conditions, the relative bioavailability between the oval shaped phase III tablets (Formulation A) and the round shaped phase II tablets (Formulation B)
- to assess the safety of the treatment with dronedarone

Study Design

This was an open-label, two-period, randomized study in healthy subjects. There were two different treatment groups, corresponding to the two dronedarone tablets; each tablet was given with labeled* dronedarone capsules. Subjects received a single 800 mg dose: dronedarone 400 mg via tablet + dronedarone 400 mg via capsules. Treatments were given in the fasted condition and there was a 7-day washout period between treatments.

*** Rationale for use of labeled dronedarone**

An internal marker, ^{13}C-labeled dronedarone, was co-administered as a capsule with each of the tablets; this co-administration provides lower within-subject variability by using adjusted pharmacokinetic (PK) parameters based on the ratio of ^{12}C/^{13}C, i.e., unlabeled versus labeled dronedarone.

Subject Demographics

Subject demographics are presented in Table 51.

Formulation

- Test product: 400 mg ^{12}C-dronedarone Phase III tablet (2E3 formulation); batch number: CL- 03936
- Internal marker: 100 mg ^{13}C- dronedarone capsules; batch number: CL- 04269
- Reference product: 200 mg ^{12}C-dronedarone Phase II tablet (2E2 formulation); batch number: 99- 02753

Pharmacokinetic Sampling

PK blood samples were collected before dosing and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours after dronedarone administration.

Pharmacokinetic Measures

The following PK measures were estimated

- dronedarone and SR35021: Cmax , tmax , AUClast , AUC, $t_{1/2}z$
- ^{13}C- dronedarone and ^{13}C- SR35021: Cmax, tmax , AUClast, AUC, $t_{1/2}z$
- dronedarone ^{12}C/^{13}C and SR35021 ^{12}C/^{13}C ratios: Cmax , AUC last and AUC

Table 51: Subject Demographic Data

Parameter (unit)	Statistics/ Category	Total (N=12)
Age (yrs)	N Mean SD Min Max	12 27.4 5.1 19 34
Weight (kg)	N Mean SD Min Max	12 72.02 6.20 61.4 80.4
Height (cm)	N Mean SD Min Max	12 176.9 6.8 163 186
Body mass index (kg/m2)	N Mean SD Min Max	12 22.9 1.9 19 26
Gender	Male Female	12 (100% 0 (0%)
Race	Caucasian Black Asian Other	12 (100%) 0 (0%) 0 (0%) 0 (0%)

Bioanalytical Method

The concentrations of dronedarone, SR35021 and their ^{13}C isotopes were determined using a validated Electrospray Liquid LC/MS method (DOH0238). The assay performance was acceptable as shown in Table 52 and
Table 53.

Table 52: ^{12}C Dronedarone and SR35021 Assay Performance

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day Precision	CV data were not provided	Cannot be assessed
Accuracy	Relative bias data were not provided. The concentrations of QC samples were within 15 % of nominal concentration	Acceptable
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.996$	Satisfactory
Between day Precision	CV data were not provided	Satisfactory
Accuracy	Relative bias data were not provided. The concentrations of QC samples were within 15 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* assay validation report includes chromatograms that demonstrate assay specificity

Table 53: Dronedarone and SR35021 Assay Performance

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.995$	Satisfactory
Between day Precision	CV data were not provided	Satisfactory
Accuracy	Relative bias data were not provided. The concentrations of QC samples were within 15 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.998$	Satisfactory
Between day Precision	CV data were not provided	Satisfactory
Accuracy	Relative bias data were not provided. The concentrations of QC samples were within 15 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* assay validation report includes chromatograms that demonstrate assay specificity

Statistical methods

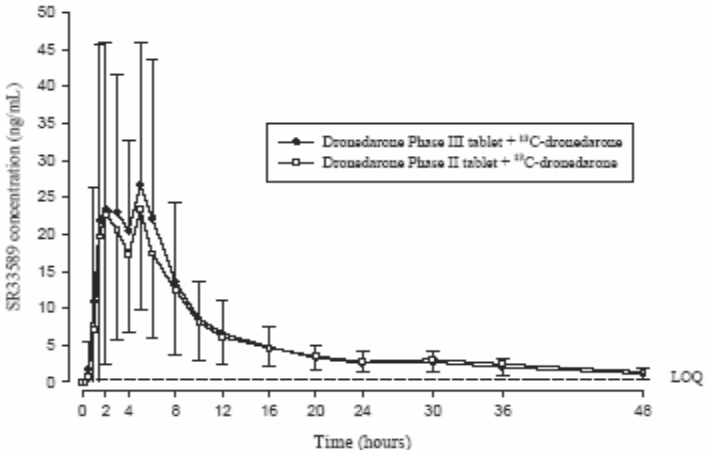
Standard pharmaco-statistical methods were used to determine the relative bioavailability of the 2E3 tablet formulation (test) to the 2E2 formulation (reference).

Results

Dronedarone Pharmacokinetics

The mean plasma concentration-time profiles of dronedarone obtained after administration of each formulation are presented in Figure 32.

Figure 32: Mean dronedarone plasma concentration-time profiles following administration of 2E3 and 2E2 dronedarone formulations



Dronedarone PK measures are presented Table 54. Geometric mean ratios and associated 90 % CI of the main dronedarone PK measures are presented in Table 55.

Table 54: Dronedarone PK measures (based on dronedarone) in healthy males following single dose administration under fasted conditions

Mean (CV%) Parameters	Phase III tablet +^{13}C-dronedarone	Phase II tablet +^{13}C-dronedarone	Ratio [90% CI] or p value	Within-subject SD[a]
C_{max} (ng/mL)	40.0 (66)	32.0 (59)	1.22 [0.95 – 1.56]	0.34
t_{max} (h)[b]	3 [1.5 – 6]	2 [1.5 – 5]	p = 0.899	-
AUC_{last} (ng.h/mL)	287 (58)	273 (53)	1.02 [0.85 – 1.22]	0.24
$t_{1/2}$ (h)	19.2 (48)	16.0 (29)	p = 0.370	-
AUC (ng.h/mL)	324 (58)[c]	307 (55)	1.09 [0.95 – 1.26][c]	0.18

Phase III (1x400mg tablet) + ^{13}C-dronedarone (4x100mg capsules): treatment A
Phase II (2x200mg tablets) + ^{13}C-dronedarone (4x100mg capsules): treatment B
a: for log-transformed parameters, b: median values [min – max], c: n=11

Table 55: Dronedarone geometric mean ratios (based on ^{12}C/^{13}C ratio) and associated 90 % confidence intervals under fasted conditions

Mean (CV%) ^{12}C/^{13}C Ratio	Phase III tablet +^{13}C-dronedarone	Phase II tablet +^{13}C-dronedarone	Ratio [90% CI]	Within-subject SD
C_{max} (ng/mL)	0.77 (37)	0.69 (29)	1.09 [0.95 – 1.26]	0.19
AUC_{last} (ng.h/mL)	0.78 (17)	0.82 (8)	0.94 [0.88 – 1.00]	0.08
AUC (ng.h/mL)	0.82 (15)[a]	0.85 (8)	0.95 [0.88 – 1.02][a]	0.09

Phase III (1x400mg tablet) + ^{13}C-dronedarone (4x100mg capsules): treatment A
Phase II (2x200mg tablets) + ^{13}C-dronedarone (4x100mg capsules): treatment B a: n=11

The PK data indicate the following:

- there is greater within subject variability using dronedarone alone, vs. the ratio of labeled dronedarone
- there is no significant difference in exposure between treatments (CIs include 1) using either analysis method

Overall, the two formulations have similar bioavailability in terms of dronedarone exposure.

Reviewer Note on SR35021

The applicant provided SR35021 PK information, but the data are not included in this review as they do not impact the BE evaluation.

Applicant's Safety Summary

No serious AEs (SAEs), deaths, or discontinuations occurred during this study. There was one treatment emergent AE reported, asthenia (system organ class: body as a whole). Other AEs of note included:

- orthostatic change in heart rate
- five subjects had a QTc-interval change (changes ranged from 30 to 38 ms) but the changes were isolated, and in all cases values stabilized on subsequent measurements. No QTc > 450 ms were reported.

Recommendations/Conclusions

The following PK information generated in Study BDR4680 is acceptable, as appropriate:

- The Phase 2 (2E2) and Phase 3 (2E3) tablets have similar bioavailability
- The use on an internal marker ^{13}C-dronedarone decreases dronedarone inter-subject PK variability

4.2.6 Assessment of food effect on pharmacokinetic parameters of a single dose (800 mg) of SR33589B and assessment of absolute bioavailability (PPK2397)

PROTOCOL #	PPK2397
INVESTIGATOR	J.M Kroodsma
STUDY SITE	U-Gene Research, Bolognalaan 40, 3584 CJ Utrecht, The Netherlands
STUDY PERIOD	June – August, 1995

Objectives (per applicant)

- To assess the influence of food intake on oral absorption of dronedarone (SR33589B)
- To assess the bioavailability of the compound and, the overall tolerability and pharmacodynamic effects of dronedarone

Reviewer's Note

Study PPK2397 does not contribute relevant biopharmaceutical information to the NDA with respect to the to-be-marketed (TBM) tablet. However, the study is being reviewed for its qualitative value as related to estimation of absolute bioavailability (BA).

Study Design

A randomized, open label and three treatment period study design was adopted. Healthy male subjects received dronedarone under the following conditions:

- 800 mg orally under fed conditions
- 800 mg orally under fasted conditions
- 60 mg IV infusion under fasted conditions

Subject Demographics

Subject demographics are presented in Table 56.

Table 56: Subject Demographic Data (Study PPK2397)

Characteristic	Parameter	Fasted → Fed → i.v. (n = 6)	Fed → Fasted → i.v. (n = 6)
Age (years)	Mean	25.0	27.3
	SD	3.4	6.5
	Minimum	21.0	20.0
	Maximum	30.0	39.0
Weight (kg)	Mean	75.3	73.7
	SD	5.4	7.3
	Minimum	68.4	65.6
	Maximum	80.8	83.2
Height (cm)	Mean	186.2	183.3
	SD	4.6	6.1
	Minimum	179.0	179.0
	Maximum	193.0	195.0

Reviewer Note on Subjects

All 12 subjects completed the study. The CYP2D6 status of subjects was recorded: three of the 12 subjects (# 4, 5, and 8) were poor metabolizers.

Formulation

- 100 mg dronedarone capsules, batch number L062J
- 1 mg/mL solution (ampoules), batch number L184T

Pharmacokinetic sampling times

Extensive blood sampling was conducted during (IV infusion) and following administration of dronedarone (oral and IV). Blood samples were collected from predose (10 minutes before dose) and up to 72 hours post dosing. Blood sampling times are reported in this study's Appendix.

Bioanalytical methods

Dronedarone and SR35021 concentrations were determined using a validated HPLC-UV method. The assay performance was acceptable as illustrated in Table 57.

Table 57: Performance of Dronedarone and SR35021 Assays (DOH0020)

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 5 to 1000 ng/mL range; $R^2 > 0.999$	Satisfactory
Between day Precision	CV for QC samples were < 10 %	Satisfactory
Accuracy	QC samples were between -5 % and +1 % of the nominal concentrations	Satisfactory
LLOQ	3 ng/ml	Satisfactory
Specificity	Chromatogram was provided	Satisfactory
	SR35021 Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.999$	Satisfactory
Between day Precision	CV for QC samples were < 8.0 %	Satisfactory
Between day Accuracy	QC samples were between -4 % and +4 % of the nominal concentrations	Satisfactory
LLOQ	2 ng/mL	Satisfactory
Specificity	Chromatogram was provided	Satisfactory

Pharmacokinetics

The following pharmacokinetic (PK) measures were determined for dronedarone and SR35021:

- Oral administration- Cmax, tmax, AUC_{0-t}, AUC, $t_{1/2}$, and F
- IV administration, Cmax, AUC_{0-t}, AUC, $t_{1/2}$, CL_T and Vd

The food effect was assessed using standard pharmaco-statistical analyses, where the fasted treatment served as reference and fed treatment as the test. Absolute BA was assessed for the fasted and fed states.

Pharmacodynamics

The following electrocardiogram (ECG) interval changes were assessed: HR PR, QRs and QT.

Reviewer Note

The ECG data were not reviewed in detail because they do not impact the absolute BA findings.

Results

Dronedarone Pharmacokinetics

The dronedarone plasma concentration-time profile following IV infusion and oral administration of dronedarone are depicted in Figure 33 and Figure 34, respectively.

Figure 33: Mean dronedarone plasma concentration-time profile following 60 mg IV dronedarone given by 60-minute infusion

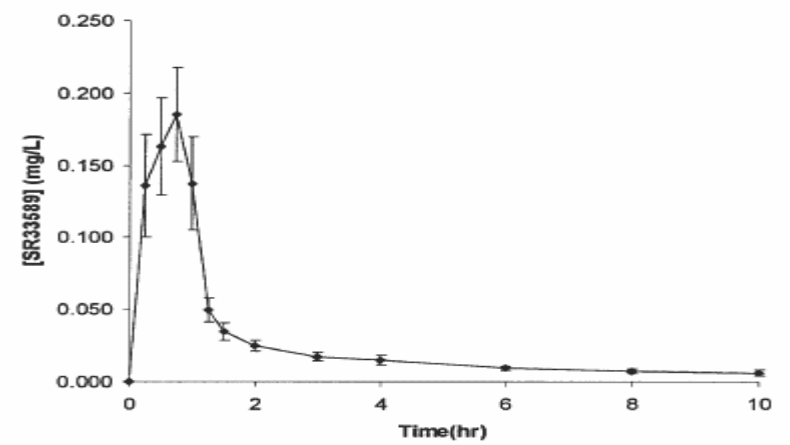
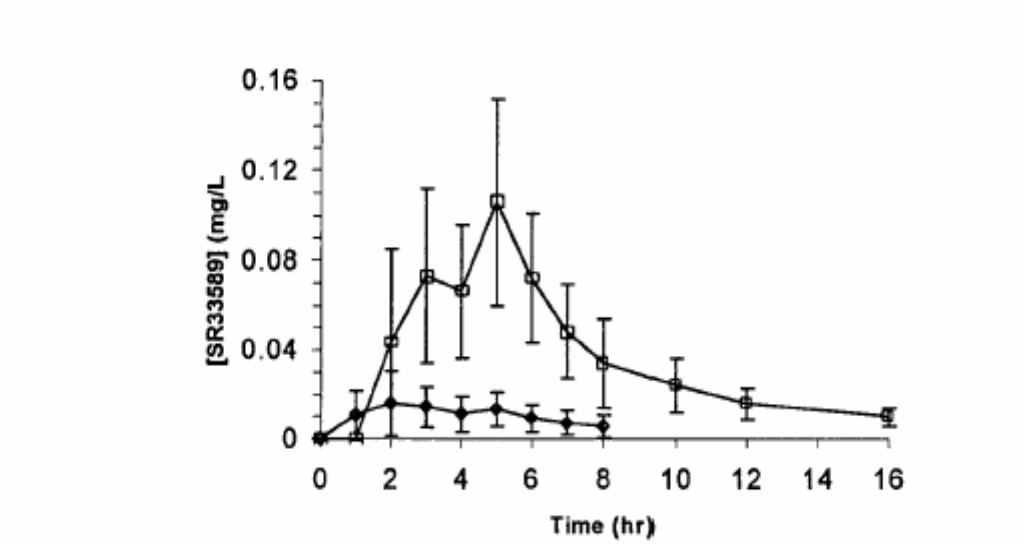


Figure 34: Mean dronedarone plasma concentration-time profile following oral administration of 800 mg dronedarone under fed (squares) or fasted (box) conditions



The mean dronedarone PK measures obtained after oral and IV administration are presented in Table 58.

IV Pharmacokinetics

After Cmax was achieved, dronedarone was rapidly cleared from the blood and widely distributed (Vz > 1500 L) following IV administration. Plasma concentration-time data exhibited high inter-patient variability during and at the end of the infusion; the reason for this finding is unclear. It should be noted that metabolite could not be detected following IV administration, suggesting that the metabolite is primarily formed during first pass or presystemic metabolism.

Table 58: Dronedarone PK Measures following 60 mg dronedarone IV infusion and 800 mg dronedarone oral (fed and fasted)

Parameter (units)	Intravenous Fasted	Oral Fasted	Oral Fed	90% CI (Oral Fed / Oral Fasted)	p-value
C_{max} (mg/l)	0.189 (0.034)	0.020 (0.012)	0.120 (0.043)	442 - 900	0.0001
t_{max} (h)	0.67 (0.12)	2.7 (1.3)	4.3 (1.1)	NPT	0.001
AUC_{0-t} (mg/l*h)	0.288 (0.051)	0.108 (0.097)	0.644 (0.282)	481-1169	0.0001
AUC (mg/l*h)	0.350 (0.054)	0.219 (0.209)†	0.721 (0.327)‡	----------	----------
$t_{½}$ (h)	7.5 (3.4)	9.3 (9.5)†	8.9 (6.1)	NPT	0.31
$Vd\lambda_z$ (l)	1837 (713)	----------	----------	----------	----------
Cl_t (l/h)	176 (34)	----------	----------	----------	----------
F (%)	----------	4 (4)†	15 (6)‡	----------	----------

†n=6, ‡n=11

NPT - non-parametric test

Oral Pharmacokinetics (Fed vs. Fasted)

Overall, food increased the exposure of dronedarone relative to the fasted state. There was an approximately 6-fold increase in mean AUC_{0-t} and Cmax in the fed state; additionally food increased Tmax by ≥ 1 hr. Data obtained in the fasted state were highly variable (CV > 50 % for all PK measures).

Absolute Bioavailability

Dronedarone exhibited relatively low absolute bioavailability (BA): 4 % in the fasted state and 15 % in the fed state. The reliability of the absolute BA estimate in the fasted state is unclear because the extrapolated fraction of the total AUC exceeded 40 % for some subjects. Typically, BA evaluations are conducted in the fasted state to minimize the effect of extrinsic factors, such as food, on formulation performance. For dronedarone, a BA assessment in the fed state appears reasonable because food appears to decrease variability relative to the fasted state and may yield more readily interpretable results. However, because the dronedarone food effect is formulation dependent the applicability of these BA results (with capsule) in the fed state to the TBM tablet formulation is unclear. It should also be noted that dronedarone was administered at a supra-therapeutic dose, 800 mg, in this study. Dronedarone exhibits nonlinear kinetics that affect the extent of absorption, therefore the absolute BA findings will be dose dependent. Due to the stated differential food effect (tablet vs. capsule) and dose dependent extent of absorption (therapeutic dose = 400 mg vs. study dose = 800 mg) the quantitative absolute BA information obtained with the capsule at the 800 mg dose should not be extrapolated to the TBM tablets that will be administered at 400 mg. In sum, the absolute BA information is not acceptable for labeling.

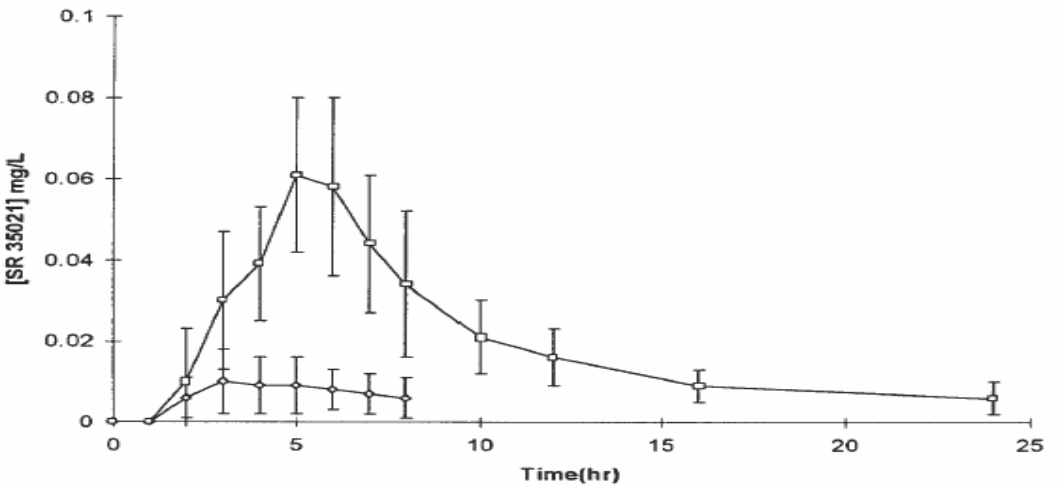
Reviewer Comment on Assay Sensitivity (impact on half-life estimation)

The reported LOQ in this study was ~ 5 ng/mL; this value exceeds that for the LC/MS/MS assays that were developed later on in the dronedarone program. The limited sensitivity of the assay used in the current study may have impacted the PK estimates; for example, the half-life reported in this study was < 10 hours whereas in later studies the half-life was > 20 hours. It is noted that the half-life could not be determined for six of the 12 subjects in the fasted state and one subject in the fed state.

SR35021 Pharmacokinetics

The mean SR35021 plasma concentration-time profiles in the fed and fasted state are depicted in Figure 35.

Figure 35: Mean SR35021 plasma concentration-time profile following oral administration of 800 mg dronedarone under fed (square) and fasted (diamond) conditions.



As noted previously, SR35021 levels were not measurable following IV administration. Following oral administration SR35021 was detectable in most patients, however; two subjects had concentrations equal to LOQ within 4 hours after drug administration.

The mean SR35021 PK measures are summarized in Table 59.

Table 59: SR35021 PK Measures in Healthy Males following 800 mg dose

Parameter (units)	Oral Fasted	Oral Fed	90% CI (Oral Fed / Oral Fasted)	p-value
C_{max} (mg/l)	0.016 (0.005)	0.065 (0.019)	293 - 761	0.0001
t_{max} (h)	4.1 (1.1)	5.8 (1.1)	NPT	0.016
AUC_{0-t} (mg/l*h)	0.082 (0.047)	0.497 (0.192)	459 - 994	0.0001
AUC (mg/l*h)	† NC	0.638 (0.327)‡	----------	---------
$t_{½}$ (h)	† NC	14.1 (8.8)‡	NP	NP

†n=2, ‡n=8
NPT - non-parametric test
NC - not calculated
NP - not performed (sample size too small)

Dronedarone Pharmacodynamics (PD)

Dronedarone PD data are summarized in Table 60 and Table 61. The PD data were not reviewed in detail because they do not impact the absolute BA information. In brief there were statistically significant differences in HR, PR and QT between the fed and fasted conditions; the differences were mainly observed at 2 hrs post dose. However, there was no clear trend, in that fed conditions did not consistently have a greater change in ECG measures than fasted conditions. Assuming similar baseline ECG values prior to dronedarone administration, the difference between fed and fasted conditions do not appear clinically significant (differences < 10 %).

Table 60: Dronedarone PD after oral administration under and fed and fasted conditions

Parameter (units)	Time (hours)	Fasted†	Fed†	Treatment p-value‡
HR (bpm)	2	55	64	0.007
	4	55	59	ns
	8	62	59	ns
	24	58	57	ns
PR (ms)	2	169	161	0.005
	4	167	172	ns
	8	158	174	0.001
	24	165	166	ns
QRS (ms)	2	93	92	ns
	4	93	93	ns
	8	92	92	ns
	24	93	92	ns
QT (ms)	2	394	369	<0.001
	4	395	378	0.015
	8	384	383	ns
	24	389	392	ns
QTc (ms)	2	375	378	ns
	4	375	373	ns
	8	386	380	ns
	24	378	379	ns

† Adjusted mean value

Table 61: Dronedarone PD after oral administration (fasted conditions) and IV administration

Parameter (units)	Time (hours)	Oral†	Intravenous†	Treatment p-value‡
HR (bpm)	2	55	55	ns
	4	55	53	ns
	8	61	58	ns
	24	58	57	ns
PR (ms)	2	169	179	0.001
	4	167	169	ns
	8	159	159	ns
	24	165	165	ns
QRS (ms)	2	93	93	ns
	4	93	92	ns
	8	92	91	ns
	24	92	90	ns
QT (ms)	2	398	390	ns
	4	398	397	ns
	8	383	390	ns
	24	390	386	ns
QTc (ms)	2	376	373	ns
	4	377	374	ns
	8	386	383	ns
	24	379	375	ns

† Adjusted mean value

Applicant's Safety Summary

Generally oral and IV dronedarone were well tolerated. However, local tolerability following IV administration was poor, leading to a serious adverse event in one patient.

Recommendations/Conclusions

Overall this reviewer does not recommend including results from Study PPK2397 in product labeling because:

- Absolute bioavailability information was obtained at the 800 (fed or fasted) vs. 400 mg (proposed) dose and dronedarone exhibits dose-dependent PK
- dronedarone exhibits a formulation dependent food-effect, which alters PK in fed state

However, if absolute BA information is deemed critical for product labeling the above limitations should be included. Overall, the following findings from the study may have qualitative utility:

1. metabolite is not formed following IV dronedarone administration suggesting the metabolite is formed pre-systemically
2. food increases dronedarone exposure
3. absolute BA of dronedarone is approximately 15 % in fed conditions following administration of capsule at 800 mg dose level.

APPENDIX to STUDY PPK2397

Blood sampling time in Study PPK2397

Intravenous Route				Oral Route (Fed and Fasted)		
Time of Sampling	Sample	Sample Number		Time of Sampling	Sample	Sample Number
T0-10min	1st sample	P0		T0-10min	1st sample	P0
T0+15min	2nd sample	P1				
T0+30min	3rd sample	P2				
T0+45min	4th sample	P3				
T1h (end of infusion)	5th sample	P4		T1h	2nd sample	P1
T1h+15min	6th sample	P5		T2h	3rd sample	P2
T1h+30min	7th sample	P6		T3h	4th sample	P3
T2h	8th sample	P7		T4h	5th sample	P4
T3h	9th sample	P8		T5h	6th sample	P5
T4h	10th sample	P9		T6h	7th sample	P6
				T7h	8th sample	P7
T6h	11th sample	P10		T8h	9th sample	P8
T8h	12th sample	P11		T10h	10th sample	P9
T10h	13th sample	P12		T12h	11th sample	P10
T12h	14th sample	P13		T16h	12th sample	P11
T16h	15th sample	P14		T24h	13th sample	P12
T24h	16th sample	P15		T36h	14th sample	P13
T48h	17th sample	P16		T48h	15th sample	P14
T72h	18th sample	P17		T72h	16th sample	P15

4.2.7 In vitro characterization of the binding of [^{14}C]-SR33589B to human plasma proteins (LPH0006).

PROTOCOL #	LPH0006
STUDY SITE	Sanofi-Synthelabo Research, Willowburn Avenue, Alnwick Northumberland, England, NE66 2JH
STUDY PERIOD	August - December 2002

Study Description

Equilibrium dialysis was used to determine the plasma protein binding of radiolabeled dronedarone in natural plasma, human serum albumin (HSA) and α1-acid glycoprotein (AAG). The following dronedarone concentrations were evaluated: 25, 50, 500, 5000, and 50,000 ng base/mL. Liquid scintillation counting was used to measure total radioactivity. Two additional experiments were conducted in conjunction with the protein binding evaluation:

1. Stability of [^{14}C]-dronedarone was studied in each matrix and dialysate by HPLC and radiochemical detection
2. Protein concentration in the dialysate was measured to ensure the exclusion of protein by the equilibrium dialysis membrane.

The protein concentration experiment was not reviewed in detail because standard equilibrium dialysis membranes are expected to exclude proteins.

Reviewer Note on Experimental Design

The study procedures were acceptable. According to the applicant, a previous study showed that ultra-filtration was not suitable for the determination of the protein binding of [^{14}C] - dronedarone due to high non-specific binding to the ultra-filtration devices. As a result equilibrium dialysis was used to determine protein binding.

Materials

- Test substance: dronedarone (dronedarone hydrochloride salt) ^{14}C in carbonyl function. The specific radioactivity was 3.65 MBq/mg base (98.8 μCi/mg base).
- Frozen plasma from six healthy male individuals was obtained from Biochemed Pharmacologicals, USA.

RESULTS

Plasma Protein Binding

The results for the dronedarone plasma protein binding are summarized in Table 62. Dronedarone was over 99 % bound at all concentrations examined (25 – 50000 ng/mL nominal concentration) and the degree of binding appeared independent of dronedarone concentration. At the clinically relevant concentration (Cmax ~ 200 ng/mL), binding of [^{14}C] - dronedarone to proteins in plasma was 99.7 % (Table 63). Generally, binding to purified human serum albumin (HSA) appeared independent of concentration; this independence was obvious at 40 mg/mL (physiological conditions), but not clear at the 2 mg/mL HSA concentration. The degree of binding to α1-acid glycoprotein (AAG) at physiological concentrations appeared largely independent of drug concentration. These data indicate that [^{14}C]-dronedarone was extensively bound to HSA and AAG, and these two proteins appear to account for the majority of binding in plasma.

Table 62: Mean Percent* of Dronedarone bound in plasma and purified plasma proteins

Nominal Concentration (ng/mL)	Plasma (n = 2)	HSA 40 mg/mL (n = 2)	HSA 2mg/mL (n = 2)	AAG (n = 4; mean ± SD)
25	99.73	98.82	81.88	77.56 ± 4.67
50	99.73	98.94	82.04	82.07 ± 5.30
500	99.70	98.93	72.29	81.83 ± 7.67
5000	99.72	98.68	80.17	87.21 ± 2.02
50000	99.71†	98.40	92.18	88.58 ± 1.88

† n = 1 due to cell blockage

* n refers to the number of experiments conducted with pooled plasma samples from six healthy male subjects.

Reviewer Comment

The sample size for the experiments presented in Table 62 is inappropriate because it may not reflect experimental variability. Ideally the number of experiments should be > 2; however, the results from the individual plasma samples (Table 63) suggest low inter-subject variability, which can be assumed to be equivalent or higher than inter-experimental variability. Consequently, the results from the protein binding study are acceptable, despite the low number of replicates. It is noted that the data provided from the two replicates (plasma and HSA) were similar.

Table 63: Mean percent ^{14}C-dronedarone bound in plasma at 200 ng/mL dronedarone concentration

Individual identity number	Percent bound Mean ± SD (n = triplicate measurements)
N17890	99.73 ± 0.019
N17895	99.70 ± 0.054
N17899	99.72 ± 0.025
N19471	99.79 ± 0.0010
N19472	99.75 ± 0.044
N19474	99.74 ± 0.054
Mean	99.74
s.d.	0.030

Equilibrium Constants

The equilibrium dissociation constant for the binding of dronedarone to HSA and AAG are presented in Table 64.

Table 64: Apparent equilibrium dissociation constants for the binding of dronedarone to purified HSA and AAG

	K_D	95% confidence interval	% CV
HSA	9.11	9.06; 9.15	0.23
AAG	0.62	0.48; 0.80	13.71
HSA (2 mg/mL)	1.16	0.60; 2.28	33.62

The apparent dissociation constants (K_D) for binding of dronedarone to purified HSA and AAG were obtained by assuming a single binding site per protein molecule. Based on these K_D values, dronedarone had a significantly higher affinity (lower K_D) for AAG than HSA (physiological concentrations). However, due to the greater physiological

concentration of HSA, and hence, greater capacity, binding was approximately three times greater to HSA as shown in Table 62.

Non-Specific Binding (Recovery of radioactivity)

The recovery of radioactivity data in plasma, HSA and AAG are presented in Table 65.

Table 65: Percent of Radiolabeled dronedarone recovered from equilibrium dialysis cells

	Recovery							
Nominal Concentration	Plasma		HSA		AAG		AAG (repeated experiment)	
	Initial	Total	Initial	Total	Initial	Total	Initial	Total
25	90.3	93.4	87.4	99.9	18.8	80.7	23.2	97.0
	95.1	98.3	89.0	100	17.8	85.1	20.6	102
50	91.2	94.5	79.8	92.0	22.0	104	26.6	103
	94.8	97.3	86.3	99.4	23.8	105	33.8	106
500	92.3	95.4	85.1	96.3	19.1	81.9	29.6	93.3
	80.3	82.3	85.9	96.1	20.1	78.6	29.2	96.0
5000	93.2	96.0	88.8	98.1	22.1	96.0	18.9	95.3
	94.5	97.4	79.7	88.3	20.4	95.6	19.3	92.5
50000	91.6	95.5	76.6	84.4	16.0	94.7	16.6	92.7
	-[†]	-[†]	91.4	99.6	16.2	92.7	17.5	105

[†] no data due to cell blockage

Initial recovery of radioactivity was generally > 80% from experiments with plasma and HSA demonstrating a low level of non-specific binding in these experiments. However, initial recovery was lower in matrices containing a lower protein concentration (AAG). The initial low recovery appeared due to non-specific binding to the cells, because the recovered amount increased significantly by washing with methanol. The initial recovery results with AAG were similar in the first and repeated experiments, but, the total recovery in the repeated experiment was almost complete vs. ~ 81 % in the first experiment. The reason for the variability in AAG results is unclear and should have been explored further by the applicant.

Reviewer Comment

The limited initial recovery with AAG suggests the protein binding results for AAG may not be reliable because radiolabeled dronedarone may have had a greater affinity for the dialysis cells than AAG thereby not accurately reflecting dronedarone-AAG binding. The applicant should have attempted to optimize the equilibrium dialysis conditions to minimize non-specific binding.

[^{14}C]- dronedarone radiochemical stability

The radiochemical purity of [^{14}C]-dronedarone in retentate and dialysate samples are shown in Table 66 and Table 67.

Table 66: Radiochemical Purity (Stability) of radiolabeled dronedarone (initial 5 µg/mL [^{14}C]-dronedarone concentration) in retentate samples

Matrix	Replicate	% Of Total Radioactivity	
		[^{14}C]-SR33589	Impurity
Plasma	1	101.09	0.37
	2	99.67	-
HSA	1	98.75	1.74
	2	97.34	1.46
Alpha-1-acid glycoprotein	1	88.24	8.49
	2	92.74	7.26

Table 67: Radiochemical purity (Stability) of radiolabeled dronedarone (initial 5 µg/mL [^{14}C]-dronedarone concentration) dialysate samples

Matrix	Replicate	% Of Total Radioactivity	
		[^{14}C]-SR33589	Impurity
Plasma	1	75.53	22.46
	2	66.79	25.03
HSA	1	90.57	8.83
	2	88.58	10.52
Alpha-1-acid glycoprotein	1	90.19	8.42
	2	91.69	7.32

Generally, the retentate samples had high radiochemical purity (> 90 %), whereas the dialysate samples were not as pure. The implications of the lack of radiochemical purity for each of the matrices are discussed as follows:

Plasma

In plasma, dialysate impurities constituted approximately 24% of total radioactivity, with [^{14}C] - dronedarone representing ~ 70 % radioactivity. These data suggest that potentially up to 30 % of the radioactivity in the dialysate may be due to radiochemical impurities and not radiolabeled dronedarone. Consequently, differential binding of radiochemical impurities to plasma proteins, compared to [^{14}C] - dronedarone, could result in an overestimation (approximately 30 %) of free fraction using total radioactivity calculations. The applicant notes that this potential overestimation was not accounted for in estimates of fractional binding of [^{14}C] - dronedarone.

HSA

The radiochemical purity of radiolabeled-dronedarone in retentate from HSA was approximately 98%. However, in dialysates, radiolabeled-dronedarone accounted for only 90% of the total radioactivity, which would result in a small overestimation of free fraction. This difference is also sufficiently small to have limited impact on estimation of the dissociation constant.

AAG

Radiochemical purity was approximately 90% in both retentate and dialysate. Since the dialysate composition of radioactive components reflects that in the retentate, there was no impact on the estimation of the free fraction or dissociation constant

Protein Concentration

There was no protein in the dialysate, whereas the retentate had a significant amount of protein (Table 68); this finding indicates that the dialysis membrane functioned appropriately.

Table 68: Protein concentration in dialysate and plasma retentate

	Total protein concentration (g/L)	
Replicate no.	Dialysate	Retentate
1	0	61
2	0	62

Recommendations/Conclusions

The lack of radiochemical purity in the plasma and HSA samples warrants cautious interpretation of all protein binding calculations. Additionally, the initial low and variable total recovery with AAG indicates that experimental conditions were not optimized in this plasma protein binding assessment. Assuming the worst case scenario with respect to radiochemical impurity, enrichment of radiochemical impurities in plasma dialysate will result in a 30% overestimation of the free fraction in plasma. Consequently, the estimate of fu in this study (0.26 ± 0.03%; n = 6 healthy male subjects) could be adjusted to 0.19% if a correction for radiochemical impurities is applied. Similarly, in experiments with HSA a 10% overestimation of fu would occur. With these caveats the following conclusions can be drawn from the protein binding experiments:

- Binding of [^{14}C]- dronedarone to plasma proteins is greater than 99 % and not concentration-dependent over the 25 to 50000 ng/mL concentration range.
- HSA is the major binding protein, with approximately three times more drug bound to HSA than AAG. These two proteins appear to account for the majority of the plasma protein binding of dronedarone.

4.2.8 In vitro characterization of the binding of ^{14}C-SR35021 to human plasma proteins (LPH0021)

PROTOCOL #	LPH0021
STUDY SITE	Sanofi-Synthelabo Research, Willowburn Avenue, Alnwick Northumberland, England, NE66 2JH
STUDY PERIOD	July - August 2001

Study Description

Equilibrium dialysis was used to determine the plasma protein binding of radiolabeled dronedarone in natural plasma, human serum albumin (HSA) and α1-acid glycoprotein (AAG). The following SR35021 concentrations were evaluated: 25, 50, 500, 5000, and 50,000 ng base/mL. Liquid scintillation counting was used to measure total radioactivity. Two additional experiments were conducted in conjunction with the protein binding evaluation:

1. Stability of [^{14}C]-SR35021 was studied in each matrix and dialysate by HPLC and radiochemical detection
2. Protein concentration in the dialysate was measured to ensure the exclusion of protein by the equilibrium dialysis membrane.

The protein concentration experiment was not reviewed in detail because standard equilibrium dialysis membranes are expected to exclude proteins.

Materials

- Test substance: SR35021 hydrochloride salt, ^{14}C in carbonyl function. The specific radioactivity was 3.79 MBq/mg
- Frozen plasma from six healthy male individuals was obtained from Biochemed Pharmacologicals, USA.

RESULTS

Plasma Protein Binding

The results for the SR35021 plasma protein binding are summarized in Table 69. SR35021 was over 98 % bound at all concentrations examined (25 – 50000 ng/mL nominal concentration) and the degree of binding appeared independent of SR35021 concentration. At the clinically relevant concentration (Cmax ~ 200 ng/mL), binding of [^{14}C]-SR35021 to proteins in plasma was 98.2 % (Table 69). Binding to purified human serum albumin (HSA) appeared independent of concentration at the 40 mg/mL HSA concentration (physiological conditions). The degree of binding to α1-acid glycoprotein (AAG) at physiological concentrations appeared dependent on drug concentration; binding of SR35021 appeared to decrease with increasing SR35021 concentration. However, the exact nature of this concentration dependence was not clear except at the extreme ends of the tested SR35021 concentrations (Binding was ~ 73 % at 25 ng/mL and ~ 30 % at 50000 ng/mL). Nevertheless, the AAG and HSA data indicate that [^{14}C]-SR35021 was extensively bound to HSA and AAG, and these two proteins appear to account for the majority of binding in plasma.

Table 69: Mean percent of ^{14}C-SR35021 bound in human plasma, HSA and AAG

Nominal [^{14}C]-SR33589 (ng/mL)	Plasma	HSA (41 mg/mL)	α_1-Acid Glycoprotein (0.6 mg/mL)
25	98.473	94.548	73.350
50	98.512	95.066	56.493
500	98.255	95.296	61.479
5000	98.618	94.611	69.140
50000	98.633	95.197	29.807

Table 70: Mean SD percent ^{14}C-SR35021 (200 ng/mL) protein bound in plasma from healthy male subjects

Individual identity number	Percent bound Mean ± s.d. (n = triplicate measurements)
N17890	97.97 ± 0.0198
N17895	97.98 (n = 2)
N17899	97.66 ± 0.349
N19471	98.54 ± 0.123
N19472	98.71 ± 0.0144
N19474	98.42 ± 0.0144
Mean	98.21
s.d.	0.40

Equilibrium Constants

The equilibrium dissociation constant for the binding of SR35021 to HSA and AAG are presented in Table 71.

Table 71: Calculated dissociation constants for the binding of ^{14}C-SR35021 to purified HSA and AAG

	K_D * (μM)	95% confidence interval	% CV
HSA (41 mg/mL)	30.23	29.67; 30.82	0.84
AAG	3.85	2.67; 5.66	19.80

* n = 1 binding site per molecule

The apparent dissociation constants (K_D) for binding of SR35021 to purified HSA and AAG were obtained by assuming a single binding site per protein molecule. Based on these K_D values, SR35021 had a significantly higher affinity (lower K_D) for AAG than HSA (physiological concentrations). However, due to the greater physiological concentration of HSA, and hence, greater capacity, binding was approximately six times greater to HSA as shown in Table 69.

Non-Specific Binding (Recovery of radioactivity)

The recovery of radioactivity data in plasma, HSA and AAG are presented in Table 72. Initial recovery of radioactivity was > 80% from experiments with plasma and HSA demonstrating a low level of non-specific binding in these experiments. However, initial recovery was lower in matrices containing a lower protein concentration (e.g. for AAG). The initial low recovery appeared due to non-specific binding to the cells, because the recovered amount increased significantly by washing with methanol.

Table 72: Recovery of radioactivity in plasma, AAG and HSA

	Recovery							
Nominal Concentration	Plasma		HSA		AAG		AAG (repeated experiment)	
	Initial	Total	Initial	Total	Initial	Total	Initial	Total
25	93.2 91.8	95.4 94.4	83.5 84.5	97.2 98.2	31.0 21.2	96.7 90.6	19.6 19.5	90.0 95.8
50	87.2 84.1	91.1 87.3	85.4 84.1	98.3 99.7	21.4 22.4	94.0 101	22.1 15.9	85.5 83.5
500	77.9 84.8	80.8 88.1	82.4 84.9	94.4 95.7	25.3 27.7	84.2 95.3	25.7 33.3	84.6 93.4
5000	90.7 93.0	95.6 97.8	71.7 90.9	78.3 99.2	51.8 55.5	95.8 96.4	54.9 62.3	92.3 96.7
50000	90.3 91.7	94.8 96.0	90.8 94.5	95.0 99.2	68.0 76.7	87.7 98.2	74.3 77.9	94.0 98.3

The initial recovery results with AAG were similar for the first and repeated experiments,

Reviewer Comment

The limited initial recovery with AAG suggests the protein binding results for AAG may not be reliable because radiolabeled SR35021 may have had a greater affinity for the dialysis cells than AAG thereby not accurately reflecting SR35021-AAG binding. The applicant should have attempted to optimize the equilibrium dialysis conditions to minimize non-specific binding.

[^{14}C]- SR35021 radiochemical stability

The radiochemical purity of [^{14}C]-SR35021 in retentate and dialysate samples are shown in Table 73 and Table 74.

Table 73: Purity (Stability) of SR35021 (initial concentration was 5 µg/mL of [^{14}C]-SR35021) in retentate samples

Matrix	Replicate	% Of Total Radioactivity	
		[^{14}C]-SR35021	Impurity
Plasma	1 2	98.74 98.90	- -
HSA	1 2	97.52 97.70	1.57 -
Alpha-1-acid glycoprotein	1 2	95.06 93.07	3.54 6.57

Table 74: Purity (Stability) of SR35021 (initial concentration was 5 µg/mL of [^{14}C]-SR35021) in dialysate samples

Matrix	Replicate	% Of Total Radioactivity	
		[^{14}C]-SR35021	Impurity
Plasma	1 2	82.27 82.16	15.66 16.79
HSA	1 2	89.10 89.91	9.68 9.39
Alpha-1-acid glycoprotein	1 2	92.62 92.11	6.38 6.26

Generally, the retentate plasma and HSA samples had higher radiochemical purity (> 92 %) than their respective dialysate samples. The implications of the lack of radiochemical purity for each of the matrices are discussed as follows.

<u>Plasma</u>

In plasma, dialysate impurities constituted approximately 16 % of total radioactivity, with [^{14}C] - SR35021 representing ~ 80 % radioactivity. These data suggest that potentially up

to 20 % of the radioactivity in the dialysate may be due to radiochemical impurities and not radiolabeled SR35021. Consequently, differential binding of radiochemical impurities to plasma proteins, compared to [^{14}C] - SR35021, could result in an overestimation (approximately 20 %) of free fraction using total radioactivity calculations. The applicant notes that this potential overestimation was not accounted for in estimates of fractional binding of [^{14}C] - SR35021.

HSA

The radiochemical purity of radiolabeled-SR35021 in retentate from HSA was approximately 98%. However, in dialysates, radiolabeled-SR35021 accounted for only 90% of the total radioactivity, which would result in a small overestimation of free fraction. This difference is also sufficiently small to have limited impact on estimation of the dissociation constant.

AAG

Radiochemical purity was approximately 93 % in both retentate and dialysate. Since the dialysate composition of radioactive components reflects that in the retentate, there was no impact on the estimation of the free fraction or dissociation constant

Protein Concentration

There was no protein in the dialysate whereas the retentate had a significant amount of protein (Table 75); this finding indicates that the dialysis membrane functioned appropriately.

Table 75: Protein concentration in dialysate and plasma retentate

	Total protein concentration (g/L)	
Replicate no.	Dialysate	Retentate
1	0	61
2	0	62

Recommendations/Conclusions

The lack of radiochemical purity in the plasma and HSA samples warrants cautious interpretation of all protein binding calculations. Additionally, the initial low recovery with AAG indicates that experimental conditions were not optimized in this plasma protein binding assessment. Assuming the worst case scenario with respect to radiochemical impurity, enrichment of radiochemical impurities in plasma dialysate will result in a 20% overestimation of the free fraction in plasma. Consequently, the estimate of fu in this study (1.79 ± 0.4 %; n = 6 healthy male subjects) could be adjusted to 1.52 % if a correction for radiochemical impurities is applied. Similarly, in experiments with HSA a 10% overestimation of fu would occur. With these caveats the following conclusions can be drawn from the protein binding experiments:

- Binding of [^{14}C]- SR35021 to plasma proteins is greater than 98 % and not concentration-dependent over the 25 to 50000 ng/mL concentration range.
- HSA is the major binding protein, with approximately six times more drug bound to HSA than AAG. These two proteins appear to account for the majority of the plasma protein binding of SR35021.

4.2.9 Effect of dronedarone on renal functions in healthy male subjects - Randomized, double-blind, placebo-controlled, two-by-two crossover in sequential groups study (PDY5487)

PROTOCOL #	PDY5487
INVESTIGATOR	Pr Jerome Biollaz
STUDY SITE	Hôpital de Beaumont, Avenue de Beaumont, 29, 1011 Lausanne - CHUV – Vaud, Switzerland
STUDY PERIOD	June to November 2003

Objectives (per applicant)

- to evaluate the effect of dronedarone on the creatinine clearance and on the glomerular filtration rate compared to placebo.
- to elucidate the mechanism of action of repeated doses of dronedarone on the renal blood flow and renal cationic transport compared to placebo
- to assess the clinical and biological tolerability of dronedarone
- to assess plasma concentration profile of dronedarone and SR35021 on the last day of treatment

Study Design

This was a randomized, placebo-controlled, double-blind, two-by-two crossover study in healthy male subjects. There was a 14-day washout between periods. Two sequential dose groups were planned*:

- Group 1 (first dose level)
  - Treatment A = placebo for seven days
  - Treatment B = dronedarone 400 mg twice daily (BID) for seven days
- Group 2 (second dose level)
  - Treatment A = placebo for seven days
  - Treatment B = dronedarone 800 mg BID for seven days

*According to the applicant, an interim analysis indicated that the second dose level of the study was not required because results were conclusive from the first dose level and did not need to be confirmed by a higher dose.

Reviewer's Note

The 400 mg BID dose is the proposed clinical dose, thus this study provides relevant information. However, information at a higher dose or alternative doses would be useful to determine if there is an exposure (concentration)-response (effect on renal function) or dose-response relationship; evaluating this relationship would facilitate dose adjustments, if needed.

Subject Demographics

Subject demographics are presented in Table 76.

Formulations

- Dronedarone (2E3 formulation), 400 mg tablet; batch number: CL-03936
- Placebo Matching tablet; batch number: CL-03812
- Sinistrin, Inutest vials containing 5g/20mL provided by Fresenius Kabi Austria GmbH (Graz, Austria); batch number 21 3063

- Para-amino-hippurate (PAH), Sodium PAH vials containing 2 g/10 mL provided by Clinalfa, Merck Biosciences AG (Läufelfingen, Switzer land); batch number AC 0465 and AC 0349

Table 76: Subject Demographic Data for Study PDY5487

Parameter (Unit)	Statistics/ Category	Total (N=12)
Age (year)	N	12
	Mean	25.8
	SD	5.1
	Min	19
	Max	38
Height (cm)	N	12
	Mean	179.3
	SD	7.3
	Min	169
	Max	192
Weight (kg)	N	12
	Mean	67.65
	SD	9.16
	Min	55.5
	Max	87.8
BMI (kg/m^2)	N	12
	Mean	20.98
	SD	1.62
	Min	19.0
	Max	24.6
Gender	Male (N, %)	12 (100)
Race	Black (N,%)	6 (50)
	Caucasian (N,%)	5 (41.7)
	Other (N,%)	1 (8.3)

Pharmacokinetics

Plasma concentrations of dronedarone and SR35021 were assessed before treatment on Day -1, before dosing on Day 6 and Day 7, then post dosing at 2, 3.5 and 5 h on Day 7. Due to the limited sampling, a formal PK analyses was not conducted, however, plasma concentrations were provided.

Pharmacodynamics

Primary

The primary PD criteria were based on the following urinary clearance evaluations on Day -1 and Day 7 and 14 Days after the last study drug was administered. Samples were collected at the 1 hour 30 minutes time point to estimate.

- renal creatinine clearance (CLcr)
- glomerular filtration rate (GFR) measured as renal sinistrin clearance

Secondary

The secondary PD criteria were the GFR estimated by systemic sinistrin clearance and the following urinary measurements on Day -1, Day 7 and Day 14. Samples were collected at the 1 hour 30 minutes time point.

- urinary flow rate (UFR)
- effective renal plasma flow (ERPF) using renal para-aminohippurate (PAH) clearance
- renal blood flow (RBF) = ERFP/(1- Hematocrit)
- filtration fraction (FF) = renal sinistrin clearance/RBF

- renal cationic transport by renal N^1-methylnicotinamide (NMN) clearance
- renal clearance ratio of creatinine over sinistrin
- renal clearance ratio of NMN over PAH.

Additionally, the following PD measurements were obtained from 24 h urine collections on Day -2, Day 6 and Day 13 (recovery: 13 days after the last study drug administration):

- renal creatinine clearance
- UFR (mL/24h)
- Osmolality
- sodium and potassium excretion

Pharmacodynamic Analyses

PD measures were log transformed prior to analysis. Standard pharmaco-statistical analyses were used to determine if dronedarone affected the PD measures, where Day 6 or 7 data were compared to baseline data.

Reviewer Comment on PD Measures and Analyses

The selected PD measures have been used to varying degrees to assess renal function. This review focuses on the CLcr, because this is the most commonly used parameter in clinical pharmacology assessments of renal function.

Bioanalytical methods

Dronedarone and SR35021 concentrations were determined using a validated liquid chromatography- tandem mass spectrometry (LC-MS/MS) method (DOH0309). The assay performance was acceptable as illustrated in Table 77 .

Table 77: Performance of Dronedarone and SR35021 Assays (DOH0309)

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.998$	Satisfactory
Between day Precision	CV data were not provided	Cannot be assessed
Accuracy	All QC samples were within 10 % of the nominal concentrations	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity*	Chromatograms were not provided	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.997$	Satisfactory
Between day Precision	CV data were not provided	Satisfactory
Between day Accuracy	All QC samples were within 10 % of the nominal concentrations	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity*	Chromatograms were not provided	Cannot be assessed

* The validation report for DOH0309 includes chromatograms and CV measures that indicate the assay is specific and precise

Results

Pharmacokinetics

The mean dronedarone and SR35021 plasma concentrations are presented in Table 78. Comparison of Day 6 and 7 plasma concentrations suggests that dronedarone and SR35021 reached steady state by Day 7. Plasma concentrations obtained in this study are consistent with previous PK data at this dose level.

Table 78: Mean (CV%) dronedarone and SR35021 plasma concentrations observed from Day - 1 to Day 7 during repeated oral administrations of dronedarone 400 mg BID in fed conditions (n = 12)

Mean (CV%) Concentrations	Day -1	Day 6	Day 7			
	0h30	0h00	0h00	2h00	3h30	5h00
Dronedarone (ng/mL)	<LOQ	34.3 (25.6)	30.3 (36.5)	69.2 (58.5)	110 (44.3)	80.5 (38.8)
SR35021 (ng/mL)	<LOQ	32.5 (27.6)	31.1 (31.6)	39.2 (30.0)	61.1 (22.9)	63.4 (20.7)

Pharmacodynamics

The estimates of urinary clearance measures on Day -1 and Day 7 following placebo or dronedarone 400 mg are summarized in Table 79 and Table 80

Table 79: Estimated D7/D-1 ratio of geometric mean renal clearances by treatment and between treatments

Parameter	Placebo D7/D-1 (%)	Dronedarone D7/D-1 (%)	(Day 7/Day -1)Dronedarone/ (Day 7/Day 1)Placebo Ratio		P-value
			Estimate (%)	95 % CI	
Sinistrin	1.35	-2.11	-3.42	[-20.41, 17.21]	0.7229
Creatinine	4.91	-13.66	-17.70	[-31.68, -0.85]	0.0405
Creatinine over sinistrin	3.42	-11.80	-14.72	[-20.72, -8.25]	<.0001
PAH	0.06	-5.72	-5.77	[-22.47, 14.51]	0.5471
NMN	-0.86	-17.74	-17.02	[-31.58, 0.65]	0.0581
NMN over PAH	-1.11	-12.75	-11.76	[-19.35, -3.45]	0.0068

P-value is the significance level of the hypothesis test: (Day7/Day-1) dronedarone/(Day7/Day-1) placebo ratio equals 1

Table 80: Estimated Day 7 geometric mean renal clearances by treatment and estimate of treatment ratio of Day 7 geometric mean clearances

Parameter	Placebo on Day 7 Estimate	Dronedarone on Day 7 Estimate	Dronedarone / Placebo Ratio on Day 7		P-value
			Estimate (%)	95% CI (%)	
Sinistrin (mL/min)	107.0	98.5	-8.01	[-19.82, 5.53]	0.2311
Creatinine (mL/min)	149.0	119.4	-19.86	[-29.78, -8.54]	0.0012
Creatinine over sinistrin	1.39	1.21	-12.81	[-17.21, -8.16]	<.0001
PAH (mL/min)	514.3	485.1	-5.68	[-17.87, 8.32]	0.4046
NMN (mL/min)	431.0	368.3	-14.56	[-25.50, -2.02]	0.0247
NMN over PAH	0.84	0.76	-9.24	[-14.86, -3.26]	0.0032

P-value is the significance level of the hypothesis test: Day7 dronedarone/placebo ratio equals 1

General Observations

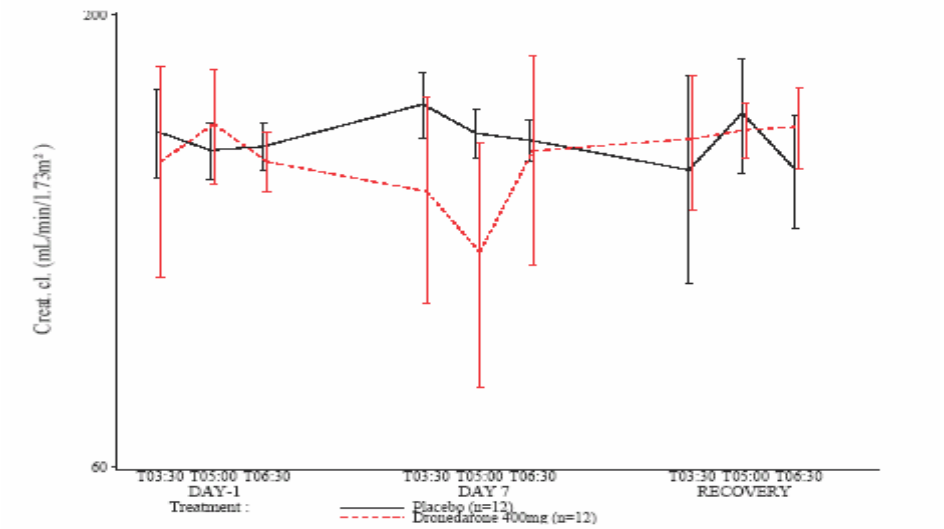
After 7 days of 400 mg BID dronedarone:

- Renal sinistrin clearance was not affected by dronedarone

- Renal creatinine clearance was significantly decreased relative to baseline and was significantly lower than placebo on Day 7
- Dronedarone did not affect the renal PAH clearance
- A significant decrease of renal NMN clearance was observed as well as a significant change in the NMN/PAH ratio
- Ratio of creatinine to sinistrin was lower for the dronedarone group than placebo, but the difference appears due to creatinine

The renal creatinine clearance values on the various study days are depicted in Figure 36 and summarized in Table 81.

Figure 36: Change in creatinine clearance^ in placebo and dronedarone groups



^the lower curve (red color) is for dronedarone and the upper curve (black color) is for placebo

Table 81: Renal Creatinine clearance by treatment and day

Treatment	Day	n	Geometric Mean	95% CI Lower	95% CI Upper	Min	Max
Placebo	Day -1	12	141.99	131.59	153.22	119.14	171.72
	Day 7	12	148.82	141.24	156.81	130.38	179.36
	Recov	12	137.37	124.41	151.68	102.95	176.66
Dronedarone 400mg	Day -1	12	138.26	127.55	149.88	102.95	162.24
	Day 7	12	119.38	105.63	134.91	73.61	148.93
	Recov	12	145.82	134.55	158.04	119.39	171.72

The creatinine clearance data indicate that placebo did not impact the creatinine clearance values. In contrast, dronedarone 400 mg BID decreased mean creatinine clearance by ~ 20 mL/min over a seven day-period; however, this decrease was recovered within 14 days after dronedarone was discontinued. This finding suggests that the effect of dronedarone on CLcr is reversible upon drug discontinuation in healthy subjects with normal renal function. The potential limitations of this study with respect to clinical utility include:

- it is unclear if this finding is applicable to patients with decreased renal function
- the time course for loss and gain of renal function could not be determined
- the study was conducted for a relatively short period of time.

The outlined limitations can be addressed using information from long-term trials, such as the pivotal trials or dose-ranging study.

There was a non-significant 4.75 % decrease in 24-hr creatinine clearance based on Day 6/Day-2 ratios (Table 82).

Table 82: Estimated Day6/Day-2 ratio of renal 24-hour creatinine clearances by treatment and between treatments

Parameter	Placebo D6/D-2 (%)	Dronedarone D6/D-2 (%)	$(\text{Day 6/Day -2})_{\text{Dronedarone}}$ / $(\text{Day 6/Day -2})_{\text{Placebo}}$ Ratio		P-value
			Estimate (%)	95% CI (%)	
Creatinine renal clearance	-7.87	-12.25	-4.75	[-17.96, 10.58]	0.5111

It is noted that the 24-hr CLcr finding was different from that for CLcr; the reason for this difference is unclear, but may be related to the lack of control of diet, exercise and other factors over the 24-hour period. For a practical perspective, the acute CLcr values are more readily attainable clinically and appear more reliable.

The impact of dronedarone administration on measures of renal function (PD measures) is summarized in Table 4.

Table 83: Impact of dronedarone administration on measures of renal function

Component	Estimates	Dronedarone vs. placebo	Comment
Renal Sinistrin	GFR	↔	No effect
CLcr	Renal function	↓	
CLcr/CL sinistrin	Renal tubular secretion of creatinine	↓	interferes
PAH	Renal Blood flow and tubular organic anion transporter (OAT)	↔	No effect on RBF
NMN renal clearance	Tubular organic cation transporter (OCT)	↓	May impact organic cations eliminated renally
24-hr creatinine clearance	Overall renal function	↔	Findings are inconclusive due to study design
Electrolytes (UFR, Na, K ions)	Excretion and osmolality	↔	No effect on physiological processes

Discussion: Interpretation of PD results

In brief, the PD findings suggest that dronedarone decreases renal function by interfering with tubular secretion of creatinine. However, this interference does not appear to significantly alter overall renal function as evidenced by the minimal impact on GFR, renal blood flow and other measures of renal function. Some investigators indicate that an apparent decrease in creatinine clearance alone does not necessarily signify a worsening of renal function. In light of the findings from the current study and the observations reported by other investigators, it is reasonable to conclude that dronedarone's impact on renal function may not be clinically significant. However, the label should include the findings from this study that suggest there may be potential increase in serum creatinine.

The decrease in the function of OCT suggests that dronedarone may affect the elimination of organic cation that are renally excreted; thus, there is a potential for drug-drug interactions to occur between dronedarone and such compounds.

Applicant's Safety Summary
No deaths, serious adverse events (SAEs) or AEs leading to treatment discontinuation occurred during the study. There were no significant changes in any laboratory test results. Additionally, no safety concerns in vital signs or ECG were noted. Headache was the most common treatment emergent AE in both treatment groups.

Recommendations/Conclusions
This study provides some insight into the short-term impact of dronedarone administration on renal function as assessed by PD measures. The overall clinical utility of this study is unclear because the time course was not well-defined and the study was conducted for a relatively short period of time. However, the study provides information on dronedarone drug-drug interaction potential with drugs with certain characteristics. The analysis should be repeated using information from long-term clinical trials; the Pharmacometric Reviewer has conducted this analyses. Despite the limitations of the current study, the following information from the study is useful for labeling as appropriate.

Relative to placebo, dronedarone at 400 mg BID for seven days in healthy subjects
1. significantly decreased the renal creatinine clearance; however, the decreased renal creatinine clearance returned to baseline level after study drug discontinuation (within 14 days). The mechanism of decreased creatinine clearance appears to be by partial inhibition of creatinine tubular secretion
2. did not alter GFR, renal blood flow or organic anion transport
3. appeared to inhibit the renal tubular organic cation transporter; this finding should be confirmed via an *in vivo* study with a renally excreted organic cation

Labeling
In light of the increase in serum creatinine, the applicant has proposed labeling that includes the following:
- precautionary language on the need to monitor serum creatinine during therapy
- use clinical judgment to determine if dronedarone use is warranted, if large increases in serum creatinine are observed.

Overall the applicant's labeling proposal appears adequate.

4.2.10 Study of the safety and pharmacokinetics of SR33589B in single oral administration in Japanese young male healthy subjects (TDU4899)

PROTOCOL #	TDU4899
INVESTIGATOR	Dr. Takanori Tanaka
STUDY SITE	Osaki Clinic, 5-7-13 Kitashinagawa, Shinagawa-ku, Tokyo, 141-0001, Japan
STUDY PERIOD	March – June 2002

Objectives (per applicant):

- To investigate the safety of SR33589B (dronedarone) after single oral dose administration to Japanese young male healthy subjects in fed and fasted conditions.
- To investigate the pharmacokinetic (PK) parameters of dronedarone and SR35021 (N-debutyl derivative) after single oral dose administration of dronedarone to Japanese young male healthy subjects in fed and fasted conditions.

Study Design

This was a randomized, placebo-controlled, double-blind, three-treatment and three-period study. A single 100, 200, 400 or 1200 mg dronedarone dose was given in the fed state. Additionally, some subjects received an 800 mg dose under fed and fasted conditions (crossover) to evaluate the food effect. Dronedarone was given orally in fed conditions (standard meal). Details of the standard meal are provided in the Appendix.

Subject Demographics

Subject demographics are presented in Table 84.

Table 84: Subject Demographic Data (Study TDU4899)

Parameter (unit)	Statistics	Placebo (N=10)	dronedarone 100 mg (N=6)	200 mg (N=6)	400 mg (N=6)	800 mg (N=6)	1200 mg (N=6)	Total (N=40)
Age (yrs)	N	10	6	6	6	6	6	40
	Mean (SD)	22.3(1.8)	21.0(1.5)	22.3(1.8)	22.5(2.1)	23.5(2.3)	23.5(1.5)	22.5(1.9)
	Min - Max	20-25	20-23	20-25	20-26	20-26	21-25	20-26
Weight (kg)	N	10	6	6	6	6	6	40
	Mean (SD)	61.49(6.67)	62.20(4.59)	62.88(5.41)	58.95(6.23)	60.00(6.08)	59.72(3.11)	60.94(5.44)
	Min - Max	50.1-74.8	57.6-68.2	54.7-68.5	52.7-69.4	55.6-70.0	55.4-63.9	50.1-74.8
Height (cm)	N	10	6	6	6	6	6	40
	Mean (SD)	172.96(7.61)	173.97(6.20)	174.27(3.12)	173.73(4.97)	168.22(4.37)	171.95(3.86)	172.56(5.57)
	Min - Max	160.2-184.8	167.8-184.8	170.3-178.5	164.9-178.4	160.6-173.2	166.4-177.2	160.2-184.8
BMI (kg/m^2)	N	10	6	6	6	6	6	40
	Mean (SD)	20.57(1.86)	20.57(1.04)	20.72(1.96)	19.50(1.33)	21.18(1.68)	20.18(0.83)	20.47(1.53)
	Min - Max	18.4-23.9	18.9-22.0	18.2-23.2	18.1-22.0	19.1-23.3	19.0-21.5	18.1-23.9

Formulation (2E3 Formulation*)

- Dronedarone 100 mg tablets, batch number CL-04600
- Dronedarone 400 mg tablets, batch number CL-04530
- Placebo 100 mg tablet, batch number CL-04601
- Placebo 400 mg tablet, batch number CL-03812

*The 2E3 formulation is adequately linked to the to-be-marketed tablet formulation

Pharmacokinetics

The following pharmacokinetic (PK) measures were determined for dronedarone and SR35021: t_{lag}, C_{max}, t_{max}, AUC_{last}, AUC_{0-24}, $t_{1/2Z}$, R_{met}, AUC, CL/F (only for SR33589), Vz/F

(only for SR33589), Ae_{0-24}, fe_{0-24}, and CL_{R0-T}. Standard pharmaco-statistical methods were used to evaluate the food effect. The test group was the fed treatment and the reference group was the fasted treatment. Dose proportionality, dose effects and metabolic ratio were also evaluated.

Pharmacokinetic sampling times

- Blood samples were collected before dosing and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 168 hours after drug administration
- Urine samples were collected over the following time intervals: 12 hours prior to dosing (H-12) to just prior to dosing (H0), time of dosing (H0) to 12 hours post dosing (H12), and 12 hours post dosing (H12) to 24 hours post dosing (H24)

Bioanalytical methods

Dronedarone and SR35021 plasma concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as illustrated in Table 85.

Table 85: Performance of Dronedarone and SR35021 Assays (DOH0239)

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day Precision	CV data were not provided	Cannot be assessed
Accuracy	QC samples were all within 15 % of the nominal concentrations for the low and medium QC samples. The majority of QC samples were within 15 % of nominal concentration (26 out of 30 samples)	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the ng/mL range; $R^2 > 0.994$	Satisfactory
Between day Precision	CV data were not provided	Cannot be assessed
Between day Accuracy (relative error)	QC samples were all within 15 % of the nominal concentrations for the low and medium QC samples. The majority of QC samples were within 15 % of nominal concentration (27 out of 30 samples)	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms and CV % were provided in the validation report that indicate assay is specific and precise

Urine concentrations of dronedarone and SR35021 were determined using the method for plasma adapted to urine; however, this method was not validated. Due to the lack of validation of the urine assay, the reliability of the urine results is unknown.

Reviewer's Note on Applicant's reported urine results

According to the applicant the fraction of the dose of dronedarone excreted unchanged in the urine was less than 0.5 % for the highest dose administered. Per protocol, no further evaluation of urine samples or PK analyses would be conducted if fe_{0-24} was < 1 %. Consequently, urinary PK parameters were not presented in this report.

Results

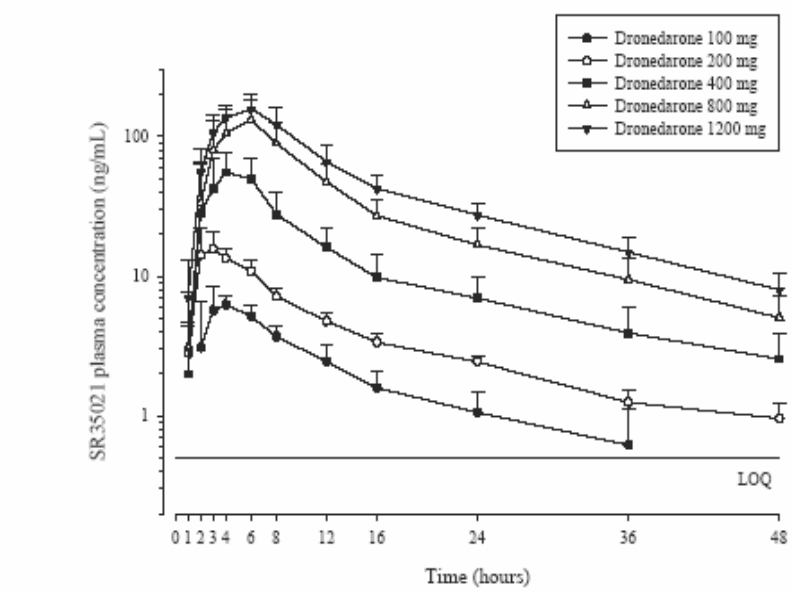
Subject Disposition (Patients contributing PK data)

Thirty-nine out of the 40 subjects completed the study; one patient in the placebo group discontinued the study for personal reasons.

Dronedarone Pharmacokinetics

The dronedarone plasma concentration-time profiles are depicted in Figure 37.

Figure 37: Mean dronedarone plasma concentration-time profile following administration of dronedarone single doses (100 to 1200 mg single doses)



After achieving Cmax plasma levels declined according to a biphasic elimination.

Mean dronedarone PK measures following administration of single dronedarone doses are summarized in Table 86.

Table 86: Mean (CV %) PK parameters of dronedarone (SR33589) after single dronedarone doses (100 to 1200 mg) in fed conditions

PK Parameter Mean (CV%)	SR33589B Dose (mg)				
	100 mg	200 mg	400 mg	800 mg	1200 mg
t_{lag} (h)[a]	0.8	0.0	0.5	0.5	0.0
C_{max} (ng/mL)	12.2 (43)	28.3 (42)	122.5 (58)	302.3 (36)	394.2 (33)
t_{max} (h)[a]	3.0	2.0	3.0	3.0	5.0
t_{last} (h)[a]	16	36	48	48	48
AUC_{last} (ng.h/mL)	62 (44)	168 (27)	701 (47)	2225 (37)	3430 (32)
$t_{1/2z}$ (h)	5.0 (40)	11.4 (20)	11.9 (17)	12.4 (14)	12.4 (12)
AUC (ng.h/mL)	67 (44)	178 (25)	712 (55)	2307 (37)	3573 (32)
CL/F (L/h)	1717 (37)	1201 (33)	663 (37)	388 (35)	366 (31)
Vz/F (L)	10808 (11)	19018 (22)	10963 (33)	6923 (39)	6518 (35)

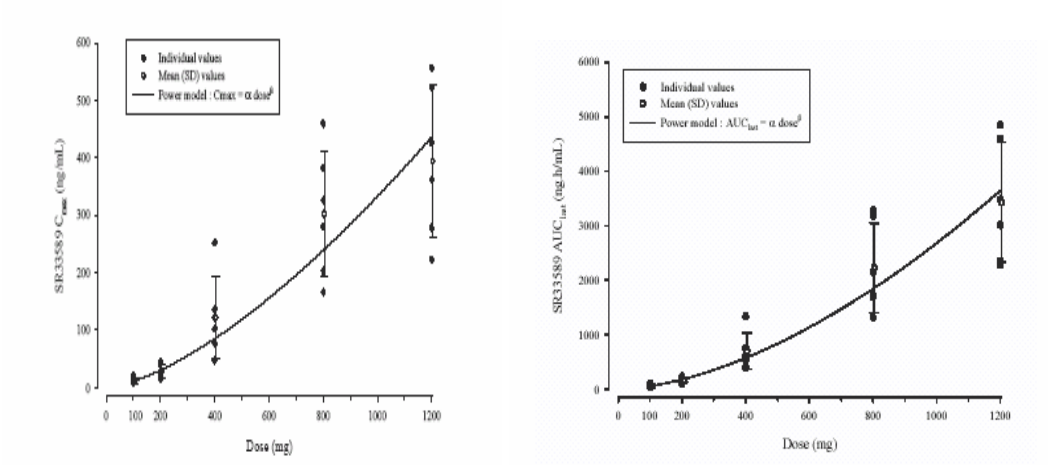
[a] : Median value.

The applicant reports that terminal half-life could not be accurately estimated in the 100 mg dose group due to insufficient quantifiable concentration. A significant dose effect was found for Tmax (p = 0.0335), but dose did not appear to affect the half-life.

Dose Proportionality (Assessment of PK Linearity)

Dronedarone Cmax, AUClast and AUC increased with the administered dose in a supra-proportional manner (Table 86 and Figure 38). This finding of supra-proportional increases in exposure with dose is consistent (of similar magnitude) with that observed in other studies. The existence of nonlinearity is supported by the varying CL/F values across the 100 to 1200 mg dose range (CL/F range: 366 to 1717 L/h).

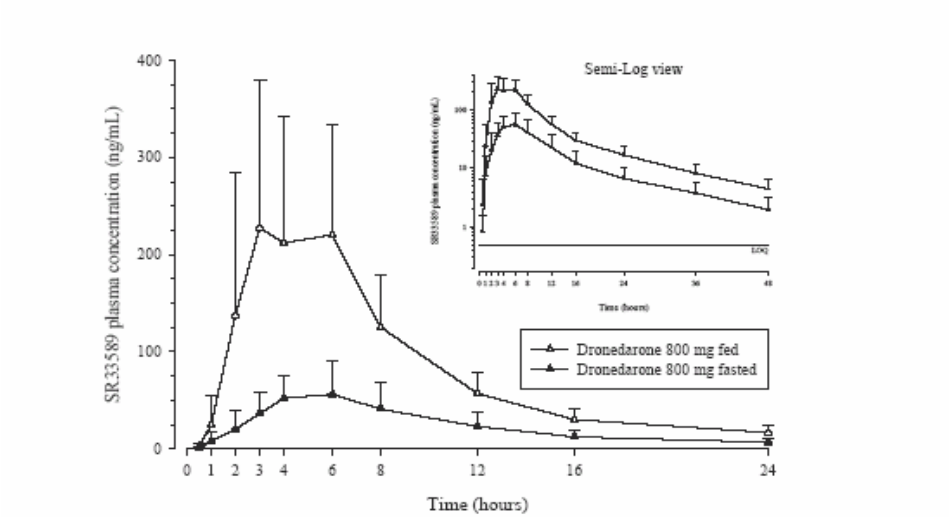
Figure 38: Individual and mean Dose-Response Plots (Cmax and AUC)



Food Effect

The dronedarone plasma concentration-time profiles of dronedarone under fed and fasted conditions are depicted in Figure 39.

Figure 39: Mean dronedarone plasma concentration-time profiles under fed and fasted conditions (800 mg dronedarone administered)



The food effect findings at the 800 mg dose level are summarized in Table 87.
Relative to the fasted state, dronedarone Cmax, AUClast, and AUC were significantly increased by food. Food effects of similar magnitude have been observed in other studies.

Table 87: Mean (CV %) PK parameters of dronedarone observed after a single 800 mg oral administration of dronedarone in fed and fasted conditions

PK Parameter Mean (CV%)	Fed Conditions	Fasted Conditions	Ratio Estimates[b] and 90% CI
C_{max} (ng/mL)	302.3 (36)	62.6 (51)	5.0 [4.24 –5.88]
t_{max} (h)[a]	3.0	4.5	p=0.460
AUC_{last} (ng.h/mL)	2225 (37)	666 (52)	3.5 [3.10 –3.95]
$t_{1/2z}$ (h)	12.4 (14)	13.4 (25)	p=0.679
AUC (ng.h/mL)	2307 (37)	707 (51)	3.4 [3.05 –3.84]

[a] : Median value,
[b] : Ratio fed / fasted, p-value for difference between regimens.

SR35021 exposure was also increased by food (Table 88 and Figure 40).

Figure 40: Mean SR35021 plasma concentration-time profile following dronedarone (800 mg) administration (fed and fasted conditions)

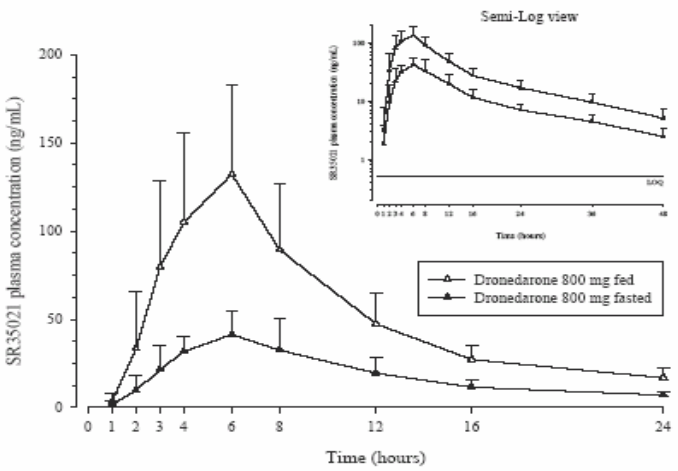


Table 88: Mean (CV %) PK parameters of SR35021 observed after dronedarone administration (800 mg) under fed and fasted conditions

PK Parameter Mean (CV%)	Fed Conditions	Fasted Conditions	Ratio Estimates[b] and 90% CI
C_{max} (ng/mL)	141.0 (29)	42.9 (29)	3.3 [2.79 –3.84]
t_{max} (h)[a]	6.0	6.0	p = 0.133
AUC_{last} (ng.h/mL)	1471 (32)	545 (28)	2.7 [2.43 –2.94]
$t_{1/2z}$ (h)	13.8 (17)	16.2 (27)	p = 0.112
AUC (ng.h/mL)	1575 (32)	607 (27)	2.6 [2.30 –2.87]

[a] : Median value, [b] : ratio Fed/Fasted, p-value for difference between regimens

Metabolic Ratio (SR35021 Pharmacokinetics)

Per the applicant's analyses plan, if a dose-by-compound interaction was absent the metabolic ratio (Rmet) was not evaluated. A dose-by-compound interaction was not

detected for Cmax; in contrast, the Rmet based on AUC decreased as dose increased (Table 89). This finding suggests that a saturable metabolic pathway exists.

Table 89: Metabolic Ratios for AUC and Cmax

PK Parameter	Dose-by-Compound p-value	Contrast	Ratio Estimate and 95% CI
(R_{met}) for C_{max}	0.284	SR35021/SR33589	0.53 [0.47 –0.60]
(R_{met}) for AUC	< 0.0001	SR35021/SR33589 100 mg	1.39 [1.14 –1.70]
		SR35021/SR33589 200 mg	1.14 [0.92 –1.42]
		SR35021/SR33589 400 mg	0.99 [0.79 –1.23]
		SR35021/SR33589 800 mg	0.69 [0.57 –0.85]
		SR35021/SR33589 1200 mg	0.64 [0.52 –0.78]

Applicant's Safety Summary

The tolerability of single oral doses of dronedarone up to 1200 mg was generally satisfactory in Japanese young male healthy subjects. All treatment-emergent adverse events (TEAE) were mild. There were no subjects who discontinued study drug due to TEAEs, and no serious AEs (SAEs) were reported. However, PR- interval (PR) prolongation and low-degree atrio-ventricular (AV) block were observed in 4 out of 6 subjects who received active drug at the 1200 mg dose. These observations appeared to be due to the pharmacological effects of the drug. No torsades de pointes were reported. There appeared to be some dose response with respect to (TEAEs) and no AEs were reported in the placebo group.

Recommendations/Conclusions

The following PK information generated in Study TDU4899 is acceptable for labeling purposes and cross-study or –population comparisons, as appropriate. In general the findings from Study TDU4899 appear quantitatively and qualitatively similar to those in other dronedarone studies.

- Dronedarone absorption is increased in the presence of food relative to the fasted state; the increase in exposure is approximately 3.5-fold for AUC and 5-fold for Cmax
- Dronedarone and SR35021 exhibited similar PK profiles, although the exposure of dronedarone was approximately twice as great as SR35021
- Supra-dose proportional PK were observed for parent drug and metabolite over the 100 to 1200 mg dose range. The relative increase of Cmax, AUClast and AUC estimated as function of a 2- fold increase of the dose, were between 2.5 and 4.2 with parent drug and between 2.4 and 3.3 with metabolite.
- The metabolic ratio based on AUC decreases when the dose increases: Rmet = 1.4 at 100 mg and Rmet = 0.6 at 1200 mg.

APPENDIX to Study TDU4899

Standard Breakfast Meal

MENU	Intake Volume (g)	Energy (Kcal)	Nutritive Value			
			Water (g)	Protein (g)	Lipids (g)	Carbohydrate (g)
Roll bread	105.0	293.0	36.8	9.2	5.4	51.9
Butter	8.0	60.0	1.3	0.0	6.5	0.0
Strawberry jam	14.0	37.0	4.4	0.1	0.0	9.4
Boiled egg	50.0	76.0	38.0	6.0	5.1	0.4
Apple juice	160.0	67.0	141.1	0.3	0.0	18.2
Total	337.0	533.0	221.6	15.6	17.0	79.9

4.2.11 Study on the tolerability of SR33589B given as a single ascending dose administered intravenously in healthy male subjects (TDU3007).

PROTOCOL #	TDU3007
INVESTIGATOR	Dr. W. Tetzloff
STUDY SITE	iphar, Institut für Klinische Pharmakologie GmbH, Arnikastrasse 4, D - 85635 Höhenkirchen- Siegertsbrunn, Germany
STUDY PERIOD	May to August 1997

Objectives (per applicant)

- To assess the local and general tolerability of single intravenous doses of SR33589B in healthy male subjects
- To evaluate the effect of single intravenous doses of dronedarone on electrocardiogram parameters, and to assess the pharmacokinetic profile of SR33589 and its N- debutyl metabolite, SR35021, after single intravenous administration.

Reviewer's Note

This review focuses on dronedarone pharmacokinetics; the efficacy information will not be reviewed in detail because IV administration is not being considered in this NDA.

Study Design

This was a randomized, placebo-controlled, double-blind, parallel group and ascending dose study. A thirty minute dronedarone infusion was given to healthy male volunteers. Each subject received a single intravenous administration of either dronedarone (10, 20, 40, 60 or 80 mg) or placebo.

Subject Demographics

Subject demographics are presented in Table 90.

Formulation (2E3 Formulation)

- Dronedarone solution for IV infusion, vials containing 4 mg/ml batch No. 96-00681
- Placebo solution for IV infusion, batch No. 96-00683

Pharmacokinetic blood sampling times

Blood samples were collected before the infusion (T0) and at 10, 20, 30 (= end of infusion), 40 , and 50 minutes, and at 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after drug administration.

Pharmacokinetics

The following pharmacokinetic measures were determined:
Dronedarone: Cmax, tmax, Cend , AUClast, AUC, $t_{½}$, CL and Vz
SR35021: Cmax, tmax, AUClast, $t_{½}$, and AUC

Table 90: Subject Demographics in Study TDU3007

Characteristics (units)	Dose (n)	Mean ± SD	Minimum	Maximum
Age (years)	10 mg (n = 3)	27.7 ± 6.0	22	34
	20 mg (n = 3)	34.3 ± 6.0	28	40
	40 mg (n = 6)	30.8 ± 6.2	23	37
	60 mg (n = 6)	33.8 ± 4.9	25	38
	80 mg (n = 6)	32.5 ± 5.2	23	38
	Placebo (n = 8)	31.9 ± 6.1	22	39
Height (cm)	10 mg (n = 3)	75.9 ± 2.7	72.9	78.2
	20 mg (n = 3)	77.7 ± 5.9	72.0	83.8
	40 mg (n = 6)	79.7 ± 8.7	67.9	88.9
	60 mg (n = 6)	79.5 ± 6.1	69.4	84.9
	80 mg (n = 6)	79.2 ± 6.2	69.5	86.0
	Placebo (n = 8)	75.5 ± 4.4	69.4	82.8
Weight (kg)	10 mg (n = 3)	183.3 ± 7.2	175	188
	20 mg (n = 3)	178.7 ± 7.5	170	183
	40 mg (n = 6)	182.3 ± 4.9	176	188
	60 mg (n = 6)	179.8 ± 4.6	172	186
	80 mg (n = 6)	178.8 ± 6.4	168	184
	Placebo (n = 8)	178.9 ± 6.3	173	190

Bioanalytical Methods

Plasma concentrations of dronedarone and SR35021 were analyzed by a validated LC/MS/MS method. The assay performance was acceptable as shown in Table 91.

Table 91: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.996$	Satisfactory
Between day precision	CVs were < 7 %	Cannot be assessed
Between day accuracy	The QC samples were within 5 % of the nominal concentrations	Acceptable
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.996$	Satisfactory
Between day precision	CV data were not provided	Cannot be assessed
Between day accuracy	The QC samples were within 3 % of the nominal concentrations	Acceptable
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

*The validation report included chromatograms that demonstrate assay specificity

Pharmacodynamics (Activity)

Changes in electrocardiogram measures such as PR and QTc prolongation, and the number of abnormal transition ST-T changes were determined.

Results

The plasma concentration time profiles for dronedarone following IV administration are depicted in Figure 41.

The pharmacokinetic parameters of dronedarone after single intravenous administration of dronedarone (10 to 80 mg) are summarized in Table 92. These data indicate that:

- Dronedarone exhibits approximately linear kinetics following IV administration over the 10 to 80 mg dose range
- The volume of distribution with dronedarone doses ≥ 40 mg is ~ 2500 to 3500 L

Figure 41: Mean dronedarone plasma concentration time profile following IV administration (30 minute infusion)

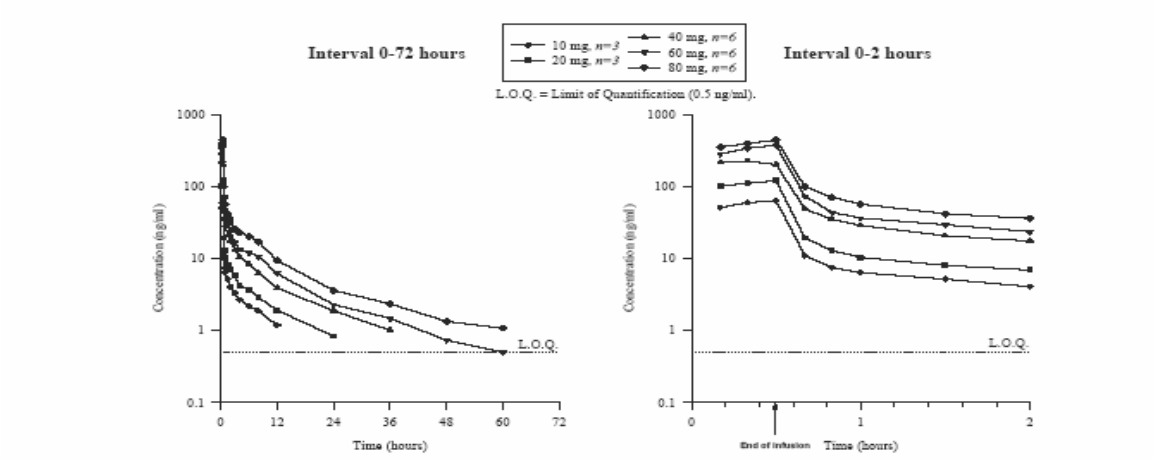


Table 92: Dronedarone PK Measures Following IV Administration

Parameters (units)	Statistics	Dose (mg) of dronedarone administered				
		10 (n = 3)	**20** (n = 3)	**40** (n = 6)	**60** (n = 6)	**80** (n = 6)
C (ng/ml)	Mean	63.0	120.4	253.0	374.2	470.1
	SD	9.4	24.3	46.5	112.3	127.2
	CV%	15	20	18	30	27
t (h)	Mean	0.50	0.45	0.33	0.44	0.44
	SD	0.00	0.09	0.15	0.09	0.09
	CV%	0	20	44	20	20
C_{end} (ng/ml)	Mean	63.0	98.9	200.3	373.2	441.1
	SD	9.4	47.1	35.4	111.4	151.0
	CV%	15	48	18	30	34
AUC_{last} (ng h/ml)	Mean	62.0	127.5	287.5	433.1	619.2
	SD	7.5	22.7	55.9	52.5	137.0
	CV%	12	18	19	12	22
$t_{½}$ (h)	Mean	6.9	10.5	13.0	15.8	18.4
	SD	1.8	1.6	3.1	3.3	3.3
	CV%	25	15	24	21	18
AUC (ng h/ml)	Mean	70.7	136.2	299.2	448.4	638.2
	SD	6.2	24.5	57.3	52.7	142.2
	CV%	9	18	19	12	22
V_Z (l)	Mean	1398	2240	2500	3104	3436
	SD	240	237	149	812	808
	CV%	17	11	6	26	24
CL (l/h)	Mean	142	150	138	136	132
	SD	13	30	25	19	34
	CV%	9	20	18	14	26

The plasma concentration time profile of SR35021 following administration of dronedarone is depicted in Figure 42. Pharmacokinetic parameters of SR35021 for the three highest doses of dronedarone in the healthy male subjects are shown in Table 93. The pharmacokinetic parameters

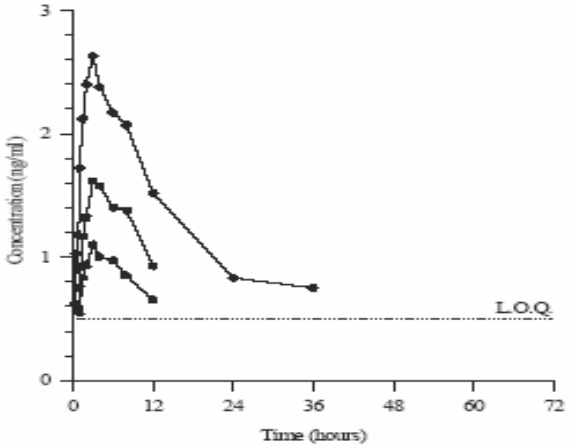
of SR35021 after single intravenous administration of the 10 and 20 mg doses could not be assessed due to low plasma concentrations.

Table 93: SR35021 PK measures following IV dronedarone administration

Parameters	Statistics	Dose (mg) of dronedarone administered		
		40 (n = 6)	**60** (n = 6)	**80** (n = 6)
C max (ng/ml)	Mean ± SD	1.2 ± 0.4	1.7 ± 0.7	2.8± 0.3
t max (h)	Mean SD	3.08 ± 1.56	4.00 ± 2.00	3.00 ± 0.63
AUClast (ng h/ml)	Mean SD	13.2 ± 4.5	28.5 ± 15.7	52.5 ± 9.8
t½ (h)	Mean SD	21.4 N/A	29.8 N/A	26.1* 6.7
AUC (ng h/ml)	Mean	32.7	69.1	75.7 ± 15.4*

*: n = 3
N/A: not applicable; n = 2

Figure 42: SR35021 Plasma Concentration Time Profile following IV Administration of Dronedarone



Applicant's Activity Highlights

According to the applicant, the exploratory activity analysis of the ECG parameters PR-interval and QTc showed a prolongation of these parameters, which is consistent with the expected electrophysiological profile of dronedarone after administration of dronedarone. There was a significant increase from baseline in the maximum PR- interval and maximum QTc within the 40 to 80 mg dose groups. There was also an increase in the maximum QTc in comparison to placebo at the 20 and 40 mg dose levels.

Reviewer's Note on Activity

As noted previously, this review focuses on the PK data rather than the PD or activity data because IV administration is not currently being considered. However, the activity findings tend to support the applicant's use of dronedarone as an anti-arrhythmic agent.

Applicant's Safety Highlights

Half of the subjects complained of injection site reactions or local pain. The highest incidence was at the 40 mg and 60 mg dose levels (five of six and four of six subjects, respectively). Only one subject complained of local reactions when placebo was administered. The systemic tolerability was good, laboratory tests, vital signs, electrocardiograms, and telemetric evaluations showed no clinically relevant deviations from baseline.

Conclusions/Recommendations

The following findings from Study TDU3007 are appropriate for labeling as appropriate

- After intravenous administration, Cmax and AUC of SR33589 increase in a dose-proportional manner over the 10 to 80 mg dronedarone dose range; this finding suggests that dronedarone exhibits linear kinetics following IV administration. The linearity was supported by the relative constant clearance over the studied dose range: CL = 132- 150 L/h
- The accuracy of the half-life estimates for the lower doses (10 and 20 mg was unclear) due to the low plasma concentrations observed in the terminal phase relative to LOQ. Based on the higher doses the mean $t_{1/2}$ following IV administration is ~ 13 to 18 hours. The volume of distribution estimates may have also been affected by the lack of assay sensitivity. Using the highest studied doses the Vz is ~ 2500 – 3500 L
- SR35021 was only measurable for the 40 mg dose of dronedarone and above. SR35021 appeared to exhibit dose proportional kinetics with respect to Cmax, but the increase of AUC last was more than dose proportional.

4.2.12 Study on the tolerability of SR33589B given as a single and multiple oral doses in healthy male subjects under non fasted conditions (TDR2395).

PROTOCOL #	TDR2395
INVESTIGATOR	Dr. W. Tetzloff
STUDY SITE	iphar, Institut für Klinische Pharmakologie GmbH, Arnikastrasse 4, D - 85635 Höhenkirchen- Siegertsbrunn, Germany
STUDY PERIOD	March to August 1996

Objectives (per applicant)

- to evaluate the tolerability of SR33589B (dronedarone) after single (one day) and multiple oral doses of 400 mg, 600 mg, 800 mg or 1000 mg twice daily, and 800 mg, 1200 mg, 1600 mg or 2000 mg once daily given for 14 days under fed conditions in healthy male subjects.
- to evaluate the pharmacokinetics and pharmacodynamics of dronedarone after single and multiple dosing.

Reviewer Note

This review focuses on the 14-day multiple dose PK and PD information: other studies address the single dose data and 7-day PK information is comparable to 14-day PK information.

Study Design

This was an ascending dose, double-blind, randomized, placebo-controlled (at each dose level) sequential group study. The following dronedarone doses were administered: 400, 600, 800 or 1000 mg twice daily, and 800, 1200, 1600 or 2000 mg once daily. Treatments lasted for 15 days: one single dose (Day 2) followed by 14-days of repeated dose (Days 5 to 18). There was a wash-out period on Days 3 and 4.

Subject Demographics

Subject demographics are presented in Table 94. Only male Caucasian subjects participated in the study. The total number of subjects included in the study was 52. Eight subjects withdrew from the study prematurely. The number of subjects who completed the study per treatment group was: placebo 11, dronedarone 800 mg QD six, dronedarone 400 mg BID six, dronedarone 1200 mg QD six, dronedarone 600 mg BID five, dronedarone 1600 mg QD six and dronedarone 800 mg BID four.

Formulation (2E3 Formulation)

- Dronedarone 200 mg capsules; batch number M304S
- Dronedarone placebo capsules; batch number M274G

Pharmacokinetic sampling times

Blood samples were collected at the following times:

- pretreatment and at 1, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours post- treatment for the single dose administration
- pretreatment and at 1, 2, 2.5, 3, 4, 5, 6, 8, 12, 16 and 24 hours after the 7- day repeated administration

- pretreatment and at 1, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours after the 14-day repeated administration.

Table 94: Subject Demographics in Study TDR2395

Parameter (units)	Treatment Group	n	Mean	SD	Minimum	Maximum
Age (years)	Placebo	12	31.4	4.4	25	38
	800 mg o.d.	9	29.1	5.5	22	39
	400 mg b.i.d.	7	29.4	5.4	25	38
	1200 mg o.d.	6	29.8	4.7	23	36
	600 mg b.i.d.	6	25.7	2.4	23	29
	1600 mg o.d.	6	28.7	4.1	24	35
	800 mg b.i.d.	6	27.3	5.4	21	33
Weight (kg)	Placebo	12	74.0	6.8	67.5	88.4
	800 mg o.d.	9	78.2	6.3	68.9	88.6
	400 mg b.i.d.	7	75.3	5.5	67.8	85.4
	1200 mg o.d.	6	76.4	6.3	65.2	84.0
	600 mg b.i.d.	6	73.9	5.9	65.1	82.6
	1600 mg o.d.	6	74.9	1.4	72.8	76.9
	800 mg b.i.d.	6	76.0	4.1	71.3	81.2
Height (cm)	Placebo	12	179.5	4.5	173	186
	800 mg o.d.	9	180.7	6.7	172	192
	400 mg b.i.d.	7	177.9	8.6	171	195
	1200 mg o.d.	6	180.7	4.8	175	189
	600 mg b.i.d.	6	180.5	5.2	175	189
	1600 mg o.d.	6	178.7	4.1	173	185
	800 mg b.i.d.	6	180.0	4.6	173	185

Pharmacokinetics

The following dronedarone and SR35021 pharmacokinetic measures were determined: $AUC_{0\text{-}12h}$ (for BID regimens), $AUC_{0\text{-}24h}$ (for QD regimens), Cmax, Cmin and tmax of dronedarone and SR35021 after single dose (Day 2) administration and 7-days (Day 11) and 14-days (Day 18) repeated dose administration.

Bioanalytical Methods

Plasma was assayed for dronedarone and its N-debutyl metabolite, SR35021, using HPLC method with UV detection. The assay performance was acceptable:

- limit of quantification was 5 ng/ml for both compounds
- CV < 10 % for SR35021 and CV < 11 % for dronedarone
- Relative bias between -3 to 2 % of nominal concentration for SR35021 and relative bias between -1 to 5 % of nominal concentration for dronedarone
- Chromatograms were not provided, but assay validation report includes chromatograms indicating assay specificity

Pharmacodynamics (Activity)

Activity: The effect of dronedarone on the electrocardiogram parameters: HR, PQ, QRS, QT and QTc intervals and T-wave amplitude. Exercise tests were conducted to assess a possible anti-adrenergic effect of dronedarone on dynamic, exercise induced tachycardia.

Analyses

<u>Pharmacokinetics</u>

The applicant conducted several standard pharmaco-statistical analyses to evaluate:

- Dose, day and dose by day effects (ANOVA).

- Time to reach steady state by comparing Study Day 18 versus Day 11 $AUC_{0\text{-}tobs}$ values, and plasma concentrations before treatment during the repeated dose phase of the study.
- Dose proportionality (power model)
- Regimen comparison- BID vs. QD (Log Regression)

Activity (Pharmacodynamics)
Several activity measurements were determined under resting and exercise conditions:

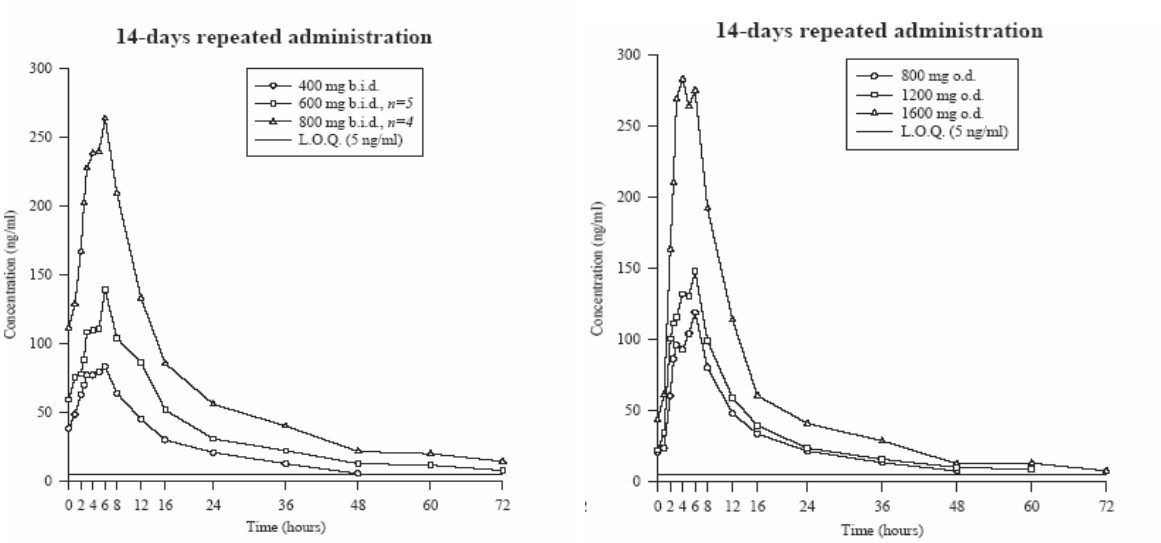
- Resting conditions
  - ECG changes from baseline and changes from Day 1 for the daily mean and the daily pretreatment (T0) values (ANOVA).
  - Analyses of the data from the multiple dose phase of the study (mixed effects modeling)
  - Daily maximum change for Days 2 and 18.
  - Dronedarone dose group compared with placebo group (ANOVA)
- Exercise tests
  - ECG and vital sign changes from pre to post-exercise
  - Daily mean for each subject was calculated.
  - Changes from Day 1 for the daily mean and the daily mean pretreatment (T0) values (mixed effects modeling)

Results

Dronedarone PK

The plasma concentration time profiles for dronedarone following single and multiple dose oral administration are depicted in Figure 43 (BID and QD).

Figure 43: Mean dronedarone plasma concentration-time profiles following BID and QD dronedarone dosing



Reviewer Note: Data available for PK analyses

It should be noted that not all subjects completed the study; therefore the number of subjects in each dose group was ≤ 6 (as shown in left panel of preceding figure). This review includes PK data from subjects who completed the study (14 days of dosing) and single dose data are presented for comparisons.

The mean (SD) PK parameters of dronedarone after repeated administration of dronedarone 400, 600 or 800 mg BID and 800, 1200 or 1600 mg QD are shown in Table 95.

Table 95: Dronedarone PK measures following administration of various dronedarone dosages

Parameter (units)	Dose Administered					
	400 mg BID	600 mg BID[a]	800 mg BID[b]	800 mg QD	1200 mg QD	1600 mg QD
14-Days Repeated Dose						
Cmax (ng/ml)	92.6 (28.8)	155.6 (71.5)	277.2 (59.3)	126.0 (35.3)	176.4 (87.7)	353.0 (164.3)
tmax (h)	4.85 (1.62)	4.80 (1.79)	5.13 (1.75)	5.50 (1.22)	4.58 (1.63)	4.33 (2.25)
Cmin (ng/ml)	37.5 (16.5)	53.3 (12.2)	106.3 (23.4)	20.1 (10.6)	21.7 (10.7)	39.1 (13.3)
$AUC_{0\text{-}12h}$ (ng h/ml)	768.6 (270.5)	1201.0 (401.5)	2346.8 (594.9)	N/A	N/A	N/A
$AUC_{0\text{-}24h}$ *(ng h/ml)	1537.2 (541.0)	2402.0 (803.0)	4693.6 (1189.8)	1294.2 (457.9)	1617.7 (853.7)	3033.4 (1180.1)
$T_{1/2}$ (h)	21.56 (9.96)	28.29 (6.19)	23.97 (4.45)	20.31 (3.03)	24.98 (13.56)	29.90 (21.76)

†For BID regimen, *$AUC0\text{-}_{24h}$ was estimated by 2 x AUC0-12h or BID regimen
n = 6 except for [a]n = 5, [b]n = 4
N/A = not applicable

Table 96: Dronedarone PK measures following single dose administration of dronedarone at different doses

Parameter (units)	Dose Administered					
	400 mg b.i.d.	600 mg b.i.d.[a]	800 mg b.i.d.[b]	800 mg o.d.	1200 mg o.d.	1600 mg o.d.
Single Dose						
C_{max} (ng/ml)	33.3 (11.1)	64.3 (19.1)	77.1 (30.5)	76.2 (34.8)	154.3 (72.0)	211.0 (34.4)
t_{max} (h)	3.67 (1.21)	3.10 (1.64)	4.38 (1.89)	4.92 (1.69)	5.26 (1.40)	5.17 (1.60)
AUC† (ng.h/ml)	183.2 (74.5)	303.7 (66.0)	395.7 (143.9)	514.2 (211.4)	1163.1 (481.4)	1497.0 (236.3)
AUC_{last} (ng.h/ml)	188.6 (83.2)	329.4 (77.9)	474.0 (231.9)	539.0 (221.1)	1288.4 (590.5)	1654.8 (181.2)

n = 6 except for [a]n = 5, [b]n = 4

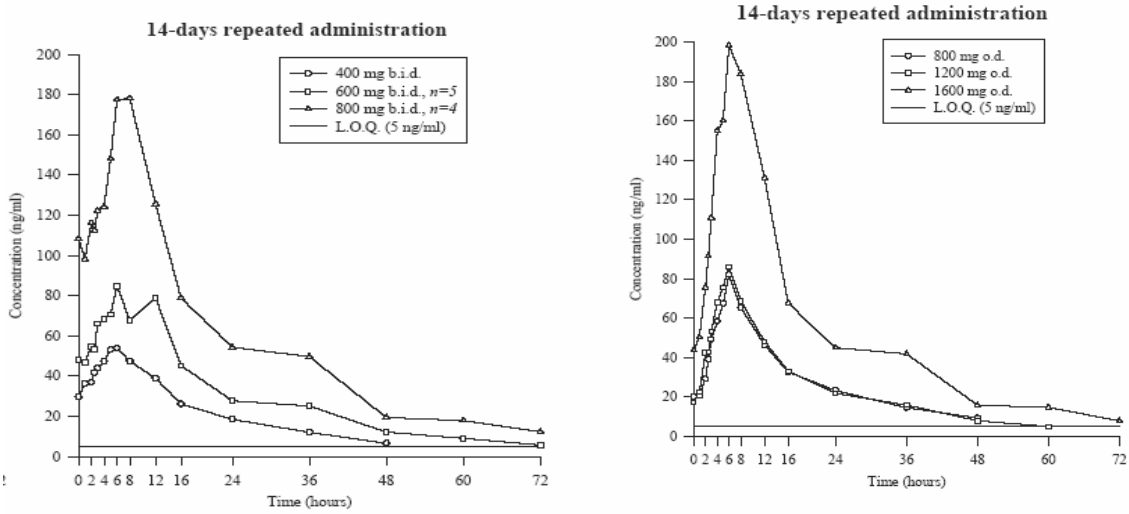
The following general observations can be made from the PK data:

- Tmax comparable across all dosage (mean and median ~ 5 hr)
- For the same total daily dose, as expected Cmin for BID dosing higher than QD dosing
- There is approximately 3 – 4 fold accumulation (14 Days vs. 1 Day, single Dose)
- Greater than proportional increases in exposure with increasing dose

SR35021 PK

The plasma concentration time profiles for dronedarone following single and multiple dose oral administration are depicted in Figure 44 (BID and QD).

Figure 44: Mean SR35021 plasma concentration time profile following administration of dronedarone



The mean (SD) PK parameters of SR35021 after repeated administration of dronedarone 400, 600 or 800 mg BID and 800, 1200 or 1600 mg QD are shown in Table 97 .

Table 97: SR35021 PK Measures Following Administration of various dronedarone doses

Parameter (units)	Dose Administered					
	400 mg BID	600 mg BID[a]	800 mg BID[b]	800 mg QD	1200 mg QD	1600 mg QD
Single Dose						
C_{max} (ng/ml)	27.8 (10.7)	33.8 (9.4)	47.7 (17.2)	53.6 (21.9)	84.2 (45.1)	135.6 (62.9)
t_{max} (h)	5.00 (1.55)	4.40 (1.52)	4.50 (1.73)	5.50 (0.84)	5.42 (1.43)	5.42 (1.43)
$AUC_{\dagger}$ (ng.h/ml)	156.0 (50.7)	204.7 (40.6)	265.8 (103.6)	442.5 (210.9)	744.1 (316.2)	1213.7 (602.5)
AUC_{last} (ng h/ml)	181.0 (76.7)	230.9 (75.3)	382.5 (215.7)	497.7 (261.0)	935.4 (444.8)	1451.9 (773.2)
14-Days Repeated Dose						
C_{max} (ng/ml)	60.7 (18.4)	92.4 (37.7)	192.7 (77.8)	86.5 (33.8)	87.1 (45.9)	211.7 (160.8)
t_{max} (h)	5.85 (0.42)	6.40 (3.29)	4.75 (3.95)	5.83 (0.41)	5.83 (0.41)	6.00 (1.26)
C_{min} (ng/ml)	29.0 (13.0)	40.4 (6.4)	83.4 (21.0)	18.7 (10.1)	17.1 (8.6)	39.2 (17.7)
AUC_{0-12h} (ng h/ml)	533.8 (172.1)	815.4 (254.7)	1711.2 (575.7)	N/A	N/A	N/A
AUC_{0-24h} * (ng h/ml)	1067.6 (344.2)	1630.8 (509.4)	3422.4 (1151.4)	1030.2 (453.1)	1082.2 (546.0)	2531.2 (711.6)

* For BID regimens, AUC_{0-24} was calculated by AUC_{0-12} x 2

The SR35021 PK exhibited similar trends as dronedarone and will not be addressed further in this review, as the PK assessment for SR35021 has been addressed in other studies.

Pharmacodynamics (Activity)
Several PD measures were determined in this study; the changes in these measures with respect to dronedarone dose are summarized in the following tables and figures, as appropriate.

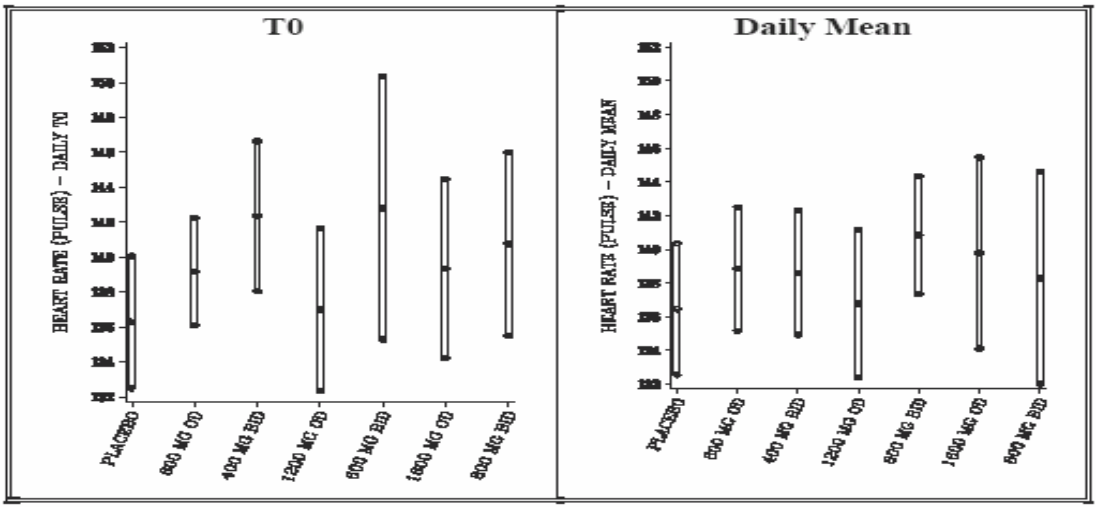
Reviewer Note
PD information was included for resting and exercise conditions. This review will focus on daily mean PD values, rather than values at specific time points, such as T0 because they had lower variability than PD measures obtained at T0 or other specific time points. Additionally, only PD data from the multiple dose phase were considered as they are the most clinically relevant. The most consistent results were obtained from the exercise tests.

Synopsis of Resting Conditions
In general, the PD data were highly variable; salient findings are summarized as follows.

- Heart Rate (HR): compared to placebo, the 1200 mg QD dose decreased the daily mean HR by -8.6 bpm (95 % confidence interval boundaries, -13.08, -3.24)
- PR Interval: compared to placebo, the 600 mg BID, 1200 mg QD and 1600 mg QD doses increased the mean PR interval; the maximal mean increase was 22.6 ms
- QT interval: compared to placebo, the 600 and 800 mg BID and 1200 and 1600 mg QD doses increased QT; the range of increase was 33 to 50 ms
- QTc interval: compared to placebo, the 1600 QD and 800 BID doses increased QTc by approximately 16 ms
- QRS interval: there were no differences for any of the treatments groups compared to placebo
- T-wave amplitude: compared to placebo, the 600 mg BID, 1600 mg BID, and 800 mg BID decreased the mean T-wave amplitude

Exercise Tests
The mean baseline values in exercise tests were variable among doses; however, the variability was minimized by correcting for baseline values. The variability in data is illustrated in the heart rate values at baseline for T0 and overall daily mean (Figure 45). TDD equals total daily dose.

Figure 45: Mean Heart Rate at T0 and overall daily mean with 95 % confidence interval at baseline



HR

The changes in heart rate during the exercise test are summarized in Figure 46 and Table 98.

Figure 46: Change in Daily Heart Rate as a function of dose during exercise test

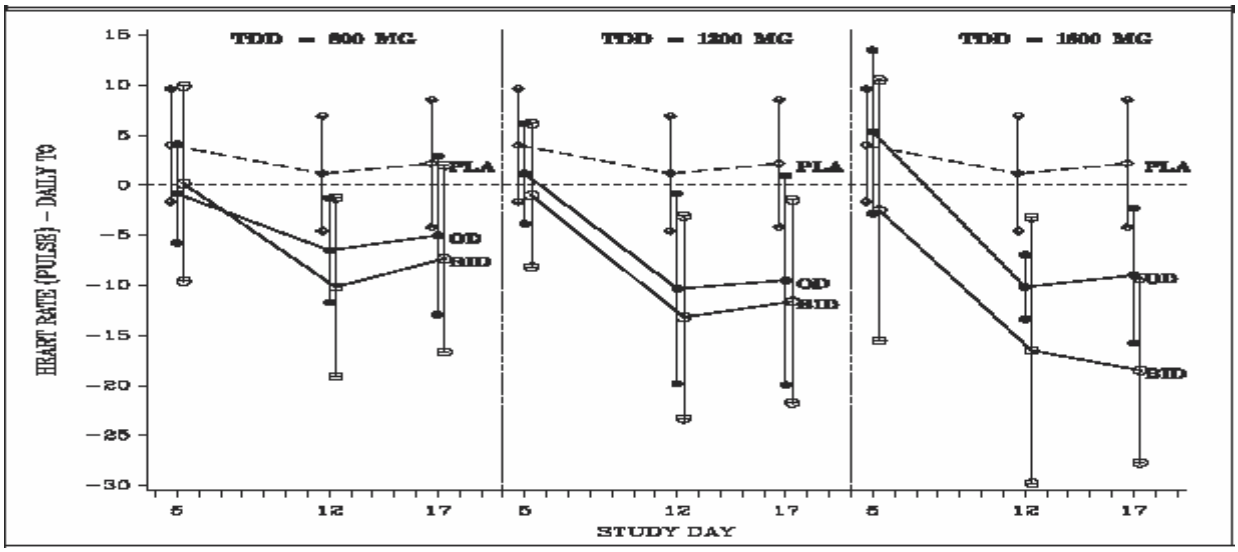


Table 98: Pairwise Comparisons (Day 12 to Day 17) of Heart Rate obtained during Exercise Test for Various dronedarone doses

Drug Dose vs. Placebo			QD vs. BID		
Dose (mg) Regimen	**Mean (95% CI)**	**p-value**	**Dose (mg) Regimen**	**Mean (95% CI)**	**p-value**
800 QD	-7.43 (-15.39, 0.53)	0.066	800 QD vs. 400 BID	3 (-6.05, 12.05)	0.506
400 BID	-10.43 (-18.39, -2.47)	0.012	1200 QD vs. 600 BID	2.48 (-7.01, 11.98)	0.599
1200 QD	-11.6 (-19.56, -3.64)	0.005	1600 QD vs. 800 BID	7.92 (-2.2, 18.04)	0.121
600 BID	-14.08 (-22.54, -5.63)	0.002	**TDD vs. Placebo**		
1600 QD	-11.27 (-19.22, -3.31)	0.007	800 TDD	-8.93 (-15.48, -2.39)	0.009
800 BID	-19.18 (-28.34, -10.03)	<0.001	1200 TDD	-12.84 (-19.54, -6.14)	<0.001
			1600 TDD	-15.22 (-22.15, -8.3)	<0.001

The HR comparisons indicate that all tested dronedarone dosages, apart from 800 mg QD, lowered HR to a greater extent than placebo. Additionally, administration of dronedarone as a daily divided dose produced a numerically greater decrease in HR than a single dose; this finding suggests that once twice daily dosing may be more effective than once daily dosing in controlling or decreasing HR. There also appeared to be a linear dose-response, as greater HR reduction was obtained with increasing dose. This bradycardic effect during exercise may be related to the antiadrenergic (Class II) properties of the drug.

PR Interval

The changes in PR during the exercise test are summarized in Figure 47 and Table 99.

The PR interval comparisons indicate that BID dronedarone dosages prolonged PR to a greater degree than placebo. There were no differences between BID and QD regimens, but in general administration of dronedarone as daily divided dose produced a numerically greater increase in PR interval than a single dose. This finding suggests that twice daily dosing may be more

effective than once daily dosing in increasing the PR interval or affecting a change in an electrophysiological (EP) parameter. There also appeared to be a linear dose-response with respect to BID dosing but not with QD dosing. The PR effect was probably related to the Class II and/or Class IV effects of the drug.

Figure 47: Change in post-exercise PR interval followiong dronedarone administration

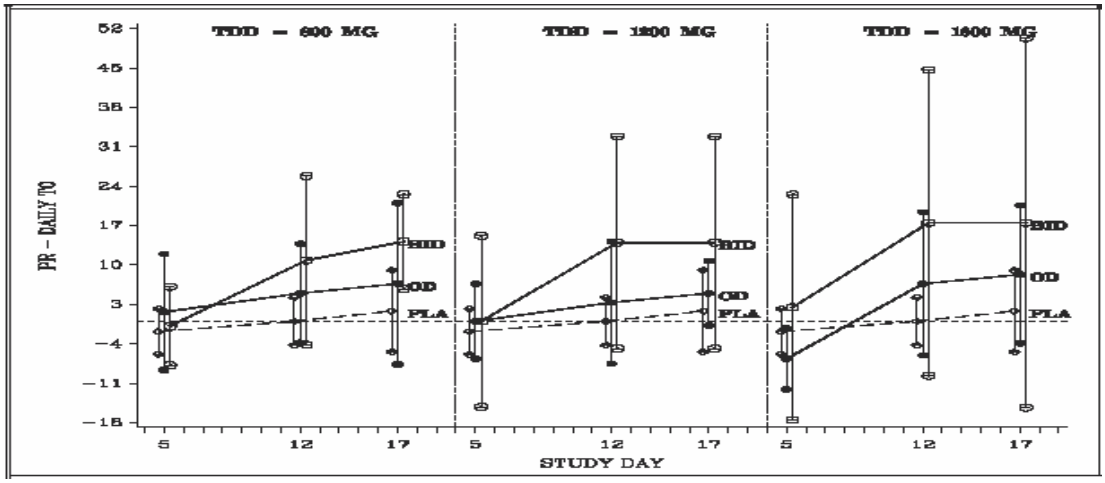


Table 99: Pairwise Comparisons (Day 12 to Day 17) of PR interval obtained during Exercise Test for Various dronedarone doses

Drug Dose vs. Placebo			QD vs. BID		
Dose (mg) Regimen	**Mean (95% CI)**	**p-value**	**Dose (mg) Regimen**	**Mean (95% CI)**	**p-value**
800 QD	4.92 (-6.36, 16.2)	0.382	800 QD vs. 400 BID	-6.67 (-19.5, 6.17)	0.299
400 BID	11.59 (0.31, 22.87)	0.044	1200 QD vs. 600 BID	-9.83 (-23.29, 3.63)	0.147
1200 QD	3.26 (-8.02, 14.54)	0.562	1600 QD vs. 800 BID	-10 (-24.35, 4.35)	0.166
600 BID	13.09 (1.1, 25.08)	0.033	**TDD vs. Placebo**		
1600 QD	6.59 (-4.69, 17.87)	0.244	800 TDD	8.26 (-1.02, 17.54)	0.079
800 BID	16.59 (3.61, 29.57)	0.014	1200 TDD	8.17 (-1.32, 17.67)	0.089
			1600 TDD	11.59 (1.77, 21.41)	0.022

QT Interval

The changes in QT interval during the exercise test are summarized in Figure 48 and Table 100.

Figure 48: Changes in QT interval during the exercise test

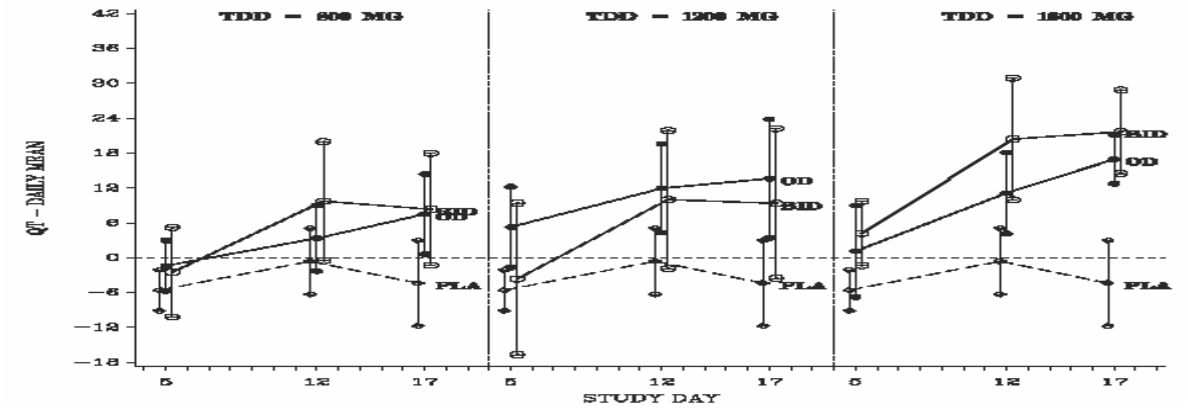


Table 100: Pairwise Comparisons (Day 12 to Day 17) of QT interval obtained during Exercise Test for Various dronedarone doses

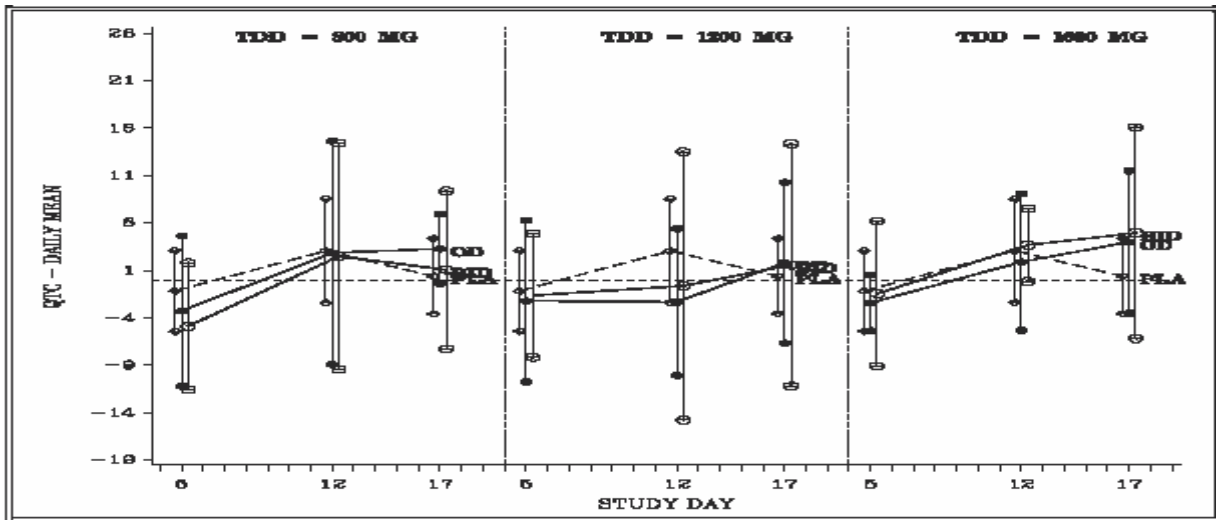
Drug Dose vs. Placebo			QD vs. BID		
Dose (mg) Regimen	**Mean (95% CI)**	**p-value**	**Dose (mg) Regimen**	**Mean (95% CI)**	**p-value**
800 QD	7.92 (0, 15.84)	0.050	800 QD vs. 400 BID	-3.61 (-12.62, 5.4)	0.422
400 BID	11.53 (3.61, 19.45)	0.005	1200 QD vs. 600 BID	3.11 (-6.34, 12.56)	0.509
1200 QD	15.28 (7.36, 23.2)	<0.001	1600 QD vs. 800 BID	-7.01 (-17.09, 3.06)	0.167
600 BID	12.17 (3.75, 20.58)	0.006	**TDD vs. Placebo**		
1600 QD	16.53 (8.61, 24.45)	<0.001	800 TDD	9.72 (3.21, 16.24)	0.005
800 BID	23.54 (14.43, 32.65)	<0.001	1200 TDD	13.72 (7.05, 20.39)	<0.001
			1600 TDD	20.03 (13.14, 26.93)	<0.001

The QT interval comparisons indicate that all tested dronedarone dosages increased QT interval relative to placebo. Additionally, administration of dronedarone as daily divided doses tended to produce a numerically greater increase in QT interval than a single dose; this finding suggests that once twice daily dosing may be more effective than once daily dosing in increasing the QT interval or affecting a change in an electrophysiological (EP) parameter. There also appeared to be a linear dose-response with respect to both the BID and QD dosing regimens. The QT prolongation is probably related to the Class III effects of dronedarone.

QTc Interval

The changes in QTc interval during the exercise test are summarized in Figure 49 and Table 101.

Figure 49: Changes in QTc interval during the exercise test



The QTc interval comparisons indicate that all tested dronedarone dosages have similar effects on the QTc interval as placebo.

Table 101: Pairwise Comparisons (Day 12 to Day 17) of QTc interval obtained during Exercise Test for Various dronedarone doses

Drug Dose vs. Placebo			o.d. vs. b.i.d.		
Dose (mg) Regimen	Mean (95% CI)	p-value	Dose (mg) Regimen	Mean (95% CI)	p-value
800 o.d.	1.34 (-6.08, 8.76)	0.716	800 o.d. vs. 400 b.i.d.	1.29 (-7.15, 9.73)	0.758
400 b.i.d.	0.05 (-7.37, 7.47)	0.989	1200 o.d. vs. 600 b.i.d.	-0.73 (-9.58, 8.12)	0.868
1200 o.d.	-1.99 (-9.41, 5.43)	0.590	1600 o.d. vs. 800 b.i.d.	-1.37 (-10.8, 8.07)	0.771
600 b.i.d.	-1.26 (-9.15, 6.62)	0.748	TDD vs. Placebo		
1600 o.d.	1.22 (-6.20, 8.64)	0.741	800 TDD	0.70 (-5.41, 6.8)	0.818
800 b.i.d.	2.59 (-5.95, 11.12)	0.543	1200 TDD	-1.63 (-7.87, 4.62)	0.601
			1600 TDD	1.90 (-4.56, 8.36)	0.554

QRS and T-wave Amplitude

Dronedarone administration did not alter the QRS or T-wave amplitude relative to placebo as shown in Table 102 and Table 103.

Table 102: Pairwise Comparisons (Day 12 to Day 17) of QRS interval obtained during Exercise Test for Various dronedarone doses

Drug Dose vs. Placebo			o.d. vs. b.i.d.		
Dose (mg) Regimen	Mean (95% CI)	p-value	Dose (mg) Regimen	Mean (95% CI)	p-value
800 o.d.	-1.36 (-5.8, 3.08)	0.539	800 o.d. vs. 400 b.i.d.	-1.18 (-6.23, 3.87)	0.638
400 b.i.d.	-0.18 (-4.61, 4.26)	0.936	1200 o.d. vs. 600 b.i.d.	-3.03 (-8.32, 2.27)	0.254
1200 o.d.	-1.15 (-5.59, 3.29)	0.603	1600 o.d. vs. 800 b.i.d.	1.39 (-4.26, 7.03)	0.621
600 b.i.d.	1.88 (-2.84, 6.59)	0.425	TDD vs. Placebo		
1600 o.d.	2.6 (-1.84, 7.04)	0.243	800 TDD	-0.77 (-4.42, 2.88)	0.673
800 b.i.d.	1.21 (-3.89, 6.32)	0.633	1200 TDD	0.36 (-3.37, 4.1)	0.844
			1600 TDD	1.91 (-1.96, 5.77)	0.324

Table 103: Pairwise Comparisons (Day 12 to Day 17) of T-wave amplitude obtained during Exercise Test for various dronedarone doses

Drug Dose vs. Placebo			o.d. vs. b.i.d.		
Dose (mg) Regimen	Mean (95% CI)	p-value	Dose (mg) Regimen	Mean (95% CI)	p-value
800 o.d.	30.37 (-91.45, 152.19)	0.616	800 o.d. vs. 400 b.i.d.	-45.28 (-183.86, 93.3)	0.512
400 b.i.d.	75.65 (-46.17, 197.47)	0.216	1200 o.d. vs. 600 b.i.d.	40.14 (-105.2, 185.48)	0.579
1200 o.d.	41.28 (-80.54, 163.09)	0.497	1600 o.d. vs. 800 b.i.d.	37.5 (-117.44, 192.44)	0.627
600 b.i.d.	1.14 (-128.32, 130.6)	0.986	TDD vs. Placebo		
1600 o.d.	10.72 (-111.1, 132.54)	0.859	800 TDD	53.01 (-47.18, 153.2)	0.291
800 b.i.d.	-26.78 (-166.93, 113.37)	0.701	1200 TDD	21.21 (-81.36, 123.77)	0.678
			1600 TDD	-8.03 (-114.04, 97.98)	0.879

Systolic and Diastolic Blood Pressure

Relative to placebo, there were statistically significant decreases in:

- Systolic blood pressure (SBP) at 1200 and 1600 mg once daily doses
- Diastolic blood pressures (DBP) at 1200 mg QD and 600 mg BID doses

There was no dose-response relationship for either of the BP decreases. The observed effect may be related to the vasodilator properties of dronedarone.

Figure 50: Change in systolic blood pressure during Exercise Test

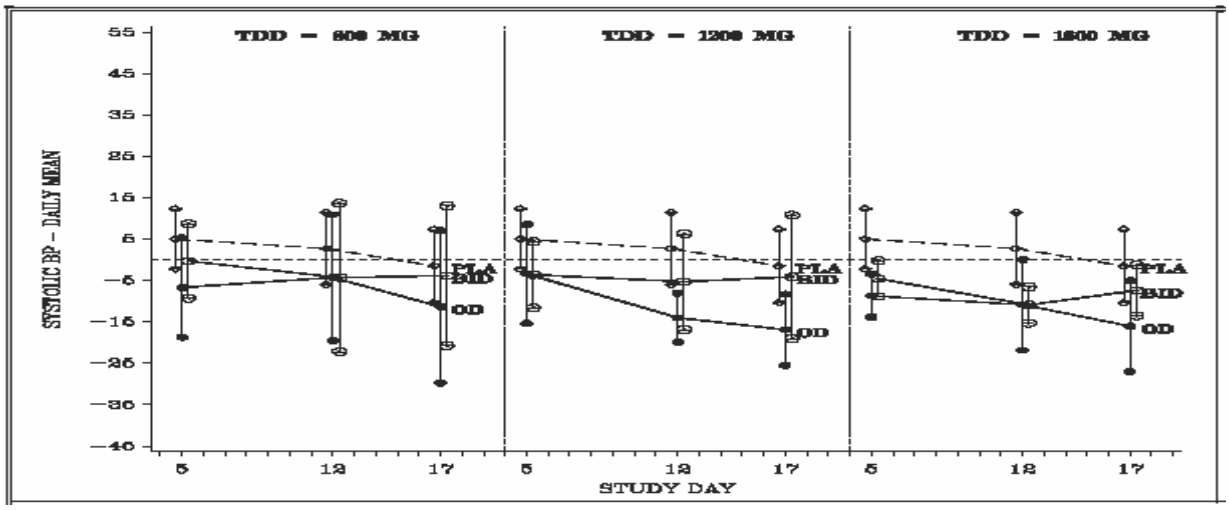
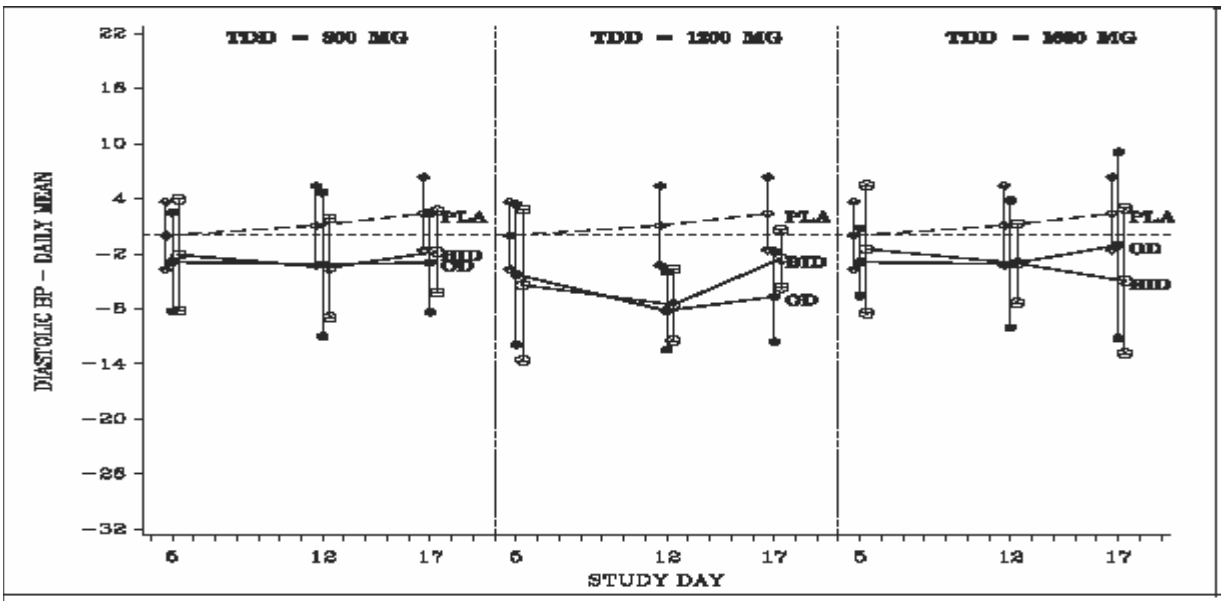


Figure 51: Change in diastolic blood pressure during Exercise Test



Applicant's Safety Analyses

According to the applicant, the investigator unblinded the study before the planned time due to relatively high incidence of adverse events (AEs); consequently, this study was stopped before initiation of the 2000 mg daily dose. Three subjects discontinued the study due to the incidence of severe AEs. The investigator indicated that these three subjects recovered from non-sustained asymptomatic monomorphic ventricular tachycardia without the need of corrective therapy and the relationship to study drug was unknown. Additionally, these severe AEs may have been

related to the prolonged telemetry (three weeks) performed in this study. Three additional subjects were discontinued from the study due to non-serious AEs: two were low degree AV block and the other due to having rash erythematous. Other alterations in ECG or clinical laboratories that were outside the normal range were not considered clinically relevant. No torsades de pointes or sustained episodes of ventricular arrhythmia were reported.

Conclusions/Recommendations

The following findings from Study TDR2395 are acceptable. The main limitation of this study is the lack of information at doses lower than the proposed clinical dose, 400 mg BID. Only one of the dosages evaluated in this study, 400 mg BID, appears clinically relevant, however the additional doses help potentially define the exposure-response relationship.

Pharmacodynamics

- Dronedarone produced a significant bradycardic effect during the exercise test, with a clear dose-response relationship: relative to placebo, the 400 mg dosage decreased heart rate by about 10 bpm. At rest, the bradycardic effect was less clear.
- Dronedarone altered some key electrophysiological measures, particularly during the exercise test. At rest, relatively high doses (1200 and 1600 mg QD) were required to demonstrate a difference between dronedarone and placebo. Two major findings from EP evaluation were:
    1. A dose-response (PR and QT interval) relationship was observed over the 400 mg to 800 mg BID range and 800 to 1600 mg QD range respectively
    2. There was a trend showing that BID dosing had a greater effect than QD dosing on the EP parameters
- Dronedarone caused decreases in 1) SBP at the 1200 and 1600 mg QD dose and 2) DBP at the 1200 mg QD dose and the 600 mg BID dose. There was no clearly dose-related effect in the BP changes.

Overall, the PD effects indicate that dronedarone possesses anti-arrhythmic activity (prolongation of cardiac repolarization) and an ability to decrease heart rate.

Pharmacokinetics

The pharmacokinetics of dronedarone have been fully characterized in other studies; PK data from Study TDR2395 can be used for comparative purposes, but are not needed for product labeling. Some PK highlights from this study are as follows:

- Steady-state was obtained within seven days of repeated administration
- Mean accumulation ratios (Rac) for dronedarone and SR35021 ranged between 1.5 and 3.6 for the QD administration and between 3.4 and 7.6 for the BID administration.
- There was a greater than dose proportional increase in exposure: For a doubling of the dose in the range of doses studies, AUC and Cmax for both SR33589 and SR35021 increased by approximately 2 - 3 fold (slightly greater than proportional).
- For both dronedarone SR35021, tmax (range 3 – 6 hours) appeared independent upon dose regimen, dose level or the day of observation.

4.2.13 Assessing the potential for SR 33589B or amiodarone to inhibit cytochrome P450 (CYP) enzymes using human liver microsomes in vitro (MIH0007)

PROTOCOL #	MIH0007
AUTHOR	William Brian
STUDY SITE	Sanofi Research Division, Malvern, PA, USA
STUDY PERIOD	November 1995

Objectives (per applicant):
To determine if dronedarone inhibits human liver CYP enzymes *in vitro*

Reviewer Note
Although amiodarone was evaluated in this study, this review focuses on the dronedarone results.

Experimental Conditions (Method)
Reagents and compounds were obtained from commercially available sources or as gifts from various companies. Human liver microsomes were obtained from Association of Human Tissue Users (Tucson, AZ).

Reviewer Note on Characteristics of Liver Donors
The majority of the donors used ethanol, tobacco or other CYP enzyme inducer which may have altered the metabolism results quantitatively. However, the use of a control group as reference renders the results useful.

The following CYP probe substrates and inhibitors were used:

Enzyme	Substrate	Inhibitor	Comment
CYP1A2	Phenacetin, 10 µM	furafylline	Acceptable
CYP2C9	Tolbutamide, 50 µM	sulfaphenazole	Acceptable
CYP2C19	Mephenytoin, 100 µM	papaverine	*Inhibitor is not a preferred or acceptable inhibitor, but has been used in literature
CYP2D6	Bufuralol, 50 µM	quinidine sulfate	Acceptable
CYP2E1	Chlorzoxazone, 100 µM	diethyldithiocarbamate	Acceptable
CYP3A4	Nifedipine, 20 µM	ketoconazole	Acceptable

Standard *in vitro* drug-drug interaction conditions were used for the experiment including presence of NADPH generating system and termination of reaction using methods determined for each assay. It is noted that expected concentrations for dronedarone were 0.2 µM based on a single oral dose of 1000 mg. Therefore the conditions for the initial study where dronedarone concentration was 50 µM, do not appear clinically relevant. However, use of the supra-therapeutic concentration is acceptable. The inhibition potential was further characterized by determining the Ki for a given enzyme, if needed. HPLC was used to quantify drug concentrations.

RESULTS
The study results are presented in Table 104. At the 50 µM dronedarone concentration, dronedarone did not affect the enzyme activity of CYP1A2, CYP2C19 or CYP2C9. For CYP2E1, the reliability of the result was unclear because the degree of inhibition (ranged

form 61 to 100 %) did not correlate with the amount of CYP2E1 activity in microsomal preparations. Dronedarone produced greater than 30 % inhibition in the activity of CYP3A4 and 2D6 relative to control group. Consequently, the Ki and type of inhibition for CYP 3A4 and 2D6 were determined. Ki values are summarized in Table 105 and Table 106.

Table 104: Effects of Dronedarone and Amiodarone on CYP Enzymes

CYP	Donor Date	Control[a]	SR33589B[a]	Amiodarone[a]	Inhibitor[a]
CYP1A2[c]	21-Jan-94	216	226 (105)[b]	217 (100)[b]	16 (7)[b]
	9-Jan-94	155	125 (81)	101 (65)	12 (8)
	23-May-94	173	131 (76)	125 (72)	22 (13)
CYP2C9[d]	7-Jan-94	130	110 (85)	108 (83)	10 (8)
	23-May-94	97	81 (84)	79 (81)	11 (12)
	15-Jun-94	87	71 (82)	75 (85)	—
CYP2C19[e]	21-Jan-94	78, 103[i]	84 (107)	86 (83)	16, 33 (21, 32)
	7-Jan-94	33, 35[i]	29 (89)	30 (86)	8, 8 (26, 23)
	28-May-94	38, 39[i]	40 (105)	36 (93)	10, 8 (26, 21)
CYP2D6[f]	7-Jan-94	39	14 (36)	28 (73)	11 (28)
	23-May-94	30	11 (36)	21 (70)	9 (29)
	3-Mar-94	48	12 (25)	30 (62)	7 (15)
CYP2E1[g]	20-May-93	515	312 (61)	235 (46)	146 (28)
	23-May-94	726	735 (101)	378 (52)	236 (32)
	21-Jan-94	1696	1197 (71)	779 (46)	401 (24)
CYP3A4[h]	21-Feb-94	469, 443[i]	258 (55)	486 (110)	26, 26 (6, 6)
	9-Jan-94	392, 419[i]	256 (65)	365 (87)	35, 37 (9, 9)
	23-May-94	327, 311[i]	183 (56)	311 (100)	24, 25 (7, 8)

Values are means of duplicate incubations.

[a] rates are expressed as pmol/mg/min

[b] Rates expressed as % of control values

[c] inhibitor was furafylline

[d] inhibitor was sulfaphenazole

[e] inhibitor was papaverine

[f] inhibitor was quinidine sulfate

[g] inhibitor was diethyldithiocarbamate

[h] inhibitor was ketoconazole

[i] inhibition by SR 33589B or amiodarone was examined in separate experiments; first and second values correspond to experiments with SR 33589B and amiodarone, respectively

— inhibitor was inadvertantly ommitted from reaction mixtures

Table 105: Apparent Ki values for Dronedarone and Amiodarone for bufuralol 1'—hydroxylation (CYP2D6 activity determinant)

	Apparent Ki Values (μM)	
Microsomal Preparation	SR 33589B	Amiodarone
HL 7-Jan-94	4.2	48.2
SD	0.3	4.5
HL 23-May-94	7.2	43.0
SD	0.8	5.0
HL 3-Mar-94	3.5	21.0
SD	0.3	2.5

[a]Values determined using SAAM II kinetics software package.
SD, Standard deviation

Table 106: Apparent Ki values for Dronedarone for nifedipine oxidation (CYP3A4 activity determinant)

Microsomal Preparation	Apparent Ki Values (μM)
HL 9-Jan-94	36.4
SD	2.9
HL 23-May-94	37.3
SD	3.2
HL 21-Feb-94	48.6
SD	3.3

[a]Values determined using SAAM II kinetics software package.
SD, Standard deviation

Conclusions

The following findings from Study MIH0007 are acceptable for labeling

- Dronedarone does not significantly inhibit the activity of CYP1A2, CYP2C9, CYP2C19 and CYP2E1 in human liver microsomes. Therefore clinically, dronedarone is not expected to inhibit the metabolism of compounds metabolized by these enzymes
- The I/Ki (assuming dronedarone concentration of 0.2 μM) value for CYP3A4 inhibition (I/Ki: 0.004 to 0.005) suggests that dronedarone is unlikely to inhibit the metabolism of drugs metabolized by CYP3A4. This conclusion can be evaluated in the context of in vivo drug-drug interaction results.
- The I/Ki (assuming dronedarone concentration of 0.2 μM) value for CYP2D6 inhibition (I/Ki: 0.028 to 0.057) suggests that dronedarone is unlikely to inhibit the metabolism of drugs predominantly metabolized by CYP2D6. This conclusion can be evaluated in the context of in vivo drug-drug interaction results.

APPENDIX

Characteristics of Human Liver Donors

Microsomal Preparation	Sex	Age (years)	Cause of Death	Known Drug Use or Medications
21-Feb-94	Female	43	Intracranial Bleed	NA
20-May-93	Male	18	Intracranial Bleed	None
9-Jan-94	Female	42	Cardiac Arrest	Tobacco/ Ethanol
23-May-94	Female	27	Closed Head Injury	Tobacco/ Ethanol
7-Jan-94	Male	41	Cranial Injury	None
3-Mar-94[a]	Female	2[b],6[c]	[b] Drowning [c] Seizure Disorder	[b] None [c] Phenobarbital
21-Jan-94	Male	43	Severe Head Injury	Tobacco/ Ethanol/ Dilantin
28-May-94	Unknown	<10	Unknown	None

NA, not available
[a] Microsome preparation is a mixture of two individuals:
[b] first individual;
[c] second individual.

4.2.14 Assessing Investigating the Potential for SR35021 to Inhibit Cytochrome P450 (CYP) Enzymes Using Human Liver Microsomes in vitro (MIH0037)

PROTOCOL #	MIH0037
AUTHOR	William Brian
STUDY SITE	Sanofi Research Division, Malvern, PA, USA
STUDY PERIOD	March – August, 1999

Objectives (per applicant)
To determine if SR35021 inhibits human liver CYP enzymes *in vitro*

Experimental Conditions (Method)
Reagents and compounds were obtained from commercially available sources or as gifts from various companies. Human liver microsomes were obtained from GENTEST, Inc. (Woburn, MA).

The following CYP probe substrates and inhibitors were used:

Enzyme	Substrate	Inhibitor	Comment
CYP1A2	Phenacetin, 10 µM	furafylline	Acceptable
CYP2A6	Coumarin, 1 µM	pilocarpine	Acceptable
CYP2C9	Tolbutamide, 200 µM	sulfaphenazole	Acceptable
CYP2C19	Mephenytoin, 75 µM	Tranylcypromine	Inhibitor is neither a preferred nor acceptable inhibitor, per Guidance. Compound has been used in literature and appears to be non-specific
CYP2D6	Bufuralol, 20 µM	quinidine sulfate	Acceptable
CYP2E1	Chlorzoxazone, 75 µM	diethyldithiocarbamate	Acceptable
CYP3A4	Nifedipine, 30 µM	ketoconazole	Acceptable

Standard *in vitro* drug-drug interaction conditions were used for the experiment including presence of NADPH generating system and termination of reaction using methods determined for each assay. It is noted that expected concentrations for SR35021 were 0.54 µM based on a single oral dose of 1600 mg. In the initial study, the SR35021 concentration was 200 µM, which is a supra-therapeutic concentration. In a subsequent study, the type of inhibition and apparent Ki values were determined. HPLC was used to quantify drug concentrations.

RESULTS
The results for SR35021 inhibition potential are summarized in Table 107. At a supra-therapeutic concentration, 200 µM, SR35021 significantly inhibited (defined as > 30% inhibition relative to control values), CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 oxidation. The relative degree of inhibition that would be obtained using lower, more clinically relevant SR35021 concentrations (~0.2 µM) is unclear. It is noted that selective inhibitor for a given enzyme produced numerically lower inhibition (measured as percent control) than SR35021, suggesting that at the high concentrations, SR35021 is as potent as the selective inhibitors.

Table 107: Effect of SR35021 on CYP isoform-selective substrate oxidation rates in human liver microsomes

Probe Assay	Human Liver	Percent of Control	
		SR35021	Selective Inhibitor
CYP1A2[a]	HG6	**6.53**	**12.2**
Phenacetin	HG56	**6.30**	**14.1**
O-deethylation	HG89	**9.04**	**10.2**
CYP2A6[b]	HG30	**<LOQ**	**46.8**
Coumarin	HG56	**<LOQ**	**44.2**
7-hydroxylation	HG66	**<LOQ**	**50.8**
CYP2C9[c]	HG6	**<LOQ**	**5.82**
Tolbutamide	HG23	**<LOQ**	**6.32**
methylhydroxylation	HG56	**<LOQ**	**16.2**
CYP2C19[d]	HG30	**<LOQ**	**16.5**
Mephenytoin	HG43	**<LOQ**	**17.2**
4'-hydroxylation	HG56	**<LOQ**	**16.9**
CYP2D6[e]	HG3	**<LOQ**	**<LOQ**
Bufuralol	HG23	**<LOQ**	**<LOQ**
hydroxylation	HG56	**<LOQ**	**21.0**
CYP2E1[f]	HG42	**32.6**	**60.9**
Chlorzoxazone	HG70	**32.0**	**57.0**
hydroxylation	HG89	**29.2**	**52.2**
CYP3A4[g, h]	HG30	**3.81**	**5.45**
Nifedipine	HG42	**4.50**	**6.77**
oxidation	HG70	**4.77**	**5.21**

Selective inhibitors were: [a] furafylline (100 μM); [b] pilocarpine (50 μM); [c] sulfaphenazole (50 μM); [d] tranylcypromine (100 μM); [e] quinidine (10 μM); [f] diethyldithiocarbamate (100 μM); [g] ketoconazole (1 μM); [h] data for CYP3A4 selective inhibition from a later experiment
<LOQ: data was below the LOQ of the assay (LOQ = 0.025 μM for CYPs 2A6, 2C9 and 0.05 μM for CYPs 2C19, 2D6)
Bolded values indicate > 30% inhibition (< 70% of control values)

Reviewer's Note
According to the applicant, addition of the isoform selective inhibitors to reaction mixtures resulted in significant inhibition relative to control reaction mixtures, confirming the ability of these CYP assays to show inhibition. Although, this statement is accurate, the suitability of the 2E1 assay systems is unclear because this system yielded greater than 50 % inhibition, which is expected for a known selective inhibitor.

Apparent Ki estimations and Inhibition Type
The type of inhibition and apparent Ki values are summarized in Table 108. Using the current CPB guidelines (I/Ki < 0.1 is unlikely to yield clinically significant inhibition), for drug-drug interaction potential, therapeutic concentrations of SR35021 are unlikely to inhibit the metabolism of compounds metabolized by any of the studied CYP enzymes. The applicant depicted the likelihood of SR35021 causing drug-drug interactions in Figure 52; the thresholds depicted in the figure are consistent with current FDA CPB guidelines.

The type of inhibition model was evaluated by the applicant, and the applicant's analyses appeared acceptable.

Table 108: Type of Inhibition and Ki values for SR35021

CYP Isoform	Model Type Observation	Mean Apparent Ki (µM)	I/Ki*
CYP1A2	mixed inhibition model best fit the data from two microsome preparations while the competitive model best fit the data for the third preparation	30.6	0.0065
CYP2A6	mixed- type inhibition model best fit the data from all three microsome preparations.	32.7	0.0061
CYP2C9	mixed- type inhibition model best fit the data from all three microsome preparations.	18.3	0.0109
CYP2C19	mixed- type inhibition model best fit the data for all three microsome preparations.	11.2	0.0179
CYP2D6	the competitive inhibition model best fit the data for all three microsome preparations.	4.37	0.0458
CYP2E1	the competitive model best fit the data for all three microsome preparations.	45.2	0.0044
CYP3A4	the competitive inhibition model best fit the data in two microsome preparations while the mixed-type model best fit the data in the third preparation.	8.12	0.0246

* I/Ki values determined using an I value of 0.2 µM

Figure 52: Dependence of I/Ki on SR35021 plasma concentrations for individual CYP isoforms

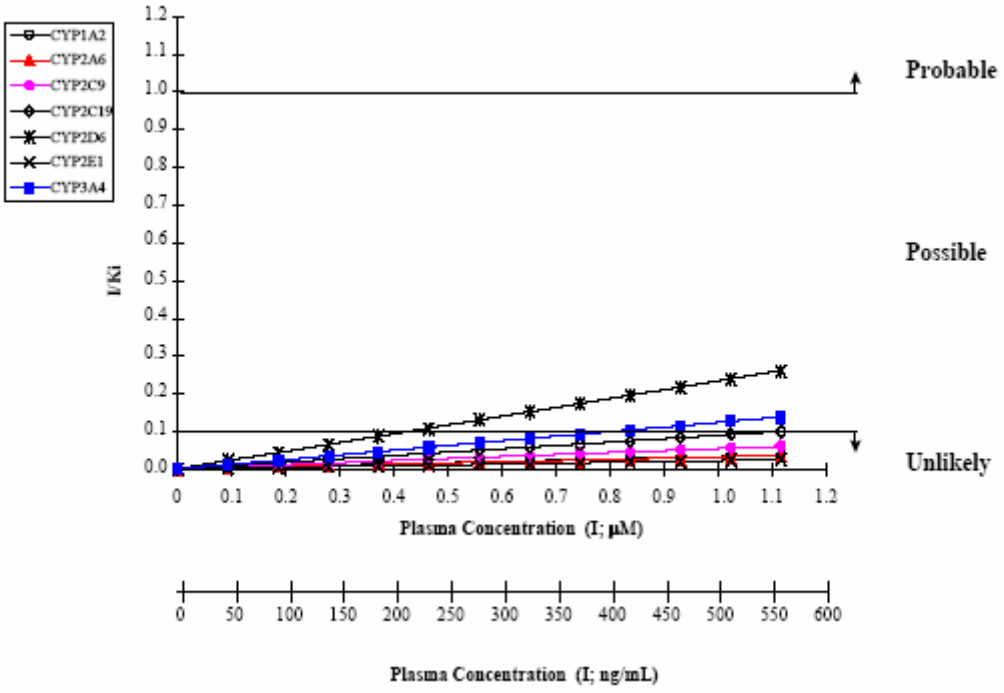


Figure 52 shows that a SR35021 concentration > 0.4 µM will be necessary to result in possible inhibition of CYP2D6; for the remaining enzymes a concentration > 0.8 will be required for possible inhibition. At the proposed clinical dose of 400 mg BID the SR35021 concentration is < 0.2 µM, thus SR35021 is unlikely to inhibit metabolism of any enzymes.

Conclusions

The following findings from Study MIH0037 are suitable for labeling

- At therapeutic concentrations, SR35021 is unlikely to cause inhibition of the major CYP enzymes. The validity of this conclusion will be evaluated during the review of in vivo drug interaction studies.
- The mechanism of enzyme inhibition by SR35021 is varied including competitive and mixed competitive

APPENDIX
Characteristics of Liver Donors

Liver Code	Gender	Age	Smoker	Race	Medical History
HG3	Female	30	N/A	Causasian	Dopamine, Lidocaine
HG6	Male	16	No	Causasian	N/A
HG23	Male	25	No	Causasian	Mannitol, Decadron
HG30	Female	28	No	Causasian	Rocephin, Zantac, Decadron, Dopamine, Atrophine, Lidocaine
HG42	Female	48	No	Causasian	N/A
HG43	Female	23	Yes	Causasian	Decadron, Lasix, Mannitol, Narcan, Dilantin, Ancef, Pavulon, Pitressin
HG56	Female	57	N/A	Causasian	N/A
HG66	Female	36	No	Causasian	Dopamine, Pitressin, DDAVP
HG70	Female	61	No	Causasian	Pitressin, Dopamine, Tagamet, Cardizem, Insulin, Aspirin
HG89	Female	71	N/A	Causasian	Ancef, Dopamine, Calan, Digoxin, Zoloft, Ativan

4.2.15 Identification of main cytochrome P450 isozymes involved in SR33589B metabolism by human microsomal fractions (MIV0159)

PROTOCOL #	MIV0159
STUDY DIRECTOR	G. Fablre
STUDY SITE	Sanofi Recherche, France
STUDY PERIOD	April – August 1992

Study Design

Standard procedures for *in vitro* metabolism studies were used. Human hepatic microsomal fractions were obtained from 15 organ donors (see Appendix for characteristics of donors). The incubation system contained drugs, microsomal fractions (2 mg/mL) and NADPH. The drug concentrations were: 1) Dronedarone, 5 µM and 2) CYP enzyme substrates and inhibitors, 0.1 to 200 µM. HPLC was used to determine the concentration of compounds. Table 109 summarizes the CYP enzymes and substrates evaluated in this study.

Table 109: CYP450 Enzyme substrates and inhibitors (per Applicant's report)

Cytochrome P450 isoform or gene subfamily	Substrates	Inhibitors
P450IA1	7-ethoxyresorufin	α-naphthoflavone
P450IA2	7-methoxycoumarin	
P450IIB	d-benzphetamine	
P450IID	debrisoquine	quinidine
P450IIIA	nifedipine	ketoconazole
Non specific		SKF-525A

Reviewer Note on Study Design Limitations

The evaluation of substrate status does not meet current FDA guidelines. It is noted that this study was conducted in 1992, when *in vitro* drug metabolism information was not well-advanced in terms of knowledge of CYP classes and their subfamilies or specific CYP substrates and inhibitors.

Compounds

- Dronedarone hydrochloride salt, batch number GD-D7-11-3
- CYP enzyme substrates and inhibitors were obtained from commercial sources

Results

Determination of Dronedarone CYP Substrate Status by Chemical Inhibition

The metabolism of dronedarone in the presence and absence of specific CYP enzyme inhibitors is summarized in Table 110. The results with the inhibitors suggest:

- Ketoconazole inhibits the metabolism of dronedarone
- Quinidine, α-naphthoflavone, and SKF-525A do not significantly inhibit the metabolism of dronedarone

Table 110: Metabolism of dronedarone in the presence of CYP enzyme inhibitors

Inhibitor	Metabolite "1"	Metabolite "8"	SR 33589
None	0.64	0.68	3.51
α-Naphthoflavone			
20 μM	TP	0.97	3.07
200 μM	TP	0.31	4.86
Quinidine			
20 μM	0.43	0.65	3.26
200 μM	0.21	0.27	3.73
Ketoconazole			
20 μM	0	0	5.13
200 μM	0	0	5.62
SKF-525A			
20 μM	0.42	0.60	3.60
200 μM	0.11	0.19	4.49

TP = technical problem
Results are expressed in μM eq. SR 33589

Based on current drug-drug interaction information and guidelines the following conclusions may be drawn from the inhibition experiment:

- Dronedarone is a CYP3A substrate
- Dronedarone is not a CYP2D6 substrate
- Dronedarone is not a CYP1A2 substrate (α-naphthoflavone is a CYP1A2 inhibitor, not a CYP1A1 inhibitor).

Dronedarone Metabolism and Metabolites

Eight metabolites were observed during the metabolism studies. The metabolites were numbered sequentially, based on their elution characteristics (retention time); some of the metabolites, such as M6, are considered minor derivatives. It should be noted that the numbering of metabolites (based on *in vitro* studies) is not clear, therefore the metabolites will be referred to by name in this report, rather than number, when possible.

From previous studies, three of these metabolites have been identified; these metabolites are depicted in Figure 12. SR34871 (M5) is O-dealkylated dronedarone; SR35021 (M8) is N-debutylated dronedarone and SR 33580 is the sulfonamide hydrolyzed dronedarone. The kinetics of dronedarone metabolism in the absence and presence (n = two donors) of the hepatic microsomal system were also evaluated (Figure 54). The profiles indicate that dronedarone is rapidly converted to three main metabolites in the hepatic microsomal system. Metabolites 1 and 8 appear at a similar rate and are considered the major metabolites. Metabolites 1 and 5 are O-dealkylated derivatives of SR35021 and dronedarone, respectively.

Figure 53: Dronedarone metabolites identified by HPLC

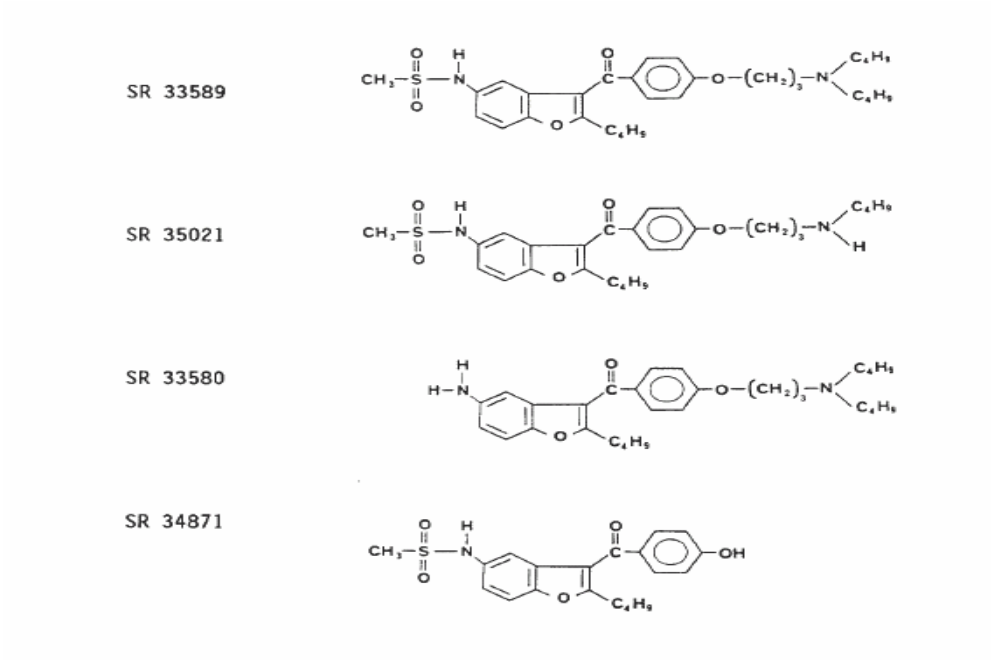
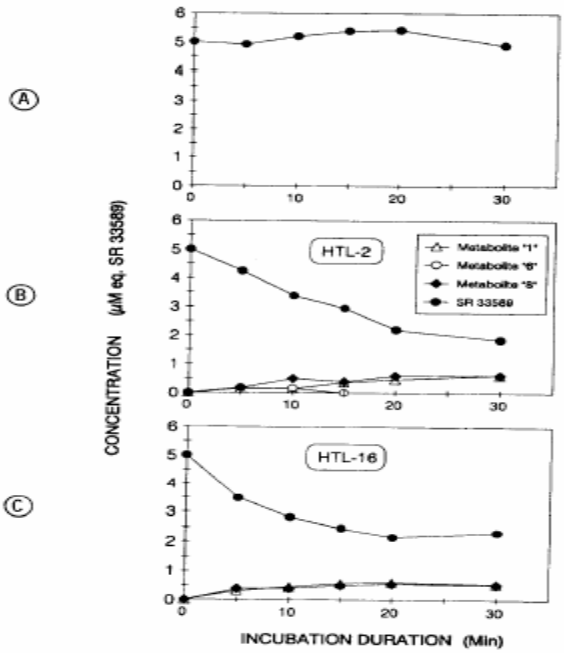


Figure 54: Kinetic profile of dronedarone metabolism



<u>Dronedarone metabolism in the presence of CYP substrates</u>
One of the CYP1A2 substrates, ethoxyresorufin, appeared to alter dronedarone metabolism, whereas phenacetin, the other CYP1A2 substrate did not alter dronedarone metabolism. The CYP substrates for the 2A6 (coumarin), 2B6 (benzphetamine), 2D6

(debrisoquine), and 3A (nifedipine and erythromycine) did not alter dronedarone metabolism (Table 111). The studied CYP2D6 substrate, d-benzphetamine, is not one of the preferred or acceptable probe substrates per current FDA guidelines, although some literature articles cite d-benzphetamine as a CYP2B6 substrate.

Table 111: Dronedarone metabolites in the presence of various CYP enzyme substrates

Substrate	Metabolite "1"	Metabolite "8"	SR 33589
None	0.64	0.68	3.51
7-Ethoxyresorufin			
20 µM	0	0.15	3.80
200 µM	0	0.15	4.51
Phenacetin			
20 µM	0.59	0.81	3.20
200 µM	0.59	0.73	3.10
7-Methoxycoumarin			
20 µM	0.64	0.92	3.40
200 µM	0.59	1.24	2.68
Coumarin			
20 µM	0.53	0.81	2.95
200 µM	0.43	1.11	2.68
d-Benzphetamine			
20 µM	0.53	0.76	3.50
200 µM	0.48	0.45	3.73
Debrisoquine			
20 µM	0.64	1.01	3.07
200 µM	0.59	0.97	2.61
Nifedipine			
20 µM	TP	0.42	3.58
200 µM	TP	0.08	5.68
Erythromycine			
20 µM	0.43	0.34	3.06
200 µM	0.11	0.08	3.73

TP = technical problem

Results are expressed in µM eq. SR 33589

The potential for selected CYP inhibitors and substrates to alter the metabolism of dronedarone and SR35021 was evaluated at different drug concentrations (Figure 55 and Figure 56).

Figure 55: Variation of dronedarone concentration with CYP inhibitor concentration in microsome

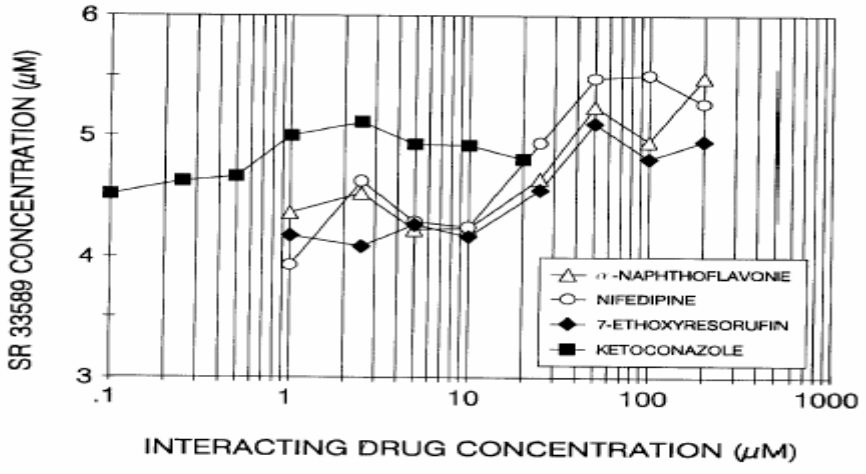
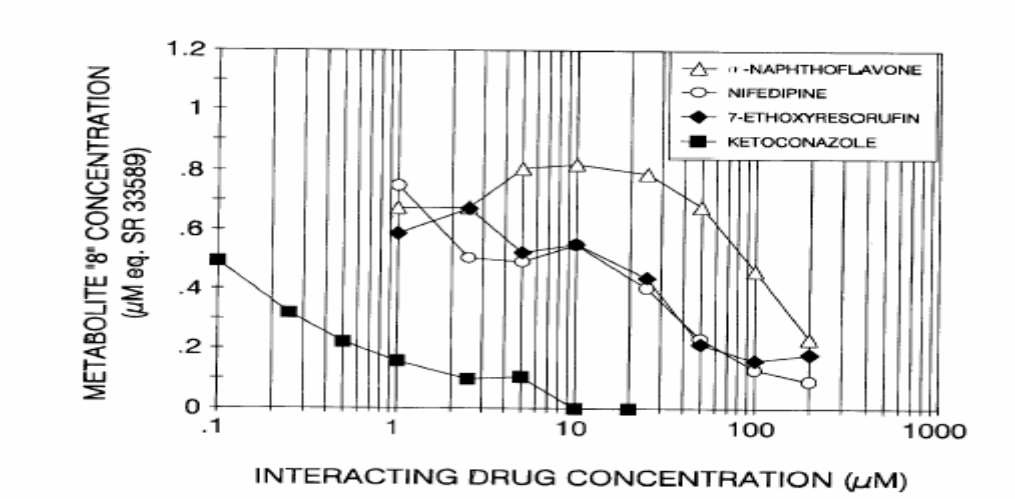


Figure 56: Variation of SR35021 concentration with CYP inhibitor concentration in microsome



The profiles in Figure 55 and Figure 56 suggest the following:

- The metabolism of dronedarone to SR35021 decreased over the 0.1 to 10 μM ketoconazole concentration range, and SR35021 is not formed at ketoconazole concentrations ≥ 10 μM.
- The metabolism of dronedarone to SR35021 is not impacted significantly by nifedipine, naphthoflavone or ethoxyresorufin at concentrations < 10 μM, but dronedarone metabolism is decreased when the concentrations of these drugs are between 20 and 100 μM. Therapeutic concentrations of the studied drugs are < 20 μM, thus, the *in vitro* concentrations that resulted in inhibition of dronedarone metabolism are unlikely to be achieved *in vivo*.

Overall these findings suggest that dronedarone is primarily metabolized to SR35021 by CYP3A and to a lesser extent by the studied CYP pathways.

Recommendations/Conclusions

The major deficiency in this study is:

Not all currently known CYP pathways were explored; the study could not determine if dronedarone is a CYP2C8, CYP2C9, CYP2C19, CYP2A6 or CYP2E1 substrate. The lack of information on these CYP enzymes can be included in the labeling, if the *in vivo* drug interaction information or other *in vitro* studies do not adequately address this deficiency. Alternatively, the applicant can conduct the relevant *in vitro* studies.

In spite of this deficiency, Study MIV0159 provides the following relevant metabolism information that is acceptable for labeling and other purposes:

- Dronedarone is metabolized by CYP3A to an N-dealkylated moiety, SR35021; this metabolite and dronedarone can undergo further metabolism
- Dronedarone is neither a CYP2D6 nor CYP1A2 substrate

APPENDIX

Caucasian human	Sex	Age	Cause of death
H(HL-1)m ; 070887-14	M	29	Autolysis (Gunshot)
H(HL-2)m ; 070887-19	M	30	Head injury (traffic accident)
H(HL-6)f ; 070887-16	F	20	Autolysis (Gunshot)
H(HL-9)m ; 070887-6	M	32	Head injury (traffic accident)
H(HL-10)m; 070887-15	M	46	Aneurysm rupture
H(HL-12)m; 070887-7	M	22	Head injury (traffic accident)
H(HL-16)m; 070887-5	M	20	Head injury (traffic accident)
H(HL-23)m; 070887-4	M	26	Head injury (traffic accident)

Caucasian human	Sex	Age	Pathology
H(HTL-2)m ; 211287-3	M	54	Pancreatic carcinoma
H(HTL-3)m ; 130887-1	M	51	Colon carcinoma
H(HTL-4)m ; 211287-1	M	36	Stomach carcinoma
H(HTL-5)m ; 211287-4	M	64	Sigmoide cancer
H(HTL-8)m ; 211287-9	M	63	Rectum carcinoma
H(HTL-12)m; 211287-6	M	56	Hepatocarcinoma
H(HTL-16)f; 211287-13	F	41	Pancreatic carcinoma

4.2.16 SR33589B metabolism using human hepatic models (MIV0158)

PROTOCOL #	MIV0158
STUDY SITE	Sanofi Recherche, France
STUDY PERIOD	April – August 1992

Study Design
Standard procedures for *in vitro* metabolism studies were used. Human hepatic microsomal fractions and primary cultures of hepatocytes were obtained from 15 organ donors (see Appendix for characteristics of donors). Incubation conditions were: incubation for 30 minutes in a system containing drugs, microsomal fractions (2 mg/mL) and NADPH. Dronedarone concentrations of 5 to 100 µM were evaluated. The glucuronidation pathway was explored using the SR34871 metabolite in the presence of 3 mM UDP-GA and Brij 58; SR34871 was selected because it had the greatest propensity towards undergoing glucuronidation. HPLC was used to determine the concentration of compounds.

Compound
Dronedarone hydrochloride salt; batch numbers DJ 07-51-5 and GD-07-11-3

Results
The kinetics of biotransformation of dronedarone, SR35021 and SR34871 are illustrated in Figure 57.

In the microsomal system the following metabolites were formed:
- Three metabolites from dronedarone
- Two metabolites from SR35021
- One metabolite from SR34871.

In another experiment, SR34871 formed the glucuronide metabolite in the presence of UDP-GA.

The identified metabolites were further characterized by MS and metabolic pathways were proposed for dronedarone and its metabolites (Figure 58, Figure 59, and Figure 60).

<u>Metabolite Characterization</u>
The following results were obtained when dronedarone metabolites were added to a medium containing dronedarone that had been incubated with human hepatocytes for 24-hours:
- S34871 was present in negligible amounts and co-eluted with one of the major dronedarone metabolites
- SR35021 was detected as a minor derivative
- Addition of ß-glucuronidase led to disappearance of a metabolite with a retention time of 6.5 minutes with a concomitant appearance of a derivative exhibiting chromatographic characteristics similar to that of SR34871
- Addition of saccharo-1,4-ß-lactone, a specific ß-glucuronidase inhibitor, inhibited the hydrolysis of the glucuronide derivative

- Several hydroxylated compounds of SR35021 and dronedarone were detected. Additionally, an acid derivative of dronedarone was observed that was obtained by a N-dealkylation process

Figure 57: Kinetics of biotransformation of dronedarone and its metabolites by human hepatic microsomal fractions

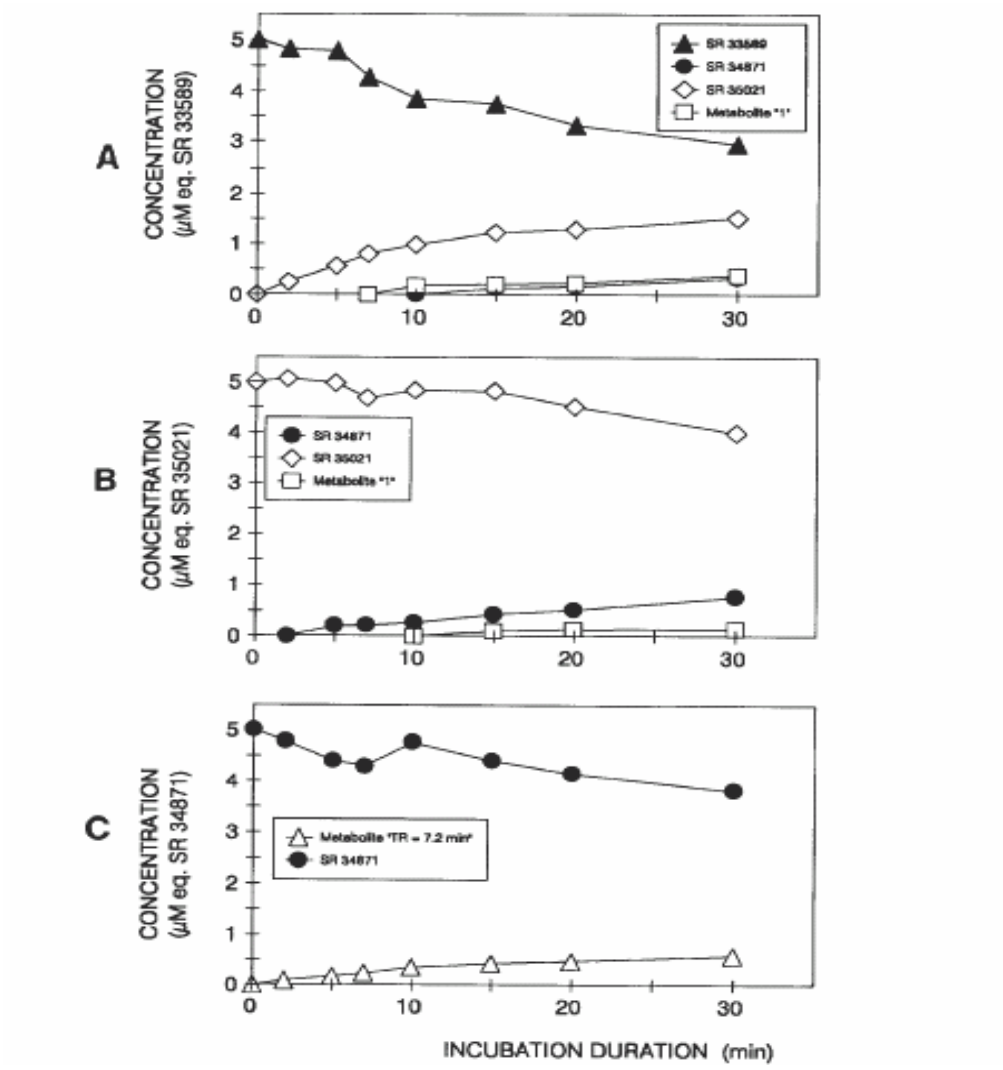


Figure 58: Proposed dronedarone metabolic pathway

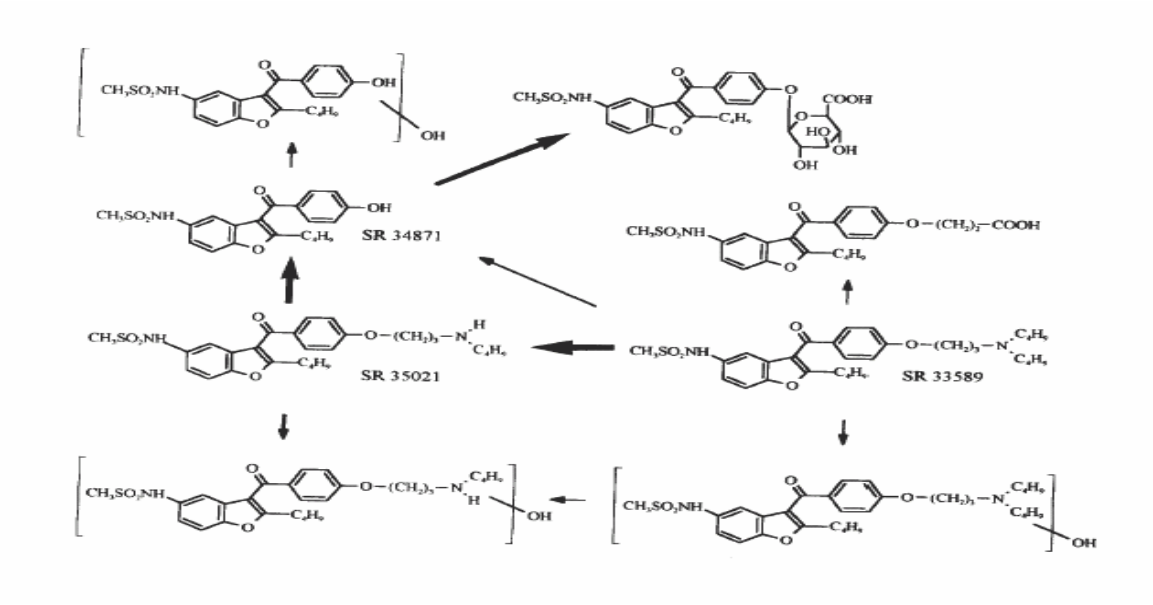


Figure 59: Proposed SR35021 metabolic pathway

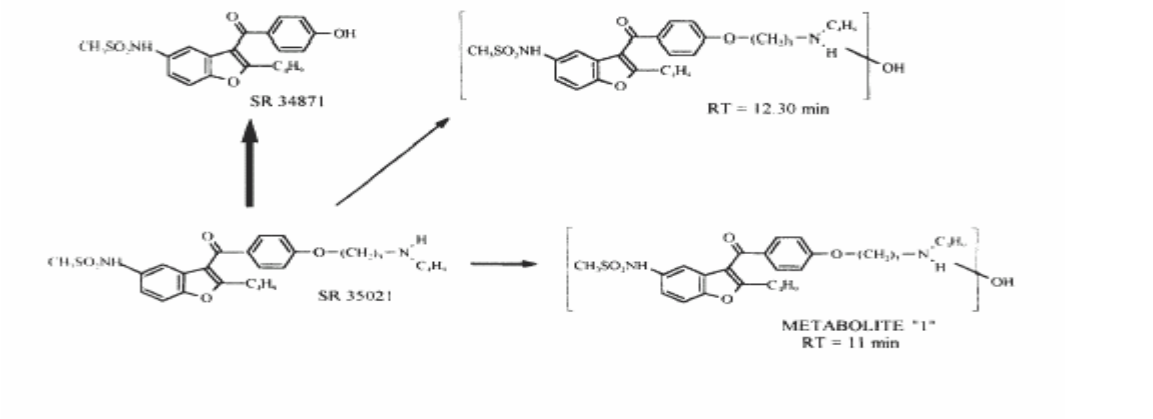
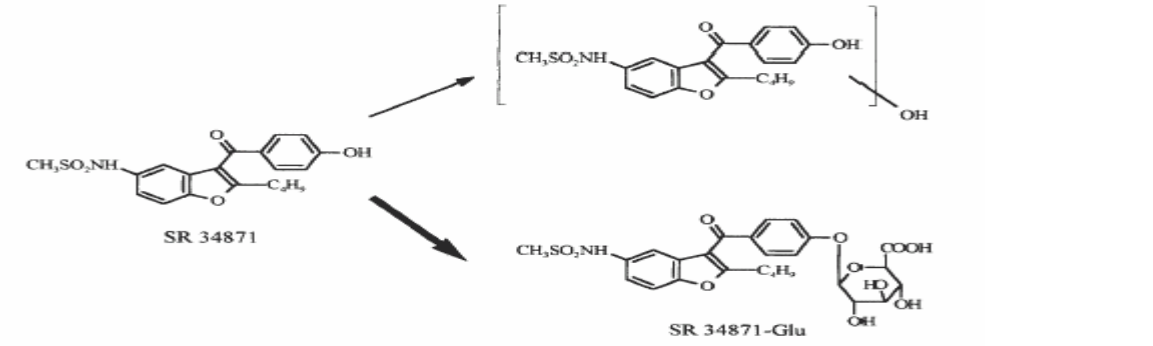


Figure 60: Proposed SR34871 metabolic pathway



Recommendations/Conclusions

The following information form Study MIV0158 is acceptable for labeling, as appropriate:

Dronedarone forms several metabolites when incubated with a human hepatocyte system; these metabolites include

- SR35021- formed by N-debutylation
- SR34871- formed by O-dealkylation of SR35021
- Acid derivative formed by dealkylation
- Numerous hydroxylated dronedarone and SR35021 derivatives

These metabolites are likely to be formed *in vivo*.

APPENDIX

Characteristics of cancer patients from who hepatic microsomal fractions were prepared

Human hepatic microsomal fraction (preparation number)	Age	Sex	Pathology
H (HTL-2)m ; 211287-3	54	M	Pancreatic carcinoma
H (HTL-66)m ; 210592-1	59	M	Colon adenocarcinoma

Characteristics of human hepatic microsomal fractions used

Human hepatic microsomal fractions (preparation number)	Protein concentration (mg/ml)	Cytochrome P450 concentration (nmole/mg)
HTL-2	15.7	0.13
HTL-66	31.6	0.44

Characteristics of patients from who human hepatocytes are prepared

Human hepatocyte preparation	Sex	Age	Pathology
HTL-82	M	70	Colon adenocarcinoma
HTL-83	F	59	Not available
HTL-87	M	66	Rectum adenocarcinoma
HTL-93	F	43	Colon adenocarcinoma

4.2.17 Regulation of the expression of cytochrome P450 gene subfamilies IA, IIA and IIIA by SR 33589B in primary cultures of human hepatocytes (MIV0144)

PROTOCOL #	MIV0144
STUDY DIRECTOR	G. Fabre
STUDY SITE	Sanofi Recherche, France
STUDY PERIOD	August 1992 to January 1993

Study Design

Two standard *in vitro* methods were used to evaluate the induction potential of dronedarone:

1. Enzymatic activity in cultured human hepatocytes (n= 4)
2. Antibody protein formation using Western blot analyses

In the hepatocyte experiment, dronedarone and model CYP inducers were incubated with hepatocytes obtained from subjects who underwent a partial hepatectomy. The characteristics of the subjects are presented in the Appendix. Enzyme activity was determined by evaluating the formation rate of specific metabolites by model CYP substrates. The substrates and inducers used for this evaluation are in Table 112.

Table 112: CYP450 Enzyme substrates and inhibitors (per Applicant's report)

CYP Enzyme	Substrate/Metabolite System	Inducer
1A2	7-ethoxyresorufin O-deethylation phenacetin O-deethylation	ß-naphthoflavone
2A6	coumarin 7-hydroxylation	dexamethasone
3A	nifedipine oxidation	phenobarbital

Reviewer Comment on Selected Enzyme Probes

The probe substrates and inducers are consistent with the recommendations in the Drug Interaction Guidance; the compounds are either preferred or acceptable substrates or inducers.

The Western blot analyses evaluated the CYP1A and CYP3A subfamilies; polyclonal antibodies for the enzymes were obtained from Inserum in France.

Compounds

- Dronedarone hydrochloride salt, batch number GD-D7-11-3 and DJ-07-51-5
- CYP enzyme substrates and inhibitors were obtained from commercial sources

Results

Hepatocytes

The results of the enzymatic studies are summarized in Table 113. The values reported indicate the degree of change in enzyme activity upon incubation with varying dronedarone concentrations and model substrates. Generally, the model inducers produced a significant increase in the metabolism of the probe substrates. Only phenobarbital yielded non-significant increases in enzyme activity (range of activity was 0.6 to 4.2). The reason for phenobarbital's poor induction is unclear.

Table 113: Metabolism of dronedarone in the presence of CYP enzyme inhibitors

Treatment	Substrates			
	7-Ethoxy resorufin (P450IA1)	Phenacetin (P450IA2)	Coumarin (P450IIA)	Nifedipine (P450IIIA)
Untreated (DMSO)	1	1	1	1
Dexamethasone 50 µM	0.3 - 1.4	1.5 - 1.5	4.0 - 8.0	1.2 - 8.2
β-Naphthoflavone 50 µM	2.4 - 18.4	3.7 - 22.1	1.2 - 1.7	0.4 - 1.8
Phenobarbital 2 mM	1.0 - 6.4	1.7 - 4.0	0.9 - 2.7	0.6 - 4.2
SR 33589B; 0.5 µM	0.6 - 2.6	1.2 - 1.4	0.8 - 1.3	0.4 - 1.1
SR 33589B; 2 µM	0.5 - 2.2	1.0 - 2.2	0.8 - 1.0	0.1 - 3.2
SR 33589B; 5 µM	0.4 - 1.6	0.7 - 1.2	0.8 - 1.7	0.3 - 1.5
SR 33589B; 20 µM	0 - 0.8	0.7 - 0.7	0.9 - 1.0	0 - 1.5
SR 33589B; 50 µM	0	NP	NP	NP

NP = not performed
n = 2 to 4 according to the availability of microsomal proteins

Overall, these findings suggest that the hepatocyte system was suitable to assess dronedarone's induction potential. Dronedarone did not induce enzymatic activity for any of the tested CYP enzymes, indicating that dronedarone is unlikely to increase the metabolism of CYP1A or CYP3A substrates at therapeutic concentrations (< 0.5 µM). It is noted that dronedarone concentrations > 5 µM were cytotoxic; these concentrations decreased the amount of protein.

Western Blot Analyses

The Western blot analyses indicated that the preparations were adequate to evaluate enzyme activity. The treatment of hepatocytes with B-naphthoflavone and dexamethasone produced increases in the protein bands corresponding to CYP1A2 and CYP3A, respectively. Dronedarone did not increase the protein bands of CYP1A2 or CYP3A; suggesting dronedarone does not induce the activity of these two enzymes.

Recommendations/Conclusions

The findings from Study MIV0144 provide the following relevant metabolism information that is acceptable for labeling and other purposes:

Enzymatic activity measured in cultured hepatocytes and Western blot analyzed indicate that dronedarone does not induce the enzymatic activity of CYP1A2, CYP2A6 or CYP3A. Based on the finding that CYP3A activity is not induced, dronedarone will not induce the enzymatic activity of CYP2C8, 2C9, or 2C19, as these enzymes are typically co expressed.

Appendix

Characteristics of patients (Caucasian humans) who underwent partial hepatectomy

Preparation	Sex	Age	Pathology
HTL-93	M	43	Colon adenocarcinoma
HTL-94	M	68	Colon adenocarcinoma
HTL-100	F	30	Hepatic adenoma
HTL-102	M	60	Colon adenocarcinoma

4.2.18 In vitro investigation of SR33589B trans-epithelial transport polarisation and inhibitory potency towards the active efflux of vincristine and digoxin using Caco-2/TC-7 cells monolayers (AIV0062)

PROTOCOL #	AIV0062
STUDY SITE	Sanofi Recherche, France
STUDY PERIOD	April – September 2000

Study Design

Standard procedures for *in vitro* drug transport studies were used. Caco-2/TC-7 cell monolayers (INSERM U-178, Villejuif – France) were used. Dronedarone was dissolved in DMSO at concentrations up to 20 mM and incubated for up to four hours. The trans-epithelial transport ("Apical → Basal" and "Basal →Apical" directions) for dronedarone (20 µM), vincristine (20 µM) and digoxin (20 µM) were evaluated in the absence and presence of 1 mM quinidine. Quinidine served as a potent efflux inhibitor. The basal to apical direction represents drug efflux. Samples were collected at 0, 1, 2 and 4 hours. In another set of experiments, the inhibition of [^{3}H]-vincristine (1 µM) and [^{3}H]-digoxin (1µM) active effluxes by cyclosporine A, verapamil, quinidine and dronedarone were assessed. The concentrations of the inhibitor ranged from 0.01 to 3000 µM. The incubation period, sampling times and transport direction were similar to those in the previously described experiment. Drug levels were quantified by HPLC with UV detection (230 nm) and liquid scintillation counting.

Experimental Design Notes (per Applicant)

- The study conditions were optimized to evaluate active efflux, rather than for the determination of an optimum 'Apical to Basal' trans-epithelial permeability.
- The highest concentration of dronedarone evaluated was 100 µM since above this value, the compound was cytotoxic as observed from the mannitol transport rate values.

Test Compounds

- Dronedarone hydrochloride salt; batch number 97-01213
- Quinidine, Sigma Chemicals
- Vincristine [G-3H]-vincristine ; specific activity = 5.5 Ci/mmol; Amersham Pharmacia Biotech
- [G-3H]-digoxin; (specific activity = 19 Ci/mmol) ; NEN Dupont
- D-[1-3H(N)]-mannitol (19.7 Ci/mmol) ; NEN Dupont
- Cyclosporine A, Sigma Chemicals
- Verapamil, Sigma Chemicals

Analyses

For each transport experiment the permeability coefficient, P_{app}, in cm/sec was determined by the following equation.

$$P_{app} = (dQ/dt) \times \left(\frac{1}{A \times Co}\right)$$

where : dQ = Amount of compound transported (expressed in nmoles)
dt = time interval during which transport is measured
A = surface area of the filter (*i.e.* 4.7 cm^2)
Co = initial concentration of test compound.

IC_{50} values were determined for each inhibitor using standard calculations.

Results

Polarisation of the trans-epithelial transport of dronedarone

The trans-epithelial transport of dronedarone in the presence and absence of quinidine is summarized in Table 114.

Table 114: Polarisation of dronedarone in vitro trans epithelial transport

SR33589 (20 µM)	P_{app} (10^{-7} cm.sec^{-1})
Apical to Basal	5.95 ± 2.12
Basal to Apical	14.80 ± 3.62
Apical to Basal + Quinidine	11.10 ± 0.00
Basal to Apical + Quinidine	17.00 ± 2.75

The results show that, under these experimental conditions, SR33589 undergoes a moderate active efflux with a nearly 2.5- fold factor between the 'Apical to Basal' and ' Basal to Apical' P app values (P_{app}BA : AB). This finding suggests dronedarone may be a moderate PGP substrate. The PGP substrate status of dronedarone could not be supported by the results obtained with quinidine, a PGP inhibitor. The presence of 1 mM quinidine did not produce any clear effect. According to the applicant, quinidine's apparent lack of effect was mostly due to the largely incomplete recovery yields observed in these experiments (only 13 to 50 % of the initial amount present in the incubation system).

Polarisation of the trans-epithelial transport of vincristine and digoxin

The trans-epithelial transport of vincristine and digoxin in the presence and absence of quinidine is summarized in Table 115.

Table 115: Polarisation of vincristine and[^{3}H] digoxin in vitro trams epithelial transport

	Vincristine *Papp* (10^{-7} cm.sec^{-1})	Digoxine *Papp* (10^{-7} cm.sec^{-1})
Apical to Basal	1.08 ± 0.65	4.59 ± 0.95
Basal to Apical	29.80 ± 2.86	113 ± 0.83
Apical to Basal + Quinidine	1.02 ± 0.29	44.60 ± 1.91
Basal to Apical + Quinidine	10.60 ± 0.82	42.10 ± 6.40

Both vincristine and digoxin exhibited a marked polarisation of their trans-epithelial transport as shown by their P_{app}BA : AB ratios (> 25). For both compounds, the presence of 1 mM quinidine drastically decreased the value of P_{app} 'Basal to Apical', indicating that drug efflux was decreased. These results demonstrated that both vincristine and digoxin active efflux were inhibited by quinidine, a broad spectrum PGP inhibitor.

Reviewer Comment on PGP Test System
The results from this study indicate that the PGP test system was suitable: digoxin is an acceptable PGP substrate and quinidine is an acceptable PGP inhibitor, per Drug-Drug interaction Guidance. Vincristine is not listed as an acceptable PGP substrate in the Guidance, however, it is structurally and pharmacologically related to vinblastine, an acceptable PGP substrate.

Inhibition of active efflux of vincristine and digoxin to determine IC values
The inhibition of the active efflux of [^{3}H]-vincristine (1 μM) and digoxin in the presence of cyclosporine, verapamil, quinidine and dronedarone were determined (Table 116 and Table 117).

Table 116: Inhibition of vincristine efflux by inhibitors

Inhibitors	IC_{20}* (μM)	IC_{50} (μM)	IC_{90}* (μM)
Cyclosporin A	0.35	1.08 ± 0.20	5
Verapamil	1	9.6 ± 8.5	2000
Quinidine	11	30.5 ± 4.8	75
SR33589B	0.30	0.97 ± 1.17	200

Table 117 Inhibition of digoxin efflux by inhibitors

Inhibitors	IC_{20}* (μM)	IC_{50} (μM)	IC_{90}* (μM)
Cyclosporin A	0.30	1.35 ± 0.33	6
SR33589B	0.22	2.05 ± 0.66	25

* IC_{20} and IC_{90} values were determined graphically

The cyclosporine A IC_{50} value with digoxin as substrate is consistent with literature values (per Guidance), suggesting that the system is suitable. Based on the digoxin information, dronedarone appears to have similar inhibitor potency as cyclosporine A.

Noting the stated limitation of the vincristine data (vincristine is not a preferred substrate), the inhibition data obtained with vincristine also support the finding that dronedarone is a potent PGP inhibitor. Dronedarone was as potent as cyclosporine A with respect to efflux inhibition and these two compounds were more potent inhibitors than verapamil and quinidine.

The dronedarone IC_{50} values exceed therapeutic dronedarone concentrations; however, the IC_{20} values are within the therapeutic concentration range. Therefore, dronedarone may have some potential to inhibit the efflux of PGP substrates. In sum, the inhibition data suggest that dronedarone is a potent PGP inhibitor at therapeutic concentrations.

Recommendations/Conclusions
There are two major deficiencies in this study:

1. The lack of optimization of system: this led to incomplete recovery yields in some experiments (< 50 % of the initial amount present in the incubation system).
2. The effect of dronedarone's active metabolite, SR35021, was not assessed. This evaluation would have been useful because SR35021 could be a potent PGP inhibitor, as is the case with a structurally related compound, amiodarone, and its active metabolite. Thus, dronedarone and SR35021 may have a potential additive to synergistic effect on

PGP inhibition that should be taken into account when attempting to predict the potential in vivo consequences of the in vitro effects demonstrated in this study

Despite the stated two limitations of the study, the findings from Study AIV0062 are acceptable for labeling, as appropriate:

1. Relative to vincristine or digoxin, which are model PGP efflux pump substrates (relative permeability > 25); dronedarone (relative permeability 2.5) has limited efflux potential.
2. SR33589 appears to be as potent an inhibitor as cyclosporine A, with respect to the ability to inhibit the efflux of digoxin and vincristine. The order of increasing numerical IC_{50} values for the two substrates, vincristine and digoxin, were:
    - For vincristine- dronedarone < cyclosporine A < verapamil < quinidine
    - For digoxin- cyclosporine A < dronedarone
3. Based on the in vitro IC20 values, dronedarone may inhibit the efflux of PGP substrates, thereby increasing the plasma exposure of PGP substrates.

4.2.19 Influence of repeated oral doses of Rifampicin [inducer of cytochrome P4503A4 (CYP3A4)] on the pharmacokinetic profile of dronedarone in healthy male subjects (INT3683)

PROTOCOL #	INT3683
INVESTIGATOR	Dr. D. E. De Vries
STUDY SITE	PHARMA BIO RESEARCH, INTERNATIONAL B.V., Science Park, 9471 GP Zuidlaren The Netherlands
STUDY PERIOD	February – March 1999

Rationale for Drug-Drug Interaction Study

	Rifampicin	Dronedarone
Indication/Mechanism of Action	Adjunctive treatment of tuberculosis; short-term management to eliminate meningococci from nasopharynx in *Neisseria meningitidis* carriers	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic
Metabolites	Forms an active metabolite, 25-0-desacetylrifampin	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	Hepatically metabolized by deacetylation with feces as primary elimination route (60% to 65%)	Primarily CYP3A substrate Potential PGP substrate and/or inhibitor
CYP Inhibition/Induction	Specific and potent CYP3A4 inducer	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	600 mg/day	400 mg BID

Objectives (per applicant)

Primary

To assess the effect of repeated oral doses of rifampicin on the pharmacokinetic profile of dronedarone (and its metabolite SR35021), given as a single oral dose of 1400 mg dronedarone in fed conditions.

Secondary

- To assess a potential pharmacodynamic resulting effect
- To assess the clinical and biological tolerability of dronedarone given alone and co-administered with rifampicin
- To document plasma concentrations of rifampicin after repeated doses.

Study Design

This was a non-randomized, open-label, non-placebo-controlled, single-group and two-period study. The two study periods were:

- Period 1: Five days in which a single oral dose of 1400 mg dronedarone given on day 1 (fed)
- Period 2: Seven days oral once daily dose of 600 mg rifampicin (fasted); on day 8 single oral dose of 1400 mg dronedarone co-administered with 600 mg rifampicin (fed)

The two doses of dronedarone were given 13 days apart.

Reviewer Note on Study Design
This study utilized a one-sequence cross-over with a single/multiple dosing regimen. The 1400 mg dronedarone dose is higher than the recommended 400 mg BID stated in the proposed label. Dronedarone has a half-life of 25-30 hours; therefore, the 5 days between the first dose of dronedarone and rifampicin is appropriate to allow for adequate drug elimination.

Subject Demographics
Subject demographics are presented in Table 118. All subjects were Caucasian males.

Table 118: Principal demographic characteristics of all subjects (INT 3683)

Parameter	Statistics	Results
Age (years)	N	12
	Mean	22.3
	SD	4.0
	Min	19
	Max	31
Height (cm)	N	12
	Mean	185.8
	SD	6.6
	Min	176
	Max	195
Weight (kg)	N	12
	Mean	80.74
	SD	9.84
	Min	62.5
	Max	96.4

Pharmacokinetic sampling times
The following pharmacokinetic blood samples were drawn at the given times:

- For dronedarone and SR35021: T – 5 min, T1h, T2h, T3h, T4h, T5h, T6h, T8h, T12h, T16h, T24h, T36h, T48h, T72h, and T96h
- For Rifampicin: Day 1 and Day 8 at T – 5 min, T1h, T1h + 55 min, T3h + 30 min, T5h + 30 min, T6h + 30 min, T8h + 30 min, T10h + 30 min, T14h + 30 min , T18h + 30 min, and T24h

Formulation

- Dronedarone: 200 mg film-coated tablets, batch number 9801501
- Rifampicin: 300 mg capsules, batch number 970002 (provided by applicant, without additional information on source)

Bioanalytical methods
Dronedarone and SR35021 concentrations were determined using a validated liquid chromatography-mass spectrometry (LC-MS/MS) method. The assay performance was acceptable as illustrated in Table 119.

Table 119: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the range of 0.5 ng/ml to 50 ng/ml; $R^2 >$ 0.993	Satisfactory
Between day Precision	CVs were not provided	Cannot assess
Accuracy	Accuracy values were not provided; however all individual QC values were within 15% of nominal concentrations	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided *	Cannot assess
	SR35021 Assay	
Linearity	The assay was linear over the range of 0.5 ng/ml to 50 ng/ml ; $R^2 >$ 0.992	Satisfactory
Between day Precision	CVs were not provided	Cannot assess
Accuracy	Accuracy values were not provided; however all individual QC values were within 15% of nominal concentrations	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided *	Cannot assess

* The validation report includes chromatograms that indicate assay specificity

Rifampicin plasma concentrations were determined using a validated high - performance liquid chromatography (HPLC) with ultraviolet detection method. The assay performance was acceptable as illustrated in Table 120.

Table 120: Performance of Rifampicin Assay

Parameter	Measure	Reviewer Comment
	Rifampicin Assay	
Linearity	The assay was linear over the 0.2 µg/ml to 20 µg/mL range; $R^2 >$ 0.998	Satisfactory
Between day Precision	CV was < 4%	Satisfactory
Accuracy	QC samples were between 2 % and 4 % of nominal concentration	Satisfactory
LLOQ	0.20 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Pharmacokinetics

The following pharmacokinetic (PK) measures were determined after each treatment:

- For dronedarone and SR35021: C_{max}, t_{max}, AUC_{last}, AUC and $t_{1/2}$
- For rifampicin: C_{max}, t_{max}, and AUC_{0-24h}

Pharmacodynamics (Activity)

The following pharmacodynamic (PD) parameters were determined: HR, and PR-, QRS-, QT-QTc-intervals, T-wave amplitude and hourly average AUC_{0-12}, peak values and time to peak values. Electrocardiogram (ECG) measurements were obtained at the following times:

- Screening
- Period 1: Day 0 at 8:00 pm, Day 1 at T-30, T2h, T4h, T6h, T8h, T12h, T24h, T48h, T72h and T96h
- Period 2: Day 1 and Day 7
- Period 2: Day 8 at T- 30 min, T2h, T4h, T6h, T8h, T12h, T24h, T48h, T72h and T96h; Day 15 (end- of- study visit).

Statistical methods

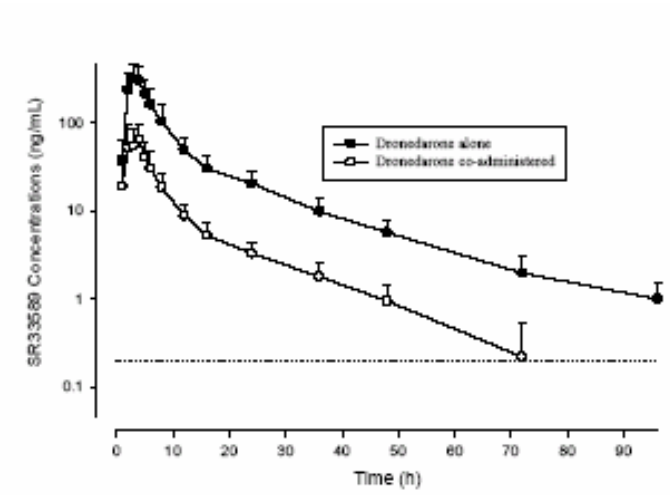
Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. Dronedarone alone was the reference treatment and dronedarone + rifampicin was the test treatment. Pharmacodynamic measures were also analyzed using standard statistical approaches.

Results

Dronedarone Pharmacokinetics

The mean dronedarone plasma concentration time profiles following administration of dronedarone alone and dronedarone co-administered with rifampicin are depicted in Figure 61.

Figure 61: Mean (SD) dronedarone plasma concentration – time profile in after dronedarone alone and dronedarone co-administered with rifampicin (n = 11)



Dronedarone PK measures are summarized in Table 121

Table 121: Mean (±SD) values of dronedarone plasma pharmacokinetic parameters after dronedarone alone and dronedarone co-administered with rifampicin (n = 11)

Parameter (units)	Dronedarone alone Period 1	Dronedarone co-administered Period 2
C_{max} (ng/mL)	353 (119)	82.6 (38.1)
t_{max} (h)	3.3 (0.8)	3.2 (0.9)
AUC_{last} (ng.h/mL)	2505 (983)	464 (190)
AUC (ng.h/mL)	2533 (991)	488 (184)
$t_{1/2}$ (h)	18.7 (3.6)	18.0 (11.0)

Dronedarone exposure was greatly decreased (>4-fold in Cmax and >5 -fold in AUC) in presence of rifampicin 600 mg (Table 122 and Table 123).

Table 122: Ratio estimates and 95% CI calculated for Cmax treatment effect (dronedarone co-administered versus dronedarone alone) of dronedarone and SR35021

Parameter	SR33589		SR35021	
(units)	Ratio	95% CI	Ratio	95% CI
C_{max} (ng/mL)	0.226	[0.15, 0.33]	1.073	[0.78, 1.48]

Reviewer Note on Confidence Intervals (Dronedarone PK)

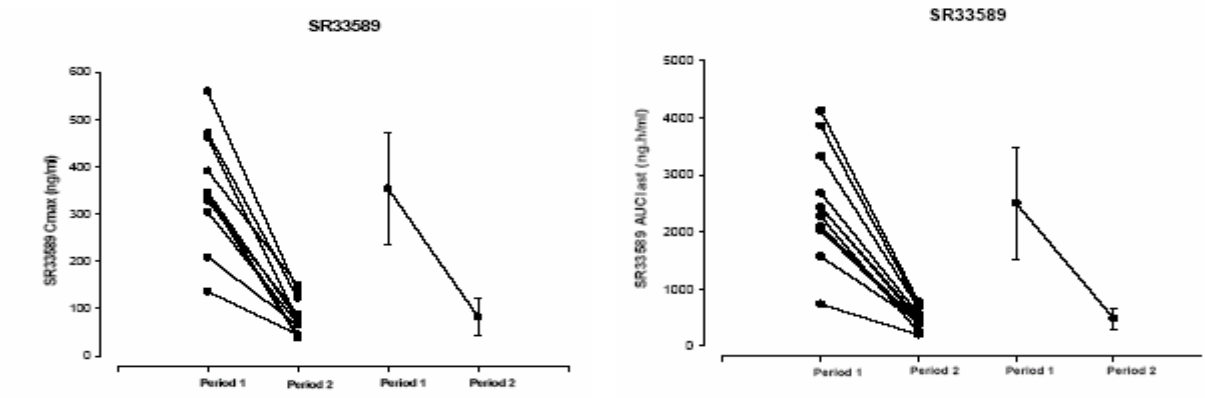
For regulatory purposes, 90 % confidence intervals are preferred over 95 % confidence intervals. In this study, the width of the confidence interval for dronedarone is not of consequence, because the geometric mean ratio is much smaller than one and the associated 90 % confidence intervals are much smaller than the default no effect range (0.8 to 1.25 based on 90 % confidence interval).

Table 123: Ratio estimates and 95% CI calculated for AUClast and AUC treatment effect (dronedarone co-administered versus dronedarone alone) of dronedarone and SR35021

Parameter (units)	SR33589		SR35021	
	Ratio	95% CI	Ratio	95% CI
AUC_{last} (ng.h/mL)	0.185	[0.12, 0.28]	0.813	[0.60, 1.10]
AUC (ng.h/mL)	0.195	[0.13, 0.29]	0.816	[0.60, 1.10]

The match stick plots in Figure 62 further illustrate the observed decrease in dronedarone exposure when co-administered with rifampicin; all subjects had a decrease in Cmax in the presence of rifampicin.

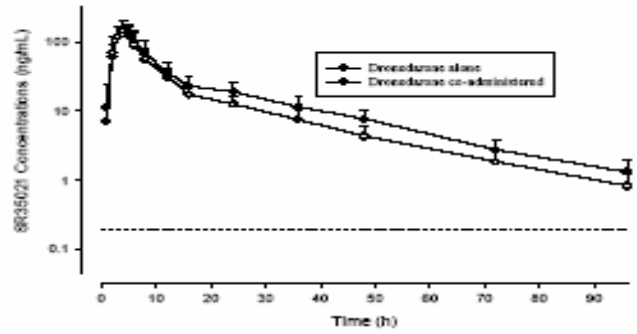
Figure 62: Individual and mean (±SD) Cmax values (ng/mL) and AUClast values (ng h/mL) of dronedarone after a single dose of dronedarone alone and dronedarone co-administered (n=11)



<u>SR35021 Pharmacokinetics</u>

The mean SR35021 plasma concentration time profiles following administration of dronedarone alone and dronedarone co-administered with rifampicin are depicted in Figure 63.

Figure 63: Mean (SD) SR35021 plasma concentrations in logarithmic scale (left) and in linear scale (right) after dronedarone alone and dronedarone co-administered (n = 11)



SR35021 PK measures are shown in Table 124.

Table 124: Mean (±SD) values of SR35021 plasma pharmacokinetic parameters after dronedarone alone and dronedarone co-administered with rifampicin (n=11)

Parameter (units)	Dronedarone alone Period 1	Dronadarone co-administered Period 2
C_{max} (ng/mL)	153 (57.1)	160 (55)
t_{max} (h)	4.2 (0.4)	3.8 (0.9)
AUC_{last} (ng.h/mL)	1655 (525)	1345 (433)
AUC (ng.h/mL)	1690 (530)	1378 (436)
$t_{1/2}$ (h)	18.2 (1.9)	20.8 (4.8)

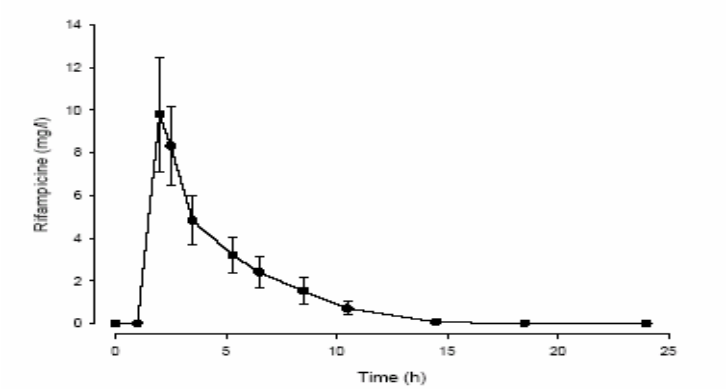
Geometric mean ratios and associated 95% CI of the SR35021 PK measures are presented in Table 122 and Table 123.

After rifampicin treatment, SR35021 Cmax and AUC values did not change significantly. The confidence interval crossed one; therefore, the results are not statistically significant.

Rifampicin Pharmacokinetics

Mean plasma concentrations after repeated administrations of rifampicin are plotted in Figure 64.

Figure 64: Mean (±SD) rifampicin plasma concentration – time profile after repeated dose rifampicin co-administered with a single oral dose dronedarone



Rifampicin PK are summarized in Table 125. The PK values are consistent with the values obtained in previous studies, suggesting that single dose administration of dronedarone does not alter rifampicin exposure.

Table 125: Mean (±SD) values of plasma pharmacokinetic parameters of rifampicin after repeated administrations of rifampicin and single dose of dronedarone

PK Measures	C_{max} (mg/L)	t_{max} (h)	AUC $_{0\text{-}24h}$ (µg.h/L)
Mean	10.5	1.2	41.4
SD	1.6	0.4	9.0

Pharmacodynamics

As shown in Table 126, relative to dronedarone alone, dronedarone plus rifampicin showed no statistically significant difference in hourly AUCs for HR, QRS interval, PR interval, QT interval, or QTc interval.

Table 126: Summary of derived variables for ECG Parameters – Difference estimates with 95% confidence intervals (average hourly AUC for values from 30 minutes pre-dose to 12h post-dose)

Parameter	Parameter	Difference Estimate	Standard Error Estimate	F test Significance level	Difference 95% CI
HEART RATE (bpm)	HEART RATE (bpm)	-1.8636	2.5254	0.4691	[-7.13, 3.40]
PR INTERVAL (ms)	PR INTERVAL (ms)	-11.3182	7.3558	0.1396	[-26.66, 4.03]
QRS INTERVAL (ms)	QRS INTERVAL (ms)	1.4818	1.2968	0.2667	[-1.22, 4.19]
QT INTERVAL (ms)	QT INTERVAL (ms)	4.4818	4.5657	0.3380	[-5.04, 14.01]
QTc INTERVAL (ms)	QTc INTERVAL (ms)	-0.3909	7.0756	0.9565	[-15.15, 14.37]
T WAVE AMPLITUDE (µV)	T WAVE AMPLITUDE (µV)	48.1091	78.6512	0.5476	[-115.95, 212.17]

Reviewer Comment on Pharmacodynamic Results

As a CYP3A4 inducer, rifampicin is expected to decrease dronedarone, a CYP3A4 substrate, exposure; therefore, its affect on PD parameters from a safety perspective is not of concern. However, dronedarone's effectiveness may be compromised because sub-therapeutic exposure will be achieved.

Applicant's Safety Summary

There were no serious adverse events (SAEs) or deaths in this study. A total of 37 treatment emergent AEs (TEAEs) were reported in this study, 11 of which occurred during co-administration of dronedarone with rifampicin. The reported AEs included headache, abdominal pain, diarrhea, nausea, tongue discoloration, euphoria, rhinitis, and chrompatopsia.

Recommendations/Conclusions

1. Rifampicin (600 mg) given once daily for 8 days induced dronedarone metabolism; consequently dronedarone plasma concentrations were decreased (Cmax decreased > 75% and AUC decreased > 80%), relative to administration of dronedarone alone.
2. Rifampicin did not affect SR 35021 exposure.
3. Sub-therapeutic dronedarone exposures did not appear to alter the HR, QRS interval, PR interval, QT interval, or QTc interval in a clinically significant manner from a safety perspective

Labeling (Precautions Section)

Applicant's proposed labeling

Co-administration of rifampicin and other potent CYP3A4 inducers such as pentobarbital, carbamazepine, phenytoin, St John's Wort are not recommended as they decrease dronedarone exposure.

Reviewer Proposed Labeling

Rifampicin and other potent CYP3A4 inducers such as pentobarbital, carbamazepine, phenytoin, St John's Wort should not be used concomitantly with dronedarone.

4.2.20 Interaction study between repeated oral doses of dronedarone and repeated oral doses of losartan in healthy young male subjects - Randomized, open-labeled, non-placebo-controlled, three-treatment, crossover study (INT 4884)

PROTOCOL #	INT4884
INVESTIGATOR	Steven De Bruyn
STUDY SITE	Research Unit Stuivenberg, SGS Biopharma, Lange Beeldekensstraat 267, B-2060 Antwerpen, Belgium
STUDY PERIOD	July – October, 2002

Rationale for Drug-Drug Interaction Study

	Losartan	Dronedarone
Indication/Mechanism of Action	Treatment of hypertension; reduce risk of stroke in patients with hypertension and left ventricular hypertrophy; treatment of diabetic nephropathy/ Angiotensin II receptor antagonist	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic
Metabolites	Active carboxylic acid	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	CYP2C9, CYP3A4	Primarily CYP3A substrate
CYP Inhibitory Potential	None reported	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Usual starting dose – 50 mg QD; Can be administered QD or BID at total daily doses of 25 to 100 mg	400 mg BID

Objectives (per applicant)

Primary

- To assess the effect of repeated oral doses of 400 mg dronedarone BID on the pharmacokinetic (PK) profile of losartan and its metabolite E-3174 after repeated oral doses of 100 mg losartan AD for 14 days
- To assess the effect of repeated oral doses of 100 mg QD losartan on the PK profile of dronedarone and its metabolite SR35021 after repeated oral doses of 400 mg BID dronedarone for 14 days

Secondary

- To assess the potential effect of dronedarone on the pharmacodynamic (PD) effect of losartan in reducing resting BP
- To assess the clinical and biological tolerability of dronedarone and losartan given alone, and also the co-administration

Study Design

This was an open-labeled, non-placebo-controlled, repeated oral dose, randomized, 3-treatment, and 3-period crossover study with a seven to thirteen day washout phase between periods. Subjects were enrolled into one of six treatment sequences as shown in Table 127. In each treatment sequence, each subject received one of the following three treatments for 14 days:

- Dronedarone (D) 400 mg BID
- Losartan (L) 100 mg QD
- Coadministration (D + L)

Subject Demographics

Subject demographics are summarized in Table 127.

Table 127: Subject Demographic Data (INT 4884)

Parameter	Statistics/ Category	Total (N=29)
Age (yrs)	N	29
	Mean	30.7
	SD	6.5
	Min	18
	Max	40
Weight (kg)	N	29
	Mean	75.77
	SD	8.53
	Min	56.8
	Max	93.7
Height (cm)	N	29
	Mean	178.5
	SD	7.6
	Min	166
	Max	191
BMI (kg/m^2)	N	29
	Mean	23.82
	SD	2.64
	Min	17.7
	Max	28.2
Gender	Male	29 (100%)
Race	Caucasian	29 (100%)

Pharmacokinetic sampling times

Pharmacokinetic blood samples were drawn as follows:

- Dronedarone and SR35021: before morning administration on Days 1, 2, 4, 8, 10, 12, and 14, and then at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours after dosing on Day 14, for each period of treatment
- Losartan and E-3174: before administration on Days 1, 2, 4, 8, 10, 12, and 14, and then at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours after dosing on Day 14, for each period of treatment

Formulation

- Dronedarone 400 mg, batch number CL-03936
- Losartan (Cozaar™, Merck) 50 mg tablets, batch number (batches 0280 0161,0280 0162, 0280 0163, 0280 0164)

Bioanalytical methods

Dronedarone and SR35021 plasma concentrations were determined using a validated liquid chromatography-tandem mass (LC-MS/MS) method (DOH0309). The assay performance was acceptable as illustrated in Table 128.

Table 128: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the range of 0.500 to 300 ng/ml; $R^2 > 0.992$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however, all individual QC values were within 15% of nominal concentrations except for a few outliers	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided *	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the range of 0.500 to 300 ng/ml; $R^2 > 0.995$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided *	Cannot be assessed

* The validation report includes chromatograms that indicate assay specificity

Losartan and E-3174 plasma concentrations were determined using a validated LC-MS/MS method (CEPHAC-CP025015). The assay performance was acceptable as illustrated in Table 129.

Table 129: Performance of Losartan and E-3174 Assay

Parameter	Measure	Reviewer Comment
	Losartan Assay	
Linearity	The assay was linear over the range of 0.500 to 1000 ng/mL; R^2 not available	Satisfactory
Between day Precision	CV varied from 1.67% to 8.37 %	Satisfactory
Accuracy	QC samples were between 3.7% and 17.73% (at LLOQ) of nominal concentrations	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory
	E-3174 Assay	
Linearity	The assay was linear over the from 0.500 ng/mL to 1000 ng/mL; R^2 not provided	Satisfactory
Between day Precision	CV varied from 2.04% to 18.5% (at LLOQ)	Satisfactory
Accuracy	QC samples were between 0.27% and 11.64% of nominal concentrations	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Pharmacokinetics

The following pharmacokinetic (PK) parameters were determined for dronedarone, SR35021, losartan, and E-3174:

- Days 1 to 13: C_{trough}
- Day 14 of each treatment: C_{max}, t_{max}, C_{min}, AUC_{0-12} (for dronedarone and

SR35021), AUC_{0-24} (for losartan and E-3174), R_{met} (for dronedarone and SR35021) using the following ratio: $AUC_{0-12\ (metabolite)}/\ AUC_{0-12\ (drug)}$

Pharmacodynamics

The following pharmacodynamic (PD) parameters were determined: changes in baseline in supine and standing position, systolic blood pressure (SBP), diastolic (DBP), and heart rate (HR).

Statistical methods

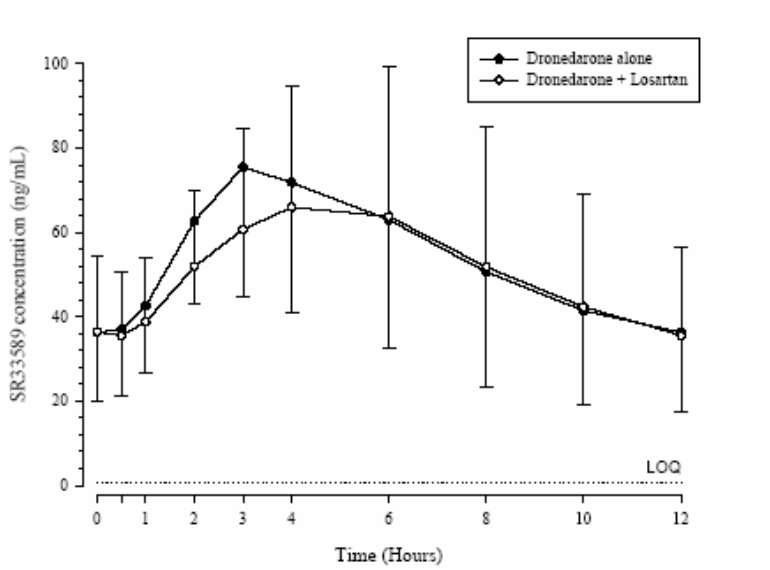
Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. Dronedarone alone was the reference treatment and dronedarone + losartan was the test treatment. Pharmacodynamic measures were also analyzed using standard statistical approaches.

Results

Dronedarone Pharmacokinetics

The mean plasma concentration-time profiles for dronedarone after administration of dronedarone 400 mg BID in the absence and presence of losartan are depicted in Figure 65.

Figure 65: Mean (±SD) dronedarone plasma concentrations after repeated oral 400 mg BID administration of dronedarone alone or coadministration (n=25)



Dronedarone PK measures are summarized in Table 130. Dronedarone exposure showed a statistically significant decrease in Cmax (~12%) but no change in AUC in the presence of losartan. The associated confidence interval for Cmax; however, nearly falls within the no effect range (0.8 to 1.25 based on 90% confidence interval). Therefore, this decrease is not clinically significant.

Table 130: Mean (CV%) dronedarone pharmacokinetic parameters, their ratio estimates, and 90% confidence intervals (n=25) after repeated oral 400 mg BID administration of dronedarone alone or co- administrated with losartan

PK Parameters	Dronedarone Alone	Dronedarone+ Losartan	Ratio Estimates[b] and 90% CI
SR33589			
C_{max} (ng/mL)	80.4 (39)	71.9 (47)	0.879 [0.79; 0.97]
t_{max} (h)[b]	3.00 [2.00 – 6.07]	4.00 [2.00 – 6.02]	p=0.0069
AUC_{0-12} (ng.h/mL)	650 (43)	616 (50)	0.930 [0.86; 1.01]

a – Ratio dronedarone + losartan/dronedarone, p-value for difference between treatments
b – Median values (Min-Max)

The match stick plots in Figure 66 and Figure 67 further illustrate the minimal decrease in dronedarone Cmax and lack of change in AUC during the coadministration of dronedarone and losartan. It should be noted that individual plots for both Cmax and AUC show both increases and decreases.

Figure 66: Individual, mean (±SD), and geometric mean Cmax values of dronedarone after repeated oral administration of dronedarone alone or in the presence of losartan (n=25)

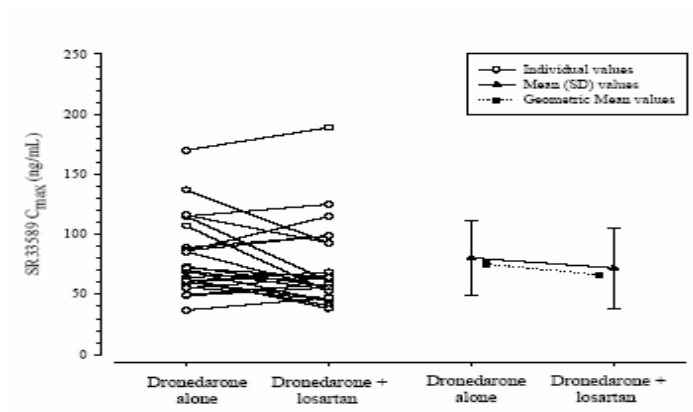
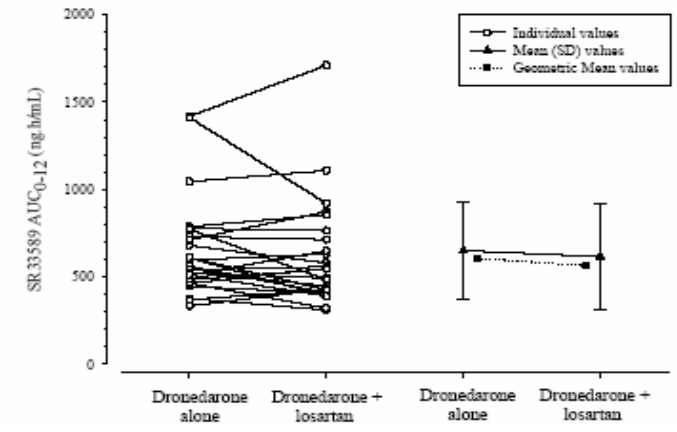


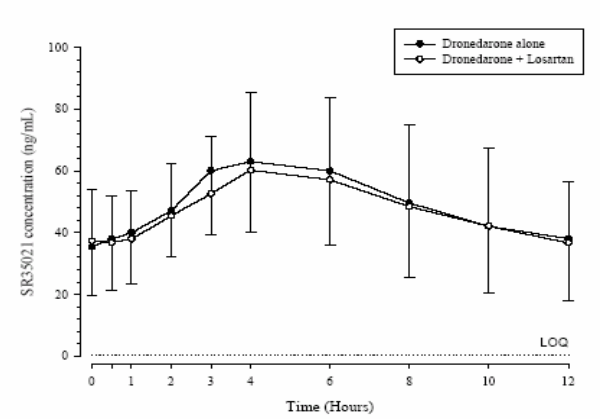
Figure 67: Individual, mean (±SD), and geometric mean AUC_{0-12} values of dronedarone after repeated oral administration of dronedarone alone or in the presence of losartan (n=25)



SR35021 Pharmacokinetics

The mean SR35021 plasma concentration-time profiles following administration of dronedarone 400 mg BID with or without losartan are depicted in Figure 68.

Figure 68: Mean (±SD) SR35021 plasma concentrations after repeated oral 400 mg BID administration of dronedarone alone or coadministered with losartan (n=25)



SR35021 PK measures are summarized in Table 131. No significant change in Cmax and AUC with co-administration of dronedarone and losartan was observed.

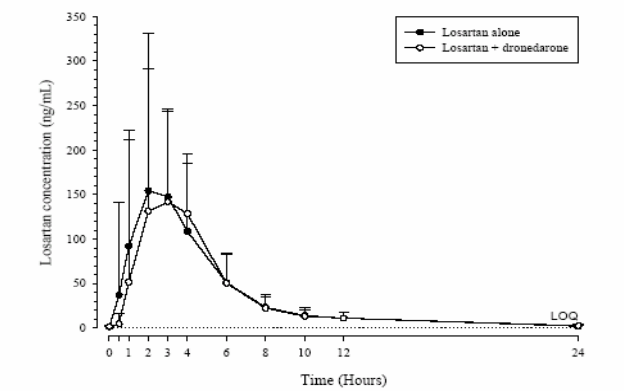
Table 131: Mean (CV %) dronedarone and SR35021 pharmacokinetic parameters, their ratio estimates, and 90% confidence intervals (n=25) following administration of dronedarone alone and in the presence of losartan

PK Parameters	Dronedarone Alone	Dronedarone + Losartan	Ratio Estimates and 90% CI
C_{max} (ng/ml)	66.4 (36)	62.8 (41)	0.942 (0.88; 1.00)
T_{max} (h)	4.00 [3.00 – 6.07]	4.00 =[3.00 – 8.00]	p=0.5590
AUC_{0-12} (ng. h/ml)	601 (41)	573 (46)	0.947 [0.90; 1.00]

Losartan Pharmacokinetics

The mean losartan plasma concentration-time profiles following administration of 100 mg QD losartan alone or coadministered with dronedarone 400 mg BID are depicted in Figure 69.

Figure 69: Mean (±SD) losartan plasma concentrations after repeated oral 100 mg QD administration of losartan alone or coadministration (n=27)



Losartan PK measures shown in Table 132 indicate no significant change in exposure was observed when losartan was coadministered with dronedarone. The mean values for Cmax and AUC shown in the match stick plots (Figure 69 and Figure 70) show a trend towards decreased exposure; however, individual subject values show both increases and decreases in Cmax and AUC.

Table 132: Mean (CV %) losartan and E-3174 pharmacokinetic parameters, their ratio estimates and 90% confidence interval (n=27) following administration of losartan alone or coadministered with dronedarone

PK Parameters	Losartan Alone	Losartan+ Dronedarone	Ratio Estimates[a] and 90% CI
Losartan			
C_{max} (ng/mL)	284 (53)	245 (75)	0.821 [0.66; 1.03]
t_{max} (h)[b]	2.02 [0.470 – 6.00]	3.00 [1.00 – 6.00]	p=0.2549
AUC_{0-24} (ng.h/mL)	842 (37)[c]	782 (47)[d]	0.925 [0.84; 1.01]
E-3174			
C_{max} (ng/mL)	459 (48)	346 (49)	0.750 [0.67; 0.84]
t_{max} (h)[b]	4.00 [2.97 – 6.03]	4.00 [3.00 – 6.02]	p=0.4806
AUC_{0-24} (ng.h/mL)	3210 (39)	2560 (40)[c]	0.788 [0.73; 0.85]

Figure 70: Individual, mean (±SD), and geometric mean Cmax values of losartan after repeated oral administration of losartan alone or coadministration with dronedarone (n=27)

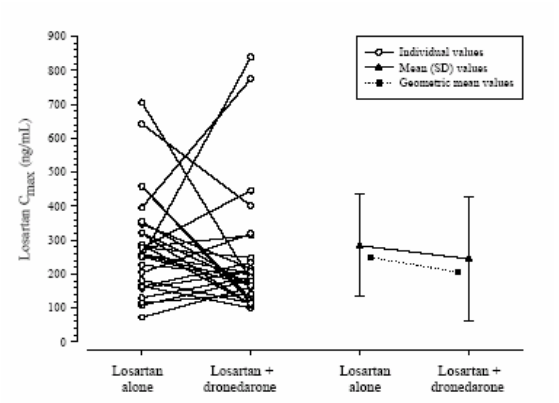
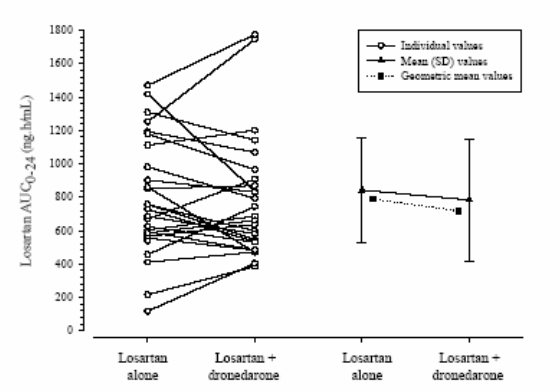


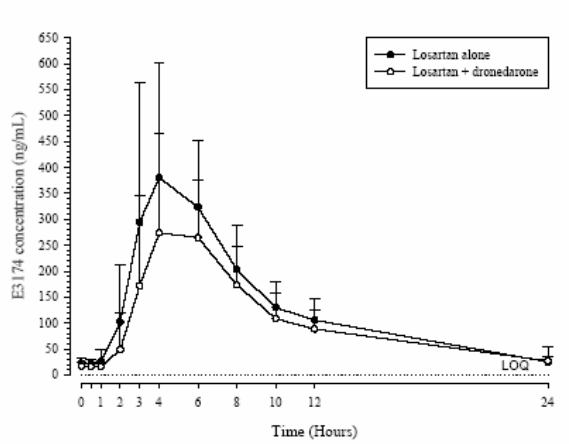
Figure 71: Individual, mean (±SD), and geometric mean AUC0-24 values of losartan after repeated oral administration of losartan alone or coadministration with dronedarone (n=27)



E-3174 Pharmacokinetics

The mean E-3174 plasma concentration-time profiles following administration of 100 mg QD losartan alone or coadministered with dronedarone 400 mg BID are depicted in Figure 72.

Figure 72: Mean (±SD) E-3174 plasma concentrations after repeated oral administration of 100 mg QD losartan alone or coadministered with dronedarone (n=27)



E-3174 PK measures are shown in Table 132. There was a statistically significant decrease in E-3174 exposure (about 25% for both Cmax and AUC) when losartan was coadministered with dronedarone relative to when losartan was administered alone.

Pharmacodynamics

Relative to dronedarone alone, dronedarone plus losartan showed the following):

- HR: Addition of dronedarone to losartan is not associated with a change in HR; however, addition of losartan to dronedarone was associated with an increase in HR of 4.05 bpm for difference in changes from baseline ($p<0.001$) at Day 14. The clinical significance of this increase is not clear.
- DBP: No treatment effect was observed
- SBP: There was a significant treatment x time interaction for SBP changes from baseline ($p=0.045$), but there was no significant treatment effect at Day 14 for SBP changes from baseline and for differences in derived AUCs, whatever the comparison, coadministration versus dronedarone or coadministration versus losartan.

Applicant's Safety Summary

There were no serious adverse events (SAEs), deaths or significant adverse events in this study. Treatment emergent adverse events (TEAEs) occurred in all three treatment groups. The incidence of TEAEs was 71.4% during treatment with dronedarone alone, 62.1% during losartan alone, and 85.2% during coadministration. Nervous system-, GI-, and general disorders were the most frequently reported TEAEs overall. Most TEAEs were of mild intensity, and all subjects recovered without corrective treatment. No subjects permanently discontinued study drug treatment due to TEAEs.

Table 133: Analysis in repeated measures of changes from baseline up to 11.5 hours and of corresponding AUC [0.5 – 11.5] – 95% confidence intervals for pairwise differences between treatments

Parameter	Derived parameter	Difference tested	Difference in Delta: Estimate	Standard error of the mean	95% confidence interval	Flag of signif. level
HR (bpm)	Delta value	SR vs L: overall	-1.68	1.31	[-4.3, 0.94]	
		SR+L vs L: overall	2.37	1.29	[-0.22, 4.96]	
		SR+L vs SR: overall	4.05	1.31	[1.43, 6.68]	**
	AUC[0.5-11.5]	SR vs L	-1.78	1.34	[-4.47, 0.91]	
		SR+L vs L	2.39	1.32	[-0.26, 5.05]	
		SR+L vs SR	4.18	1.34	[1.48, 6.87]	**
DBP (mmHg)	Delta value	SR vs L: overall	0.75	1.30	[-1.87, 3.37]	
		SR+L vs L: overall	1.15	1.29	[-1.44, 3.74]	
		SR+L vs SR: overall	0.40	1.31	[-2.22, 3.03]	
	AUC[0.5-11.5]	SR vs L	0.81	1.34	[-1.88, 3.5]	
		SR+L vs L	1.34	1.32	[-1.31, 4]	
		SR+L vs SR	0.53	1.34	[-2.16, 3.23]	
SBP (mmHg)	Delta value	SR vs L: overall	1.75	1.65	[-1.56, 5.06]	
		SR+L vs L: overall	0.36	1.63	[-2.91, 3.63]	
		SR+L vs SR: overall	-1.39	1.65	[-4.7, 1.92]	
	AUC[0.5-11.5]	SR vs L	1.71	1.67	[-1.64, 5.05]	
		SR+L vs L	-0.45	1.65	[-3.76, 2.86]	
		SR+L vs SR	-2.15	1.67	[-5.5, 1.2]	

Recommendations/Conclusions

1. Losartan (100 mg) does not affect the PK of dronedarone
2. The active metabolite of losartan, E-3174, showed a statistically significant decrease in exposure (about 25% for both Cmax and AUC) after administration of losartan with dronedarone, relative to losartan alone. Losartan undergoes minimal conversion to its metabolite. Therefore, this decrease in exposure is not likely to cause a decrease in losartan's therapeutic effect.
3. There were no significant treatment effects on SBP and DBP after administration of losartan and dronedarone.
4. The addition of losartan to dronedarone (but not the reverse) caused an increase in HR of 4.05 bpm; however, the clinical implication of this increase is not clear.

Labeling

Applicant's Proposed Labeling: No interaction was observed between dronedarone and losartan.

Reviewer's Comment: The proposed labeling is acceptable based on the PK information in INT 4884. No dose adjustments for dronedarone or losartan are needed when administered together.

4.2.21 Pharmacokinetic interaction of repeated oral 40 mg o.d. pantoprazole on repeated oral 400 mg b.i.d. dronedarone in healthy young male subjects - Open-labeled, non placebo-controlled, randomized, 2-treatment, 2-period crossover study (INT3560)

PROTOCOL #	INT 3560
INVESTIGATOR	Dr. Nicolas Fauchoux
STUDY SITE	Biotrial, Rue Jean-Louis Bertrand, Technopole Atalante Villejean, 35000 Rennes, France
STUDY PERIOD	October - November 2002

Rationale for Drug-Drug Interaction Study

	Pantoprazole	Dronedarone
Indication/Mechanism of Action	Short-term treatment of erosive esophagitis associated with gastroesophageal reflux disease ; maintenance of healing of erosive esophagitis; treatment of pathological hypersecretory conditions/	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic
Metabolites	Several metabolites with no significant pharmacologic activity	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	CYP2C19, CYP3A4	Primarily CYP3A substrate
CYP Inhibitory Potential	None	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	40 mg	400 mg BID

Objectives (per applicant)

Primary: To assess the effect of repeated oral doses of pantoprazole on the pharmacokinetic (PK) profile of dronedarone and its N-debutyl metabolite, SR35021, after repeated oral doses of dronedarone given in fed conditions.

Secondary: To assess the clinical and biological safety of dronedarone given alone and of dronedarone + pantoprazole co-administration in healthy male subjects.

Study Design

This was an open-labeled, non-placebo-controlled, repeated-dose, randomized, 2-treatment, and 2-period crossover study with a washout period of 10 days. Subjects were randomized to one of two treatment sequences (Sequence 1: Treatment A then Treatment B; Sequence 2: Treatment B then Treatment A) that included the following treatment periods:

- Treatment A (dronedarone alone): 400 mg twice a day (BID) dronedarone for seven days
- Treatment B (dronedarone co-administered with pantoprazole): 400 mg BID dronedarone + 40 mg once a day (QD) pantoprazole for seven days

Subject Demographics

Subject demographics are presented in Table 134.

Table 134: Summary of subject demographic data (INT 3560)

Parameter (Unit)	Statistics / Category	Total (N=18)
Age (years)	N	18
	Mean (SD)	28.0 (5.6)
	Min - Max	21 - 40
Weight (kg)	N	18
	Mean (SD)	74.03 (8.23)
	Min - Max	57.0 - 88.5
Height (cm)	N	18
	Mean (SD)	178.6 (7.7)
	Min - Max	165 - 194
BMI (kg/m^2)	N	18
	Mean (SD)	23.23 (2.37)
	Min - Max	19.5 - 27.5
Gender	Male (N,%)	18 (100)
Race	Caucasian (N,%)	18 (100)

Pharmacokinetic sampling times

Pharmacokinetic blood samples were drawn as follows:

- Dronedarone and SR35021: before dose administration on Days 1, 2, 4, 6, 7, and on Day 7 at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours after dosing.
- Pantoprazole: before dose administration on Day 1 and Day 7, and on Day 7 at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after the co-administration.

Formulation

- Dronedarone 400 mg tablets (formula 2E3) batch number CL-03936
- Pantoprazole (Inipomp™, Sanofi-Synthelabo) 40 mg enteric-coated tablets, batch number (22007)

Bioanalytical methods

Dronedarone and SR35021 plasma assays

Dronedarone and SR35021 plasma concentrations were determined by a validated Liquid Chromatography-Mass Spectrometry (LC-MS/MS) method (DOH0239). The assay performance was acceptable as shown in Table 135.

Table 135: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	Linear over range of 0.5 to 300 ng/ml; $R^2 > 0.996$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided *	Cannot be assessed
	SR35021 Assay	
Linearity	Linear over range of 0.5 to 300 ng/ml; $R^2 > 0.995$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided *	Cannot be assessed

* The validation report includes chromatograms that indicate assay specificity

Pantoprazole assay

Pantoprazole plasma concentrations were determined by a validated LC-MS/MS method. The assay performance was acceptable as shown in Table 136.

Table 136: Performance of Pantoprazole Assay

Parameter	Measure	Reviewer Comment
	Pantoprazole Assay	
Linearity	Linear over the range of 20.0 to 2000 ng/mL; $R^2 > 0.999$	Satisfactory
Between day Precision	CV was < 10%	Satisfactory
Accuracy	QC samples were between 1.06% and 3.5% of nominal concentration	Satisfactory
LLOQ	20 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Pharmacokinetics

The following pharmacokinetic (PK) parameters were determined:

- Dronedarone and SR35021: Ctrough, tmax, Cmax, AUC0-12, Rmet ($AUC_{0\text{-}12\ metabolite}/AUC_{0\text{-}12\ drug}$)
- Pantoprazole: Ctrough, Cmax, tmax, $AUC_{0\text{-}24}$

Statistical methods

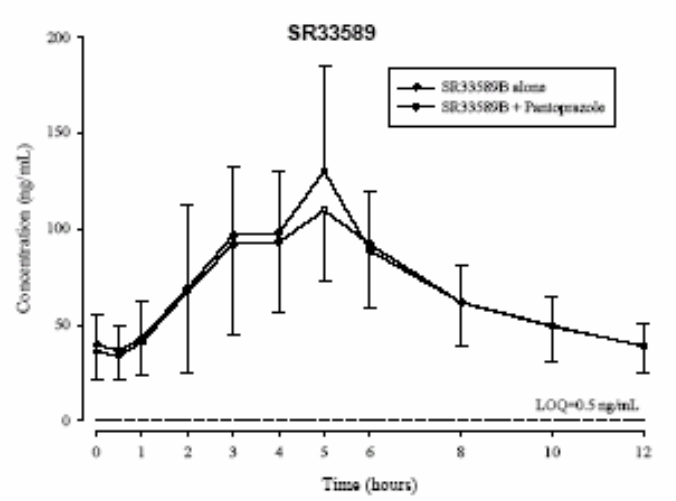
Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. Dronedarone alone was the reference treatment and dronedarone + pantoprazole was the test treatment.

Results

Dronedarone Pharmacokinetics

The mean plasma concentration-time profiles for dronedarone following administration of dronedarone 400 mg BID in the absence and presence of pantoprazole are depicted in Figure 73.

Figure 73: Mean (SD) dronedarone plasma concentrations observed after seven days repeated administration of dronedarone alone or co-administered with pantoprazole (n=17)



Dronedarone PK measures and ratio estimates are summarized in Table 137 and Table 138. There was no statistically significant change observed in dronedarone exposure when dronedarone was administered with pantoprazole. The 90% confidence intervals are almost entirely within the no effect range (0.8 to 1.25), suggesting the interaction is not clinically significant.

Table 137: Mean (SD) and CV% values of dronedarone and SR35021 pharmacokinetic parameters obtained after seven days repeated administration of dronedarone alone or co-administered with pantoprazole (n=17)

PK Parameter *Mean (SD) – CV%*	SR33589B Alone	SR33589B + Pantoprazole
	SR33589	
C_{max} (ng/mL)	122 (42.6) 35%	138 (53.3) 39%
t_{max} (h)[a]	5.00 [3.00-6.00]	5.00 [2.00-5.00]
AUC_{0-12} (ng.h/mL)	817 (283) 35%	849 (239) 28%
C_{trough} (ng/mL)	36.0 (14.0) 39%	39.6 (15.9) 40%
	SR35021	
C_{max} (ng/mL)	119 (37.2) 31%	127 (42.0) 33%
t_{max} (h)[a]	5.00 [3.00-6.00]	5.00[3.00-6.00]
AUC_{0-12} (ng.h/mL)	930 (320) 34%	951 (309) 32%
C_{trough} (ng/mL)	48.1 (22.5) 47%	52.2 (18.3) 35%
$R_{met\ (AUC0-12)}$ Geometric mean	1.14	1.10

[a] Median and range for t_{max}

Table 138: Treatment ratio estimates (dronedarone + pantoprazole vs. dronedarone alone) and 90% confidence interval

Parameter	Ratio Estimate	90% CI of Ratio Estimate
	SR33589	
C_{max}	1.13	[0.98; 1.31]
AUC_{0-12}	1.07	[1.00; 1.16]
t_{max}*	0.00	[-0.50; 0.50]
	SR35021	
C_{max}	1.07	[0.94; 1.20]
AUC_{0-12}	1.03	[0.97; 1.09]
t_{max}*	0.00	[-0.50; 0.50]
R_{met}	0.96	[0.90; 1.02]

Figure 74: Individual and mean (SD) dronedarone Cmax values (ng/mL) obtained after 7 days repeated administration of dronedarone alone or co-administered with pantoprazole (n=17)

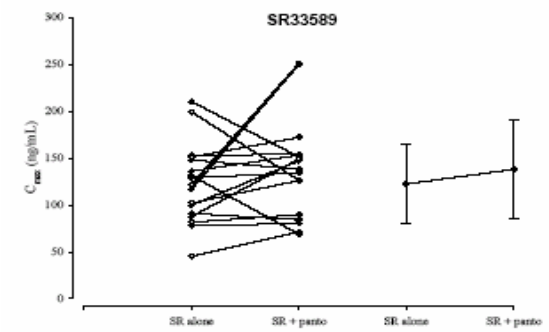
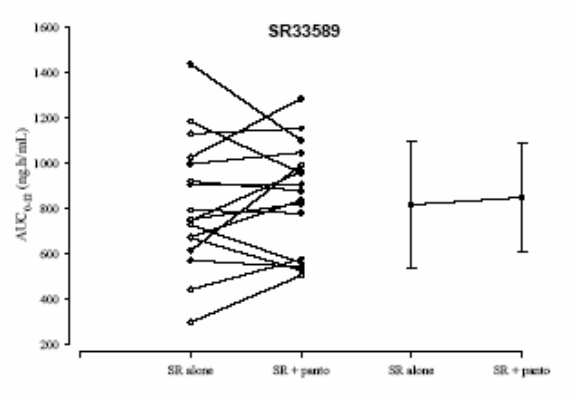


Figure 75: Individual and mean ± (SD) dronedarone AUC0-12 values (ng h/mL) obtained after 7 days repeated administration of dronedarone alone or co-administered with pantoprazole (n=17)

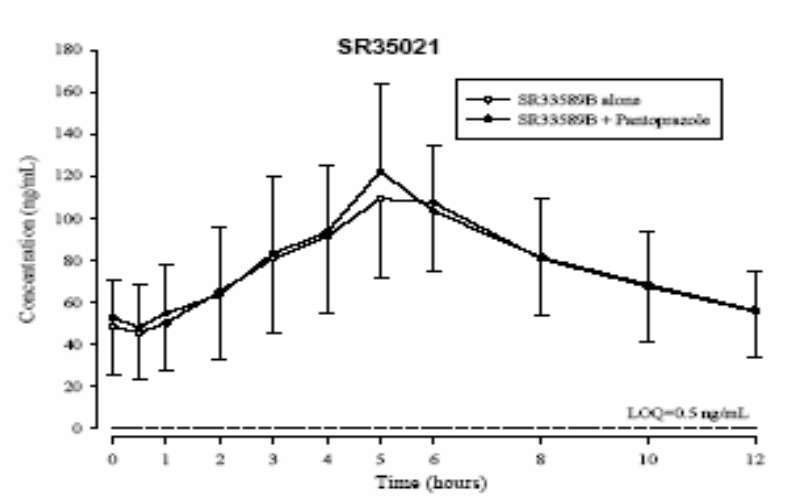


The match stick plots for dronedarone Cmax and AUC values are shown in Figure 74 and Figure 75. Although the plots for the mean values show a minimal upward trend in Cmax and AUC, there are some individual subject plots that show both increases and decreases.

<u>SR35021 Pharmacokinetics</u>

The mean plasma concentration-time profiles for SR35021 following administration of dronedarone 400 mg BID in the absence and presence of pantoprazole are depicted in Figure 76.

Figure 76: Mean (SD) SR35021 plasma concentrations observed after 7 days repeated administration of dronedarone alone or co-administered with pantoprazole (n=17)

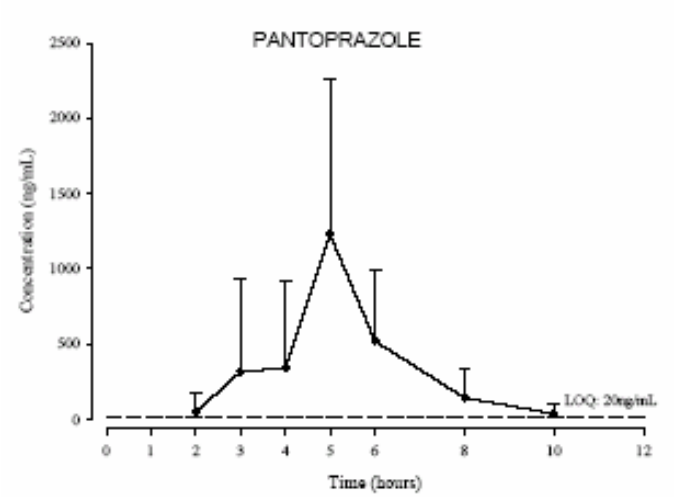


SR35021 PK and ratio estimates are summarized in Table 137 and Table 138. There was no statistically significant change observed in exposure of SR35021 when dronedarone was administered with pantoprazole.

<u>Pantoprazole Pharmacokinetics</u>

The mean pantoprazole plasma concentration-time profiles following administration of pantoprazole 40 mg QD co-administered with dronedarone 400 mg BID are depicted in Figure 77.

Figure 77: Mean (SD) pantoprazole plasma concentrations obtained after a 7-day repeated pantoprazole co-administration with dronedarone



Pantoprazole PK are summarized in Table 139. The PK values are consistent with the values obtained in previous studies, suggesting that single dose administration of dronedarone does not alter pantoprazole exposure.

Table 139: Descriptive statistics of pantoprazole pharmacokinetic parameters obtained after repeated pantoprazole co-administration with dronedarone (Day 7)

Parameter	C_{max} (ng/mL)	t_{max} (hours)	AUC_{0-24h} (ng.h/mL)
N	17	17	17
Mean (SD)	1671 (825)	4.59 (1.00)	5367 (3240)
CV%	49	22	60
Minimum - Maximum	450 - 3083	3.00 – 6.00	1562 – 12237
Median	1712	5.00	4886
Geometric Mean	1470	4.47	4452

Applicant's Safety Summary

There were no serious adverse events (SAEs), deaths or significant adverse events in this study. Treatment emergent adverse events (TEAEs) occurred in both treatment groups. The incidence of TEAEs was 22.2% during treatment with dronedarone alone, and 58.8% during coadministration. GI, nervous system, and general disorders were the most frequently reported TEAEs overall. One subject permanently discontinued study drug treatment due to TEAEs.

Recommendations/Conclusions

Pantoprazole (40 mg) once daily over 7 days did not cause a statistically significant change in exposure of dronedarone or SR35021, indicating that pantoprazole does not affect the PK of dronedarone.

Labeling

Sponsor's Proposed Labeling

Other Information
Pantoprazole (40 mg once daily), a drug increasing gastric pH without any effect on cytochrome P450, did not interact significantly on dronedarone pharmacokinetics.

The proposed labeling is acceptable based on the PK information in INT3560.
No dose adjustments for dronedarone or pantoprazole are needed when administered together.

Reviewer Proposed Alternative Language

Pantoprazole (40 mg once daily), a drug increasing gastric pH without any effect on cytochrome P450, did not have a significant effect on dronedarone pharmacokinetics.

4.2.22 Interaction study between repeated oral doses of dronedarone and repeated oral doses of simvastatin in healthy male subjects - randomized, open-labeled, 3-treatment, cross-over study (INT 4880)

PROTOCOL #	INT4880
INVESTIGATOR	Dr Regine Rouzier
STUDY SITE	Center CAP, Clinique Rech, 9, Avenue Charles Flahault, 34094 Montpellier Cedex 5
STUDY PERIOD	Nov 2001 – April 2002

Rationale for Drug-Drug Interaction Study

	Simvastatin	Dronedarone
Indication/Mechanism of Action	Lipid-altering agent/Inhibitor of HMG-CoA reductase	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic
Metabolites	β-hydroxyacid of simvastatin, 6'-hydroxy, 6'-hydroxymethyl, 6'-exomethylene derivatives (metabolites are active)	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	Hydrolysis, hepatic first-pass metabolism, CYP3A4 substrate	Primarily CYP3A substrate
CYP Inhibitory Potential	None	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Recommended – 20-40 mg/day; Max – 80 mg/day	400 mg BID

Objectives (per applicant)

Primary objectives

- To assess the effect of repeated oral doses of dronedarone on the PK profile of simvastatin (SV) and its metabolite, simvastatin acid (SVA), after repeated oral doses of 40 mg QD SV
- To assess the effect of repeated oral doses of SV on the PK profile of dronedarone and its metabolite SR35021 after repeated oral doses of 400 mg BID dronedarone

Secondary objectives

To assess the clinical and biological tolerability of dronedarone given alone, of SV give alone and of dronedarone co-administered with SV

Study Design

This was an open-label, repeated oral dose, randomized, and 3-treatment by 3-period crossover study, with washouts of seven to 13 days between periods. Subjects were randomly allocated to one of six sequences that included (in varying order), the three following treatment periods:

- Period 1: Repeated oral administrations of dronedarone 400 mg at 8:00 AM and at 08:00 PM at the end of a standardized meal for 14 days
- Period 2: Repeated oral administrations of 40 mg SV at 8:00 AM at the end of a standardized breakfast for 14 days

- Period 3: Repeated oral administrations of dronedarone 400 mg and SV 40 mg at 8:00 AM at the end of a standardized breakfast and repeated oral administrations of dronedarone 400 mg at 08:00 PM at the end of a standardized dinner for 14 days

Subject Demographics

Subject demographics are presented in Table 140.

Table 140: Summary of subject demographic data (INT 4880)

Parameter (unit)	Statistics/Category	Total (N=24)
Age (years)	N Mean (SD) Min - Max	24 27.5 (4.9) 20-35
Weight (kg)	N Mean (SD) Min - Max	24 73.59 (7.86) 58.2-88.4
Height (cm)	N Mean (SD) Min - Max	24 179.3 (5.3) 164-189
Body mass index (kg/m2)	N Mean (SD) Min - Max	24 22.86 (1.93) 19.9-26.1
Gender	Male (N,%)	24 (100%)
Race	Caucasian (N,%)	24 (100%)

Pharmacokinetic sampling times

Pharmacokinetic blood samples were drawn as follows:

- dronedarone and SR35021: before morning administration on Day 1, 3, 7, 10 and 12 and before morning administration and then 0.5, 1, 2, 3, 4, 6, 8, 10, 12 hours after dosing on Day 14, for each period of treatment.
- Simvastatin and SVA: before administration on Day 1, 3, 7, 10 and 12 and before administration and then 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after dosing on Day 14, for each period of treatment.

Formulation

- Dronedarone 400 mg tablets, batch number CL-03936.
- Simvastatin 20 mg tablets, batch number 214509

Pharmacokinetics

The following pharmacokinetic (PK) parameters were determined for dronedarone, SR35021, SV and SVA at Day 14 of each period of treatment: C_{max}, t_{max}, C_{max}, C_{trough}, AUC_{0-12}, AUC_{0-24}, R_{met} ($AUC_{0-12\ metabolite}/AUC_{0-12\ drug}$).

Pharmacodynamics

The following pharmacodynamic (PD) parameters were determined: HR, PR-interval, QRS-interval, QT-interval, QTc-interval, T-wave amplitude.

Statistical methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. Dronedarone alone was the reference treatment and dronedarone + simvastatin was the test treatment.

Bioanalytical methods

The plasma concentrations of the dronedarone and its circulating metabolite SR35021 (N-debutyl) were determined by a validated liquid chromatography-mass spectrometry (LC-MS/MS) method. The assay performance was acceptable as shown in Table 141.

Table 141: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the range of 0.5 to 300 ng/ml; $R^2 > 0.996$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided *	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the range of 0.500 to 300 ng/ml; $R^2 > 0.990$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided *	Cannot be assessed

* The validation report includes chromatograms that indicate assay specificity

The plasma concentrations of SV and SVA were determined by a validated LC-MS/MS method. The assay performance was acceptable as shown in Table 142.

Table 142: Performance of Simvastatin and Simvastatin Acid

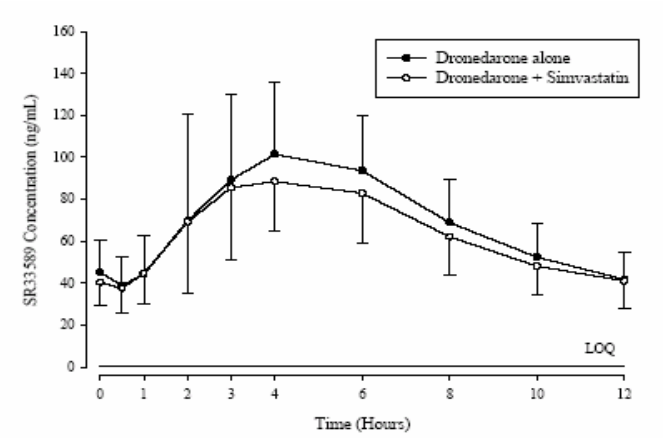
Parameter	Measure	Reviewer Comment
	Simvastatin Assay	
Linearity	The assay was linear over the range of 0.5 to 1000 ng/mL; $R^2 > 0.994$	Satisfactory
Between day Precision	CV < 6.7%	Satisfactory
Accuracy	QC samples were between 0.6 and 7.8 % of nominal concentration	Satisfactory
LLOQ	0.1 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory
	Simvastatin Acid Assay	
Linearity	The assay was linear over the range of 0.5 ng/mL to 1000 ng/mL; $R^2 > 0.992$	Satisfactory
Between day Precision	CV < 7.0	Satisfactory
Accuracy	QC samples were between -4.0 and 3.0 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Results

Dronedarone Pharmacokinetics

The mean dronedarone plasma concentration-time profiles for dronedarone 400 mg BID in the absence and presence of simvastatin are depicted in Figure 78.

Figure 78: Mean (SD) dronedarone plasma concentrations observed after repeated dronedarone 400 mg BID oral administrations, alone or co-administered with SV 40 mg (n=23)



Dronedarone PK measures are summarized in Table 143. Dronedarone exposure was similar in the presence and absence of simvastatin as shown in Table 143. The associated confidence intervals were almost entirely within the no effect range (0.8 to 1.25 based on 90% confidence interval); suggesting, this change is not clinically significant.

Table 143: Mean (CV%) dronedarone and SR35021 PK parameters, their ratio estimates and 90% CI, observed on Day 14 (n=23)

PK Parameter Mean (CV%)	Dronedarone alone	Dronedarone + Simvastatin	Ratio estimates[b] and 90% CI
SR33589			
C_{max} (ng/mL)	118.7 (37)	104.2 (25)	0.89 [0.78 ; 1.02]
t_{max} (h)[a]	4	3	p=0.126
AUC_{0-12} (ng.h/mL)	846 (30)	777 (25)	0.92 [0.85 ; 1.00]
SR35021			
C_{max} (ng/mL)	87.2 (23)	79.9 (24)	0.92 [0.84 ; 1.00]
t_{max} (h)[a]	6	6	p=0.245
AUC_{0-12} (ng.h/mL)	755 (24)	678 (27)	0.89 [0.84 ; 0.95]
R_{mat} (AUC_{0-12})	0.93 (26)	0.89 (23)	0.97 [0.90 ; 1.04]

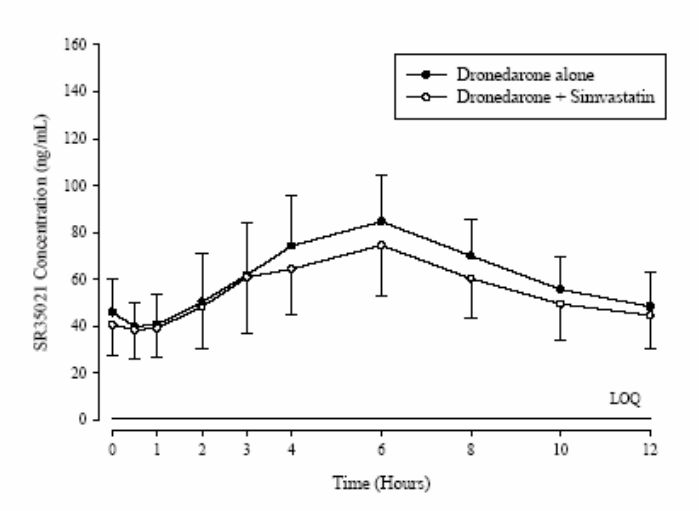
a : Median values, b : ratio dronedarone + simvastatin / dronedarone, p-value for difference between regimens

SR35021 Pharmacokinetics

The mean plasma concentration-time profiles for SR35021 following administration of dronedarone with or without simvastatin are depicted in Figure 79. SR35021 PK are summarized in Table 143.

SR35021 exposure was similar in the presence and absence of simvastatin.

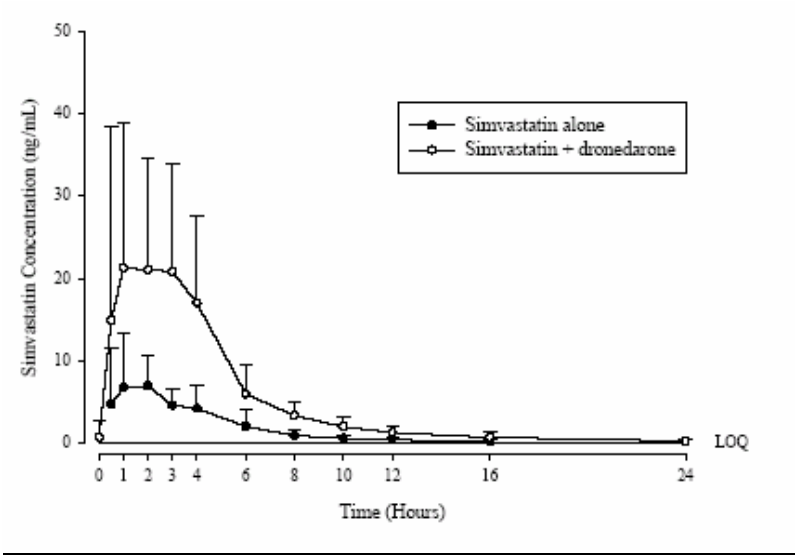
Figure 79: Mean (SD) SR35021 plasma concentrations observed after repeated dronedarone 400 mg BID oral administrations, alone or co-administered with SV 40 mg (n=23)



Simvastatin Pharmacokinetics

The mean simvastatin plasma concentration-time profiles following administration of 40 mg QD simvastatin alone or coadministered with dronedarone 400 mg BID are depicted in Figure 80.

Figure 80: Mean (SD) SV plasma concentrations observed after repeated SV 40 mg QD administrations, alone or co-administered with dronedarone 400 mg BID (n=24)



SV PK measures are summarized in Table 144.

Table 144: Mean (CV%) SV and SVA PK parameters, their ratio estimates and 90% CI, observed on Day 14 (n=24)

PK Parameter Mean (CV%)	Simvastatin alone	Simvastatin + Dronedarone	Ratio estimates[b] and 90% CI
Simvastatin			
C_{max} (ng/mL)	10.7 (55)	38.6 (42)	3.75 [3.16 ; 4.44]
t_{max} (h)[a]	2	2	p=0.767
AUC_{0-24} (ng.h/mL)	34.4[c] (44)	125.8[d] (30)	3.90 [3.18 ; 4.76]
Simvastatin acid			
C_{max} (ng/mL)	3.8 (57)	8.1 (43)	2.14 [1.76 ; 2.60]
t_{max} (h)[a]	5	4	p=0.072
AUC_{0-24} (ng.h/mL)	29.3[c] (44)	60.3[c] (48)	1.96 [1.63 ; 2.35]

a : Median values, b : ratio simvastatin + dronedarone / simvastatin, p-value for difference between regimens, c: n=23, d: n=22

As shown in Table 144, simvastatin exposure was increased in the presence of dronedarone by almost 4-fold for both Cmax and AUC. Clinically, dronedarone may increase the therapeutic and undesirable side effects of simvastatin when administered together. Simvastatin (and other HMG-CoA reductase inhibitors that are CYP3A4 substrates) may require dose adjustments and safety monitoring (discussed further in Labeling section) when given with dronedarone.

The match stick plots for SV Cmax and AUC are shown in Figure 81 and Figure 82. These plots further illustrate the increase in SV exposure when co-administered with dronedarone.

Figure 81: Individual, mean (SD) and geometric mean SV Cmax values observed after repeated oral administration of SV alone or co-administered with dronedarone (n=24)

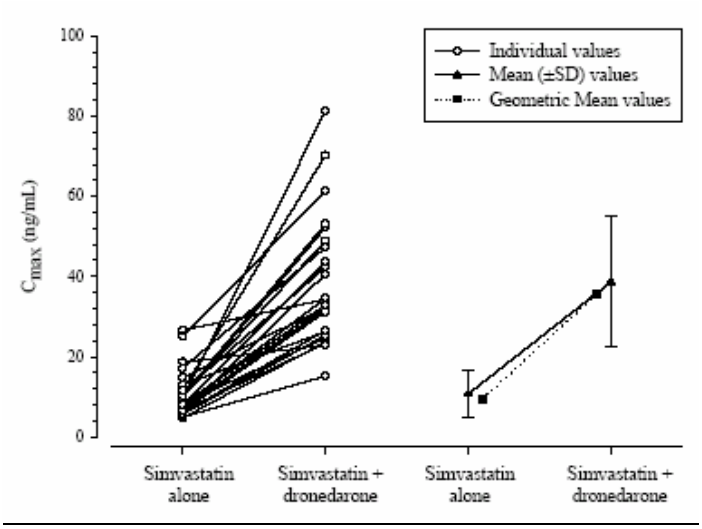
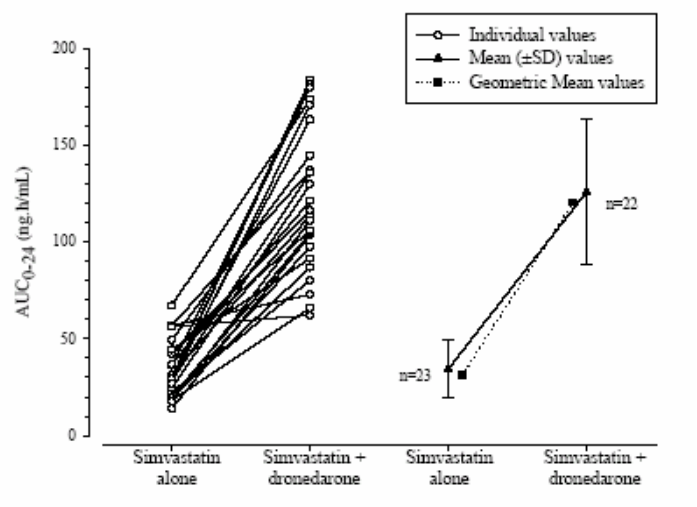


Figure 82: Individual, mean (SD) and geometric mean SV AUC0-24 values observed after repeated oral administration of SV alone or co-administered with dronedarone (n=24)

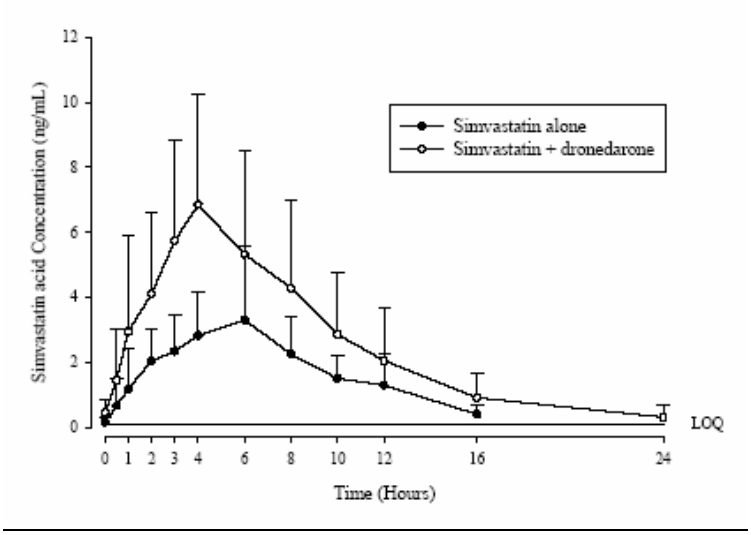


SVA Pharmacokinetics

The mean SVA plasma concentration-time profiles following administration of 40 mg QD simvastatin alone or coadministered with dronedarone 400 mg BID are depicted in Figure 83.

SVA PK are summarized in Table 144. SVA exposure increased by approximately 2-fold for both Cmax and AUC. Clinically, this increase in exposure may affect the activity, therapeutic and undesirable side effects, of simvastatin. Again, dose adjustments are needed and will be discussed in the section on Labeling.

Figure 83: Mean (SD) SVA plasma concentrations observed after repeated SV 40 mg QD oral administrations, alone or co-administered with dronedarone 400 mg BID (n=24).



The match stick plots for SV Cmax and AUC are shown in Figure 84 and Figure 85. These plots further illustrate the increase in SVA exposure when co-administered with dronedarone.

Reviewer Comment on SVA Cmax and AUC Plots After Administration of Simvastatin with and without Dronedarone

- Cmax: Overall, there is an increase in Cmax and most subjects have an increase; however, a few individual plots show a clear decrease.
- AUC: Overall, there is an increase in AUC; however, a few of the individual plots show a slight decrease.

Figure 84: Individual, mean (SD) and geometric mean SVA Cmax values observed after repeated oral administration of SV alone or co-administered with dronedarone (n=24)

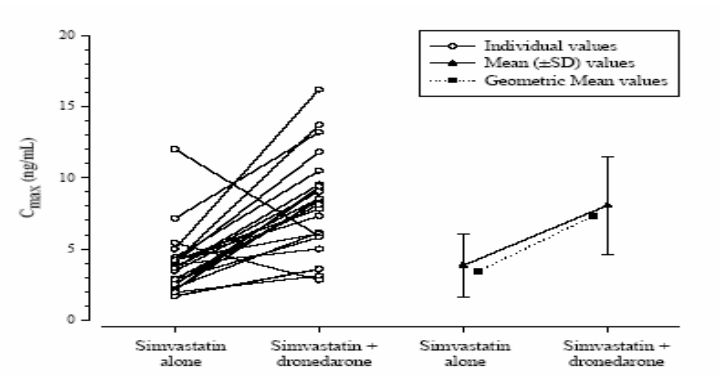
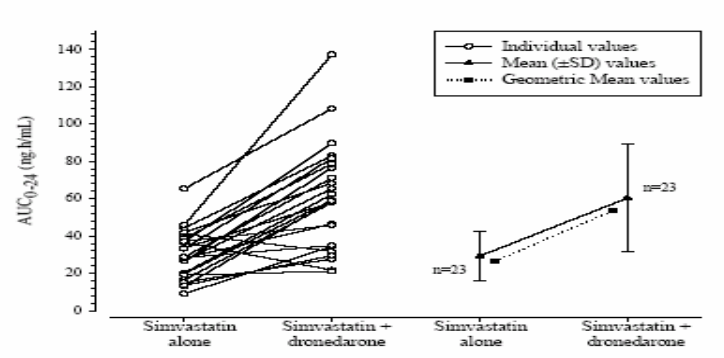


Figure 85: Individual, mean (SD) and geometric mean SVA AUC0-24 values observed after repeated oral administration of SV alone or co-administered with dronedarone (n=24)



Applicant's Safety Summary

There were no deaths or serious adverse events (SAEs) reported during this study.
Four subjects reported treatment emergent adverse events (TEAEs) on both dronedarone alone, and on dronedarone co-administered, *versus* five subjects on SV alone. One subject discontinued treatment due to an AE. The reported AEs that occurred during the co-administration of dronedarone and simvastatin included pain, headache, and rash.

Recommendations/Conclusions

- Simvastatin (40 mg) given once daily over 14 days did not affect dronedarone pharmacokinetics.
- Dronedarone (400 mg) given twice daily over 14 days inhibited simvastatin metabolism; consequently, plasma concentrations for simvastatin and its metabolite were elevated (simvastatin: 4-fold increase in Cmax and AUC, SVA: 2-fold increase in Cmax and AUC).

Labeling

Sponsor's Proposed Labeling
Dronedarone (400 mg twice daily) increased simvastatin and simvastatin acid exposure by 4-fold and 2-fold, respectively.

Reviewer's Comments on Labeling
The proposed labeling is not acceptable. Due to the large increase in simvastatin exposure when co-administered with dronedarone, simvastatin dose adjustments and monitoring should be included in the label. The following statement is recommended.

> *In patients taking simvastatin concomitantly with dronedarone, therapy should be started or adjusted to the lowest dose of simvastatin (10 mg) (See **PRECAUTIONS**). Treatment with an alternative HMG Co-A reductase inhibitor that is not a CYP3A substrate should be considered.*

4.2.23 Pharmacokinetic and Pharmacodynamic Effects of Single and Repeated Oral Doses of SR33589B and of Propranolol Given Alone or Coadministered in Healthy Male Subjects (INT 2636)

PROTOCOL #	INT2636
INVESTIGATOR	Wolfgang Tetzloff, MD
STUDY SITE	Iphar Institut fur Klinische Pharmakologie GmbH, Germany
STUDY PERIOD	January – May 1996

Background Information on Study Drugs (Propranolol and Dronedarone)

	Propranolol	Dronedarone
Indication	Beta blocker; Used in the management of hypertension, angina, cardiac arrhythmias, ventricular tachycardias, and essential tremor; used to reduce cardiovascular mortality post-myocardial infarction; used for prophylaxis of migraines	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic.
Metabolites	4-hydroxypropranolol (HOP), naphthoxylactic acid, and propranolol glucuronide	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites.
Metabolic Pathway	Extensive first pass metabolism, mostly by CYP2D6. (Some metabolism by CYP1A2 and 2C19). Cleared by the urine.	Primarily CYP3A substrate.
CYP Inhibitory Potential	N/A	Low to moderate potential to inhibit CYP3A and CYP2D6, as well as PGP.
Highest Recommended Dose/Studied Dose	Available in oral and injectable formulations. The dose can range from 30 – 640 mg/day depending on the indication. The dose can be titrated.	800 mg once daily (oral)

Objectives (per applicant)

- Primary: to assess the effect of repeated oral doses of dronedarone on propranolol pharmacokinetics at steady state
- Secondary:
  - to assess the effect of repeated oral doses of dronedarone on propranolol pharmacodynamics at steady state
  - to assess the pharmacokinetic (PK) and pharmacodynamic (PD) interaction of a single oral dose of dronedarone and a single oral dose of propranolol
  - to assess the tolerability of dronedarone and propranolol given alone or together

Study Design

This was an open-label and non placebo-controlled study. The study treatments were given according to the following schedule:

- Days 2 – 8: 80 mg propranolol QD
- Days 9 – 22: washout period
- Day 23: 800 mg dronedarone (one dose)
- Days 26 – 32: 80 mg propranolol and 800 mg dronedarone QD

Subjects received dronedarone and propranolol after a standard breakfast.

Reviewer Note on Study Design
Identifying metabolic differences in patient groups based on genetic polymorphisms should be understood and examined in this study. The reason for this is due to the variation in metabolism of CYP2D6 among people of different populations. The dose of dronedarone used in this study was 800 mg QD, which is the proposed therapeutic dose of 400 mg BID.

Subject Demographics
The study was conducted in Caucasian males. Subject demographic characteristics are shown in Table 145.

Table 145: Demographic characteristics (INT2636)

Parameter (Units)	Mean	SD	Minimum	Maximum
Age (years)	27.8	5.1	20.0	36.0
Weight (kg)	70.9	5.5	60.1	80.8
Height (cm)	176.4	5.8	164.0	185.0

Pharmacokinetic sampling times
Blood samples were collected at:

- Pretreatment: Days 2, 3, 5, 7, 23, 26, 27, 29, and 31.
- Post-treatment:
  - Days 2, 3, and 26 at 1, 2, 3, 4, 5, 6, 8, and 12 hours
  - Days 8 and 32 at 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours

Formulation

- Dronedarone: 100 mg capsules, batch number M303S
- Propranolol (Avlocardyl®): 40 mg tablet, batch number 4227

Bioanalytical methods
Dronedarone and SR35021: Plasma concentrations were measured using high performance liquid chromatography (HPLC) with ultraviolet (UV) detection. The assay method was acceptable as illustrated in Table 146.

Table 146: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 5.0 to 1000 ng/mL range	Satisfactory
Between day Precision	CV was < 9% of nominal concentration	Satisfactory
Accuracy	QC samples were between 3% to 7% of nominal concentration	Satisfactory
LLOQ	5.0 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 5.0 to 1001.9 ng/mL range	Satisfactory
Between day Precision	CV was < 11% of nominal concentration	Satisfactory
Accuracy	QC samples were between 3% to 15% of nominal concentration	Satisfactory
LLOQ	5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms were provided in the validation report indicating assay specificity.

Propranolol: Plasma concentrations were measured using HPLC with fluorimetric detection, after liquid extraction. The assay performance was acceptable as illustrated in Table 147.

Table 147: Performance of Propranolol Assay

Parameter	Measure	Reviewer Comment
	Propranolol Assay	
Linearity	The linear range of the assay was not provided.	Cannot be assessed
Between day Precision	CV was < 6 % of nominal concentration.	Satisfactory
Accuracy	QC samples were between 3.12% to 4.91% of nominal concentration	Satisfactory
LLOQ	1.0 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms were provided in the validation report indicating assay specificity.

Pharmacokinetics

The following pharmacokinetic (PK) parameters were measured for dronedarone and SR35021:

Days 23, 26, and 32: C_{max}, t_{max}, AUC_{0-24}

Day 32: R_{ac} (ratio accumulation factor) = AUC_{0-24} repeated dose / AUC_{0-24} single dose

Days 26, 27, 29, 31, 32, and 33: C_{bt} (trough concentration)

The following PK parameters were measured for propranolol:

- Days 2, 7, 26, and 32: C_{max}, t_{max}, AUC_{0-12}, and AUC_{last}
- Days 8 and 32: R_{ac} = AUC_{last} repeated dose / AUC_{last} single dose
- Days 3, 5, 7, 8, 9, 26, 27, 29, 31, 32, and 33: C_{bt}

Pharmacodynamics

The following pharmacodynamic (PD) parameters were determined:

- Vital signs (heart rate, systolic blood pressure, and diastolic blood pressure)
- Electrocardiogram (ECG) at rest and after submaximal exercise on Days 1 (pretreatment), 2, 8, 23, 26, and 32 at T0, T1, T3, and T8.

Statistical methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. The time to reach steady state was assessed.

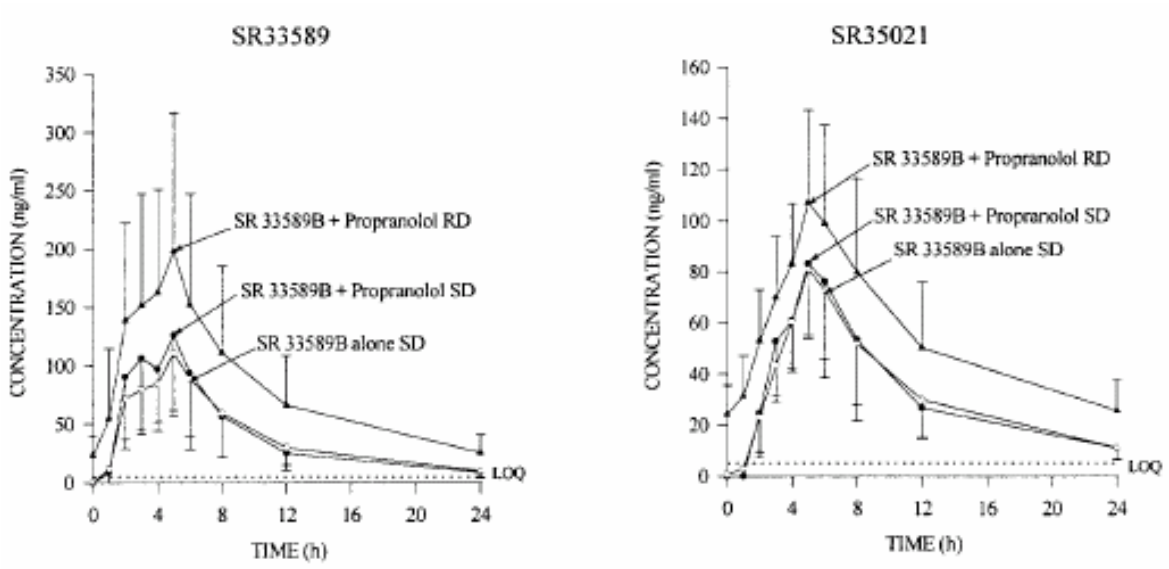
Resting vital signs were summarized by the parameter AUC_{0-8}, and analyzed for 'treatment' effects and chronological ('time') effects using repeated measures analysis of variance. Exercise vital signs were analyzed in a similar manner.

Results

Dronedarone and SR35021

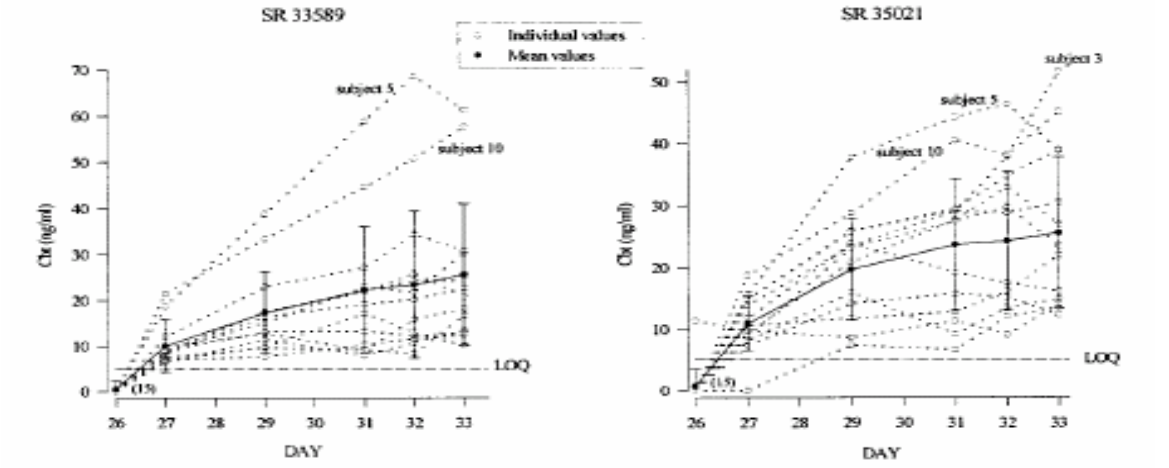
The mean plasma concentration versus time curves of dronedarone and SR35021 obtained after single and repeated administrations of dronedarone alone or with propranolol are shown in Figure 86.

Figure 86: Time course of mean values of plasma concentrations of dronedarone and SR35021 obtained after single (SD) and repeated daily (RD) doses of 800 mg dronedarone alone or combined with daily doses of 80 mg propranolol



Individual and mean C_{bt} values of dronedarone and SR35021 after coadministration of dronedarone plus propranolol for seven days are shown in Figure 87.

Figure 87: Individual and mean C_{bt} values of dronedarone and SR35021 obtained after repeated daily doses of 800 mg dronedarone alone or combined with daily doses of 80 mg of propranolol on Days 26 to 33



Based on statistical analyses, steady state was reached by the sixth daily administration of dronedarone.

Table 148, Table 149, Table 150, and Table 151 show the dronedarone and SR35021 PK measures after the administration of dronedarone alone (Day 23) or with propranolol (Days 26-32).

Table 148: Dronedarone PK Measures Following Administration of Dronedarone +/- Propranolol

SR33589 Parameters (units)		SR33589B Alone	SR33589B + Propranolol	
		Single Dose (Day 23)	Single Dose (Day 26)	Repeated Dose (Day 32)
C_{max} (ng/ml)	Mean	140.5	131.2	219.9
	SD	59.9	58.3	104.5
	CV%	43	44	48
t_{max} (h)	Mean	3.63	4.25	4.06
	SD	1.37	1.39	1.57
	CV%	38	33	39
AUC_{0-24} (ng.h/ml)	Mean	983.1	950.9	1943.0
	SD	447.1	419.3	1098.9
	CV%	45	44	57

Table 149: Confidence intervals (CI) for dronedarone PK parameters obtained after administration of dronedarone alone (Day 23) versus dronedarone plus propranolol (Day 26)

SR33589B alone (Day 23) versus SR33589B + Propranolol (Day 26)			
SR33589 Parameter	'Treatment' Effect P-Value*	90% CI	95% CI
C_{max}	0.3570	0.78, 1.08	0.75, 1.12
AUC_{0-24}	0.5865	0.86, 1.08	0.84, 1.11

* = statistically significant if $p < 0.05$

Table 150: Mean, SD, and CV% for SR35021 pharmacokinetic parameters

SR35021 Parameters (units)		SR33589B Alone	SR33589B + Propranolol	
		Single Dose (Day 23)	Single Dose (Day 26)	Repeated Dose (Day 32)
C_{max} (ng/ml)	Mean	85.9	90.2	111.3
	SD	28.8	32.8	36.1
	CV%	34	36	32
t_{max} (h)	Mean	5.13	5.13	4.94
	SD	0.72	1.20	1.44
	CV%	14	23	29
AUC_{0-24} (ng.h/ml)	Mean	768.6	759.6	1295.7
	SD	278.4	284.7	510.7
	CV%	36	37	39

Table 151: Confidence intervals for SR35021 PK parameters obtained after administration of dronedarone alone (Day 23) versus dronedarone plus propranolol (Day 26)

SR33589B alone (Day 23) versus SR33589B + Propranolol (Day 26)			
SR35021 Parameter	'Treatment' Effect P-Value*	90% CI	95% CI
C_{max}	0.5201	0.93, 1.16	0.91, 1.19
AUC_{0-24}	0.8217	0.86, 1.12	0.83, 1.16

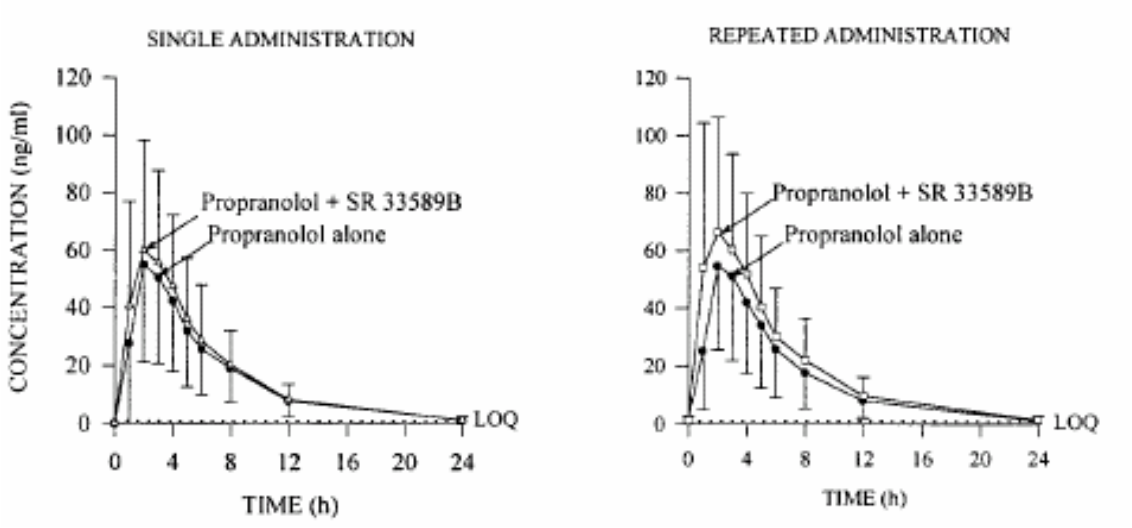
* = statistically significant if $p < 0.05$

The C_{max} and AUC of dronedarone and SR35021 are not altered upon single dose. The increase in dronedarone exposure upon repeated doses of dronedarone and propranolol is likely due to dronedarone accumulation.

Propranolol

Mean propranolol plasma concentrations versus time curves obtained after single and repeated administrations of propranolol alone or with dronedarone are shown in Figure 88.

Figure 88: Time course of mean values for plasma concentrations of propranolol obtained after single and repeated daily doses of 80 mg propranolol alone or combined with daily doses of 800 mg dronedarone



The mean, SD, and CV% values of propranolol PK measures after single and repeated daily dosing of propranolol alone (Days 2 and 8) or coadministered with dronedarone (Days 26 and 32) are shown in Table 152. P values and confidence intervals (CI) are shown in Table 153 and Table 154.

Table 152: Mean, standard deviation (SD) and coefficient of variance (CV%) for propranolol pharmacokinetics parameters

Propranolol Parameters (units)	Statistic	Propranolol Alone		SR33589B + Propranolol	
		Single Dose (Day 2)	Repeated Dose (Day 8)	Single Dose (Day 26)	Repeated Dose (Day 32)
C_{max} (ng/ml)	Mean	59.79	57.68	68.65	75.38
	SD	33.77	31.47	40.53	42.05
	CV%	56	55	59	56
t_{max} (h)	Mean	2.19	2.26	2.06	2.00
	SD	0.66	0.57	1.06	0.89
	CV%	30	25	51	45
AUC_{0-12} (ng.h/ml)	Mean	318.75	313.88	359.14	403.76
	SD	178.62	175.01	188.07	234.77
	CV%	56	56	52	58
AUC_{last} (ng.h/ml)	Mean	360.85	354.73	403.30	455.06
	SD	210.30	214.63	225.67	284.21
	CV%	58	61	56	62
R_{ac}	Mean	-	1.00	-	1.16
	SD	-	0.25	-	0.20
	CV%	-	25	-	17

Table 153: Confidence intervals (CIs) for propranolol PK parameters obtained after single dosing with propranolol alone (Day 2) versus dronedarone plus propranolol (Day 26)

Single Dosing: Propranolol Alone (Day 2) versus SR33589B + Propranolol (Day 26)			
Propranolol Parameter	**'Treatment' Effect P-Value***	**90% CI**	**95% CI**
C_{max}	0.1359	0.98, 1.39	0.95, 1.44
AUC_{0-12}	0.0692	1.02, 1.34	0.99, 1.38
AUC_{last}	0.0944	1.00, 1.33	0.97, 1.37

* = statistically significant if p <0.05

Table 153 shows that dronedarone did not significantly change propranolol PK (CIs included), however the CI's were outside of the no-effect interval.

Table 154: Confidence intervals for propranolol PK parameters obtained after repeated dosing with propranolol alone (Day 8) versus dronedarone plus propranolol (Day 32)

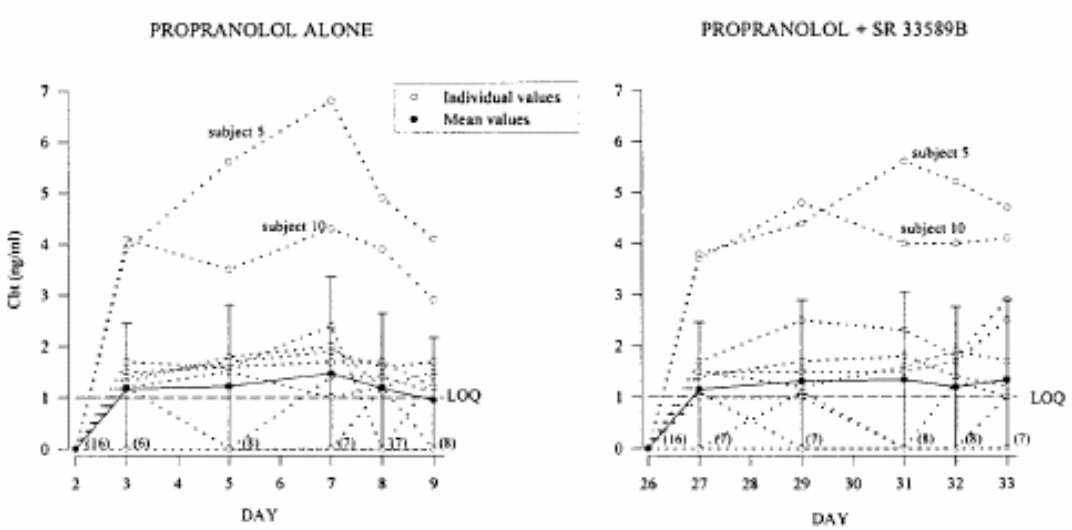
Repeated Dosing: Propranolol Alone (Day 8) versus SR33589B + Propranolol (Day 32)			
Propranolol Parameter	**'Treatment' Effect P-Value***	**90% CI**	**95% CI**
C_{max}	0.0061	1.16, 1.69	1.12, 1.76
AUC_{0-12}	0.0050	1.16, 1.62	1.12, 1.68
AUC_{last}	0.0053	1.16, 1.62	1.11, 1.68
R_{ac}	0.0234	1.05, 1.33	1.03, 1.37

* = statistically significant if p <0.05

Table 154 shows a significant change in propranolol PK levels after repeated dosing of dronedarone and propranolol.

Individual and mean values for the C_{bt} of propranolol on Days 3 to 9 after the administration of propranolol alone on Days 2 to 9, and on Days 27 to 33 after administration of dronedarone plus propranolol on Days 26 to 32 are shown in Figure 89.

Figure 89: Individual and mean C_{bt} values of propranolol obtained after repeated daily doses of 80 mg propranolol alone or combined with daily doses of 800 mg dronedarone



The combined analysis of C_{bt} values for Days 3 to 9 and those observed for days 27 to 33 showed no statistically significant 'day' effect, 'treatment' effect, or 'day-by-treatment' interactions.

Propranolol steady state was reached 24 hours after the first dose, whether propranolol was administered alone or coadministered with dronedarone.

Pharmacodynamics

1. Resting Conditions

AUC values for heart rate (HR) and ECG parameters are shown in Table 155.

Table 155: Summary of AUC_{0-8} values for ECG parameters at rest after repeated dosing of propranolol with or without dronedarone

Parameter (units)	Day 8 vs. Day 1 Mean Value (%)		Day 32 vs. Day 1 Mean Value (%)		Day 32 vs. Day 8	
					Mean Value	P-Value*
HR (bpm.h)	-45.5	(-8.9)	-32.7	(-6.4)	12.8	0.184
PQ (ms.h)	42.4	(3.9)	139.3	(11.9)	96.9	<0.001
QRS (ms.h)	-0.1	(0.0)	6.3	(0.7)	6.4	0.394
QT (ms.h)	111.3	(3.6)	137.1	(4.4)	25.9	0.467
QTc (ms.h)	-59.7	(-1.9)	15.6	(0.5)	75.3	<0.001
T-wave (mm.h)	1275.6	(28.3)	153.5	(7.9)	-1122.1	0.001

Day 1 = Baseline (pretreatment), Day 8 = last day of repeated dosing (steady state) with propranolol, Day 32 = last day of repeated dosing of SR33589B plus propranolol
% = percent change from Day 1
* = statistically significant if $p<0.05$

Resting ECG heart rate decreased compared to baseline after repeated once daily dosing of propranolol alone (-9%), and after coadministration of dronedarone and propranolol (-6%). The changes from baseline in resting ECG parameters after single oral administration of propranolol or single oral coadministration of dronedarone and propranolol were similar to those seen after repeated dosing.

Resting HR, systolic blood pressure (BP), and diastolic BP (Table 156) decreased after repeated oral administration of propranolol alone and after coadministration with dronedarone.

Table 156: Summary of AUC_{0-8} values for vital signs at rest after repeated dosing of propranolol with or without dronedarone

Parameter (Units)	Day 8 vs. Day 1 Mean Value (%)		Day 32 vs. Day 1 Mean Value (%)		Day 32 vs. Day 8	
					Mean Value	P-Value*
HR (bpm.h)	-42.7	(-8.1)	-22.2	(-4.3)	20.4	0.038
SBP (mmHg.h)	-48.3	(-5.0)	-71.8	(-7.6)	-23.6	0.055
DBP (mmHg.h)	-52.3	(-9.9)	-61.9	(-11.9)	-9.7	0.324

Day 1 = Baseline (pretreatment), Day 8 = last day of repeated dosing (steady state) with propranolol, Day 32 = last day of repeated dosing of SR33589B plus propranolol
% = percent change from Day 1
* = statistically significant if $p<0.05$

2. Exercise Conditions

The changes in PD measures under exercise conditions are shown in Table 157.

Table 157: Summary of AUC_{0-8} values for vital signs during submaximal exercise after repeated dosing of propranolol with or without dronedarone

Parameter (Units)	Day 8 vs. Day 1 Mean (%)		Day 32 vs. Day 1 Mean (%)		Day 32 vs. Day 8	
					Mean	P-Value
HR (bpm.h)	-176.0	(-16.1)	-226.8	(-20.7)	-50.8	<0.001
SBP (mmHg.h)	-170.3	(-11.7)	-266.8	(-18.2)	-96.6	<0.001
DBP (mmHg.h	-11.5	(-1.5)	-46.8	(-6.9)	-35.3	0.005

Day 1 = pretreatment, Day 8 = last day of repeated dosing (steady state) with propranolol,
Day 32 = last day of repeated dosing of SR33589B plus propranolol
% = percent change from Day 1
* = statistically significant if p<0.05

During submaximal exercise, there was a decrease in HR, systolic BP, and diastolic BP from baseline after repeated oral administration of propranolol alone and after coadministration with dronedarone.

The decreases in HR, systolic BP, and diastolic BP were all statistically significantly greater after the drugs were coadministered compared to propranolol alone.

According to the applicant, none of the changes in the ECG parameters or vital signs at rest or during submaximal exercise were considered to be clinically relevant. The applicant's conclusion appears reasonable as only small decreases in HR, systolic BP, and diastolic BP were seen. Also, the dose of propranolol can be titrated if needed to counter undesirable effects.

Applicant's Safety Summary

Five subjects reported nine adverse events (AEs) during the study. None of the AEs were considered by the investigator to be serious; three were of moderate intensity, and the other six were of mild intensity. Of the three AEs of moderate intensity, one was in the propranolol alone arm and the other two were in the propranolol and dronedarone arm. None of the AEs required corrective therapy, however, three subjects discontinued. No deaths were reported.

Recommendations/Conclusions

1. Repeated dose administration of dronedarone and propranolol significantly increased plasma concentrations of propranolol at steady state (16% to 33%).
2. Single dose administration of 800 mg dronedarone and 80 mg propranolol did not modify the PK profile of propranolol, dronedarone, or SR35021, relative to administration of dronedarone or propranolol alone.
3. The PD effects (HR, systolic BP, diastolic BP, and ECG parameters) of propranolol or dronedarone given alone were potentiated when the two compounds were coadministered.

Reviewer Comment

At steady state, mean plasma levels of propranolol coadministered with dronedarone were higher than those obtained after repeated administration of propranolol alone. This may be explained by the inhibition of CYP2D6 mediated metabolism of propranolol since it has been demonstrated that dronedarone can potentially inhibit CYP3A4 and 2D6. However, these increases (plasma concentrations of 16% to 33%) do not appear clinically relevant.

Applicant's Proposed Labeling
Due to the pharmacokinetic interaction and possible pharmacodynamic interaction, beta blockers should be used with caution concomitantly with dronedarone.

Reviewer Note on Label
The sponsor adequately states a caution against using propranolol while taking dronedarone. The labeling is acceptable. Propranolol doses can be titrated to achieve the desired effect.

4.2.24 Interaction study between repeated oral doses of dronedarone and repeated ascending oral doses of verapamil in healthy young male subjects - Three-group, randomized, open-labeled, three-treatment, crossover study (INT 4882)

PROTOCOL #	INT4882
INVESTIGATOR	Wolfgang Tetzloff, MD
STUDY SITE	MDS Pharma Services, Arnikastrasse 4; 85635 Hohenkirchen-Siegerstsbrunn; Germany
STUDY PERIOD	May – September 2002

Background Information on Study Drugs (Verapamil and Dronedarone)

	Calan (Verapamil)	Dronedarone (SR33589)
Indication	Calcium Channel Blocker; For the treatment of angina, arrhythmias, and essential hypertension.	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic.
Metabolites	Twelve metabolites have been identified in plasma, mostly in trace amounts. The major metabolite is norverapamil.	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites.
Metabolic Pathway	First-pass effect; Predominantly biotransformed by CYP3A4, however CYP1A2 and members of the CYP2C family are also involved in the metabolism. 70% is excreted in the urine as metabolites.	Primarily CYP3A substrate.
CYP Inhibitory Potential	Predominantly CYP3A4.	Low to moderate potential to inhibit CYP3A and CYP2D6, as well as PGP.
Highest Recommended Dose/Studied Dose	Available in sustained release (SR) and immediate release (IR) formulations. The dose can range from 80 – 480 mg/day depending on the indication and can be titrated.	400 mg BID.

Objectives (per applicant)

- Primary:
  - to assess the effect of repeated oral doses of 400 mg BID dronedarone on the pharmacokinetic (PK) profile of verapamil and its metabolite norverapamil after repeated oral doses of verapamil sustained release (SR) formulation for 14 days
  - to assess the effect of repeated oral doses of verapamil SR formulation on the PK profile of dronedarone and its metabolite SR35021 after repeated oral doses of 400 mg BID dronedarone for 14 days
  - to assess the pharmacodynamics of dronedarone and ascending doses of verapamil given alone and coadministered (magnitude of the prolongation of PR-interval and of QTc) at the end of the repeated doses

Secondary: to assess the clinical and biological tolerability of dronedarone given alone, of verapamil SR formulation given alone at different dose levels, and of dronedarone coadministered with verapamil SR formulation

Study Design

This was an open-label, non placebo-controlled, 3-group, randomized, 3-treatment (dronedarone alone, verapamil alone, and coadministration), and 3-period crossover design with 7- to 14-day washout between periods. The treatment period was 14 days.

Reviewer Note on Study Design

The study design was consistent with the FDA recommended Drug-Drug Interaction Guidance. The doses used in the study were the proposed therapeutic doses. The formulation of verapamil, Isoptin SR was used because it is more common, and the Covera-HS formulation was not appropriate for an interaction study because of its PK profile.

The study was stopped after Group 1 due to a documented PK interaction. It was decided not to continue onto Groups 2 and 3. This is a conservative approach, and is acceptable.

Subject Demographics

The study was conducted in healthy, young, male subjects. Subject demographic characteristics are shown in Table 158.

Table 158: Summary of subject characteristics (INT4882)

Treatment Sequence/ Parameter (Unit)	123 (N=4)	132 (N=4)	213 (N=3)	231 (N=4)	312 (N=3)	321 (N=3)	Total (N=21)
Age (yrs)							
N	4	4	3	4	3	3	21
Mean (SD)	30.3 (3.1)	30.8 (9.6)	31.0 (4.4)	29.0 (5.6)	33.0 (5.3)	30.3 (5.0)	30.6 (5.3)
Min – max	26 - 33	22 - 40	28 - 36	24 - 36	27 - 37	25 - 35	22 - 40
Weight (kg)							
N	4	4	3	4	3	3	21
Mean (SD)	80.43 (5.22)	71.63 (2.57)	79.57 (6.87)	76.07 (10.61)	75.40 (6.16)	73.90 (2.77)	76.15 (6.45)
Min – max	73.1 - 85.3	69.0 - 74.3	75.4 - 87.5	63.8 - 86.8	70.2 - 82.2	72.2 - 77.1	63.8 - 87.5
Height (cm)							
N	4	4	3	4	3	3	21
Mean (SD)	177.3 (3.6)	179.8 (1.7)	180.7 (4.6)	183.5 (3.3)	176.0 (2.6)	179.3 (4.9)	179.5 (3.9)
Min – max	172 - 180	178 - 182	178 - 186	179 - 187	174 - 179	176 - 185	172 - 187
BMI (kg/m²)							
N	4	4	3	4	3	3	21
Mean (SD)	25.60 (0.78)	22.18 (0.39)	24.33 (0.84)	22.55 (2.78)	24.43 (2.66)	22.97 (0.45)	23.64 (1.93)
Min - max	24.7 - 26.6	21.8 - 22.6	23.8 - 25.3	18.8 - 24.8	21.9 - 27.2	22.5 - 23.4	18.8 - 27.2
Gender (n, %)							
Male	4 (100)	4 (100)	3 (100)	4 (100)	3 (100)	3 (100)	21 (100)
Race (n, %)							
Caucasian	4 (100)	4 (100)	3 (100)	4 (100)	3 (100)	3 (100)	21 (100)

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The treatment in any sequence is defined as follows: 1=dronedarone; 2=verapamil; and 3=coadministration

Formulation

- Dronedarone: 400 mg tablet, batch number CL-04530
- Verapamil: 120 mg tablet (Isoptin SR™), batch number 39911

Pharmacokinetic sampling times

Plasma concentrations of dronedarone, SR35021, verapamil, and norverapamil were determined at scheduled times.

- Dronedarone and SR35021 samples were collected:
  - On Days 1, 2, 4, 8, 12, and 14: before morning administration
  - On Day 14: at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 hours after dosing

- Verapamil and norverapamil samples were collected:
    - On Days 1, 2, 4, 8, 12, and 14: before morning administration
    - On Day 14: at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours after dosing

Pharmacokinetics
The following pharmacokinetic (PK) parameters were measured for dronedarone and SR35021: C_{trough}, C_{max}, t_{max}, AUC_{0-12}, and R_{met}.
The following PK parameters were measured for verapamil and norverapamil: C_{trough}, C_{max}, t_{max}, AUC_{0-24}, and R_{met}.

Pharmacodynamics
The following pharmacodynamic (PD) parameters were determined from 12-lead electrocardiogram (ECG) parameters (manual reading):
- primary criteria: PR- and QTcB/F calculation
- secondary criteria: QRS- and QT-intervals, and HR

Bioanalytical methods
Dronedarone and SR35021: Plasma concentrations were determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method (DOH0239). The assay method was acceptable as illustrated in Table 159.

Table 159: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.50 to 300 ng/mL range; $R^2 > 0.996$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers.	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.50 to 300 ng/mL range; $R^2 > 0.991$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers.	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms were provided in the validation report indicating assay specificity.

Verapamil and Norverapamil: Plasma concentrations were determined by a validated high-performance liquid chromatography (HPLC) method with ultraviolet (UV) detection. The assay performance was acceptable as illustrated in Table 160.

Table 160: Performance of Verapamil and Norverapamil Assays

Parameter	Measure	Reviewer Comment
	Verapamil Assay	
Linearity	The assay was linear over the 10.0 to 500 ng/mL range; $R^2 > 0.994$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were within 15% of nominal concentrations.	Satisfactory
LLOQ	10.0 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	Norverapamil Assay	
Linearity	The assay was linear over the 10.0 to 500 ng/mL range; $R^2 > 0.995$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers.	Satisfactory
LLOQ	10.0 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms were provided in the validation report indicating assay specificity.

Statistical methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. The time to reach steady state was assessed.

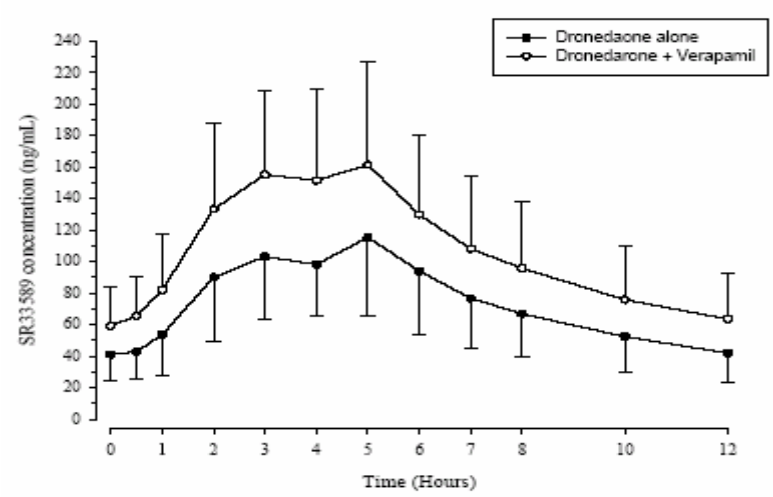
Pharmacodynamic measures were also analyzed using standard statistical approaches. The PD analysis consisted of a comparison of effects on PR-interval prolongation and cardiac repolarization (QTcB, QTcF) after repeated administration of each treatment (verapamil or dronedarone) alone and of the coadministration (verapamil + dronedarone) for PR-interval, QTcB and QTcF.

Results

Dronedarone and SR35021

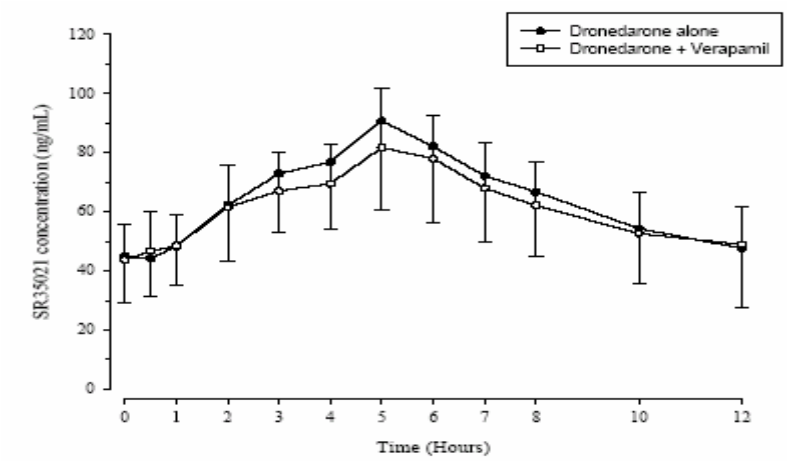
The mean plasma concentration time profiles of dronedarone are shown in Figure 90.

Figure 90: Mean (SD) dronedarone plasma concentrations after repeated oral administration of dronedarone alone (400 mg BID) or coadministration with verapamil (240 mg QD) – Day 14



The mean plasma concentration time profiles of SR35021 are shown in Figure 91.

Figure 91: Mean SR35021 plasma concentrations after repeated oral administration of dronedarone alone (400 mg BID) or coadministration with verapamil (240 mg QD) – Day 14



Mean trough concentrations of dronedarone and SR35021 are graphically summarized in Figure 92 and Figure 93.

Figure 92: Mean dronedarone C_{trough} observed after repeated oral administration of dronedarone alone or coadministration with verapamil

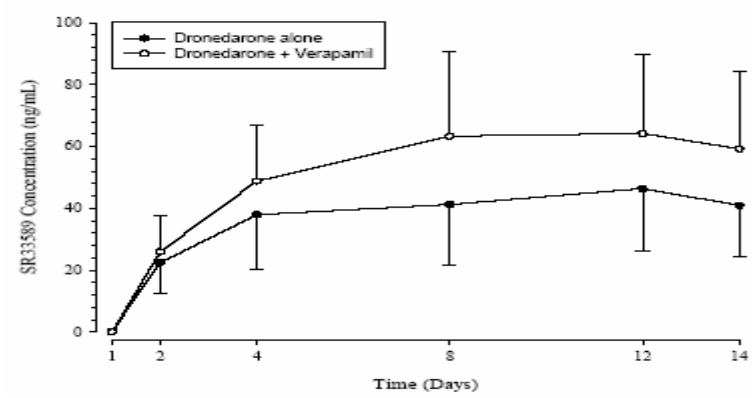
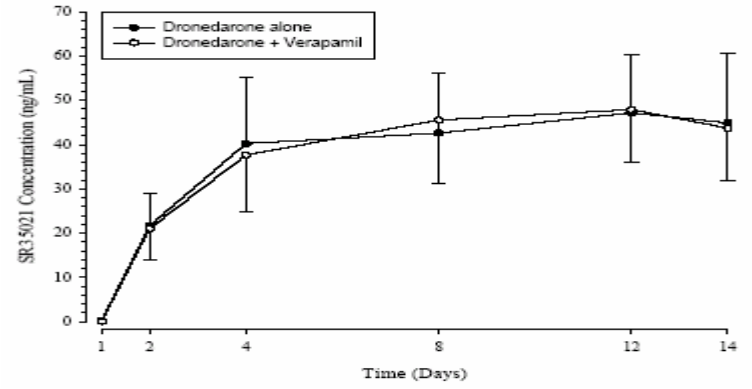


Figure 93: Mean SR35021 C_{trough} observed after repeated oral administration of dronedarone alone or coadministration



Average steady state for dronedarone and SR35021 were reached within four days for dronedarone alone or coadministration with verapamil.

Table 161: Mean (coefficient of variation [CV%]) pharmacokinetic parameters of dronedarone and SR35021 and their ratio estimates and 90 % CI obtained after repeated doses of dronedarone or coadministration with verapamil

PK Parameters	Dronedarone Alone[a]	Dronedarone + Verapamil[b]	Ratio Estimates[c] and 90% CI
Dronedarone			
C_{max} (ng/mL)	135 (32)	188 (30)	1.42 [1.31 - 1.53]
t_{max} (h)[d]	3.00 [2.00 - 5.00]	3.00 [2.00 - 5.00]	p=0.78
AUC_{0-12} (ng.h/mL)	895 (34)	1310 (35)	1.48 [1.38 - 1.58]
SR35021			
C_{max} (ng/mL)	98.0 (33)	88.2 (19)	0.93 [0.83 - 1.04]
t_{max} (h)[d]	5.00 [2.00 - 7.00]	5.00 [2.00 - 7.00]	p=0.22
AUC_{0-12} (ng.h/mL)	781 (27)	742 (19)	0.98 [0.92 - 1.04]

[a] n=19
[b] n=18
[c] Ratio dronedarone + verapamil/dronedarone, p-value for difference between treatments
[d] Median values [Min – Max]

Table 161 shows the dronedarone and SR35021 PK parameters, their ratio estimates, and 90% confidence intervals. The statistical analysis performed on the PK parameters showed that:

- C_{max} and AUC_{0-12} of dronedarone obtained after coadministration were increased by 1.42-fold and 1.48-fold, respectively compared with those observed after dronedarone alone: the 90% CIs were outside the equivalence interval of 0.80 to 1.25
- C_{max} and AUC_{0-12} of SR35021 obtained after coadministration were similar compared with those observed after dronedarone alone: the 90% CIs were within the equivalence interval of 0.80 to 1.25
- Median t_{max} of dronedarone and SR35021 were similar after dronedarone alone or coadministration

These results show that the steady state of dronedarone was increased in the presence of verapamil, potentially leading to increased exposure of the drug as verapamil inhibited dronedarone metabolism.

<u>Verapamil and Norverapamil</u>

Figure 94and Figure 95 show that the mean plasma concentrations of verapamil and norverapamil were increased after concomitant repeated oral administration of dronedarone compared to verapamil alone.

Steady State

The average verapamil steady state was reached at about Day 3 when verapamil was administered alone, and delayed to Day 4 when coadministered with dronedarone. Average norverapamil steady state was reached at about Day 2 when verapamil was administered alone and at about Day 3 when coadministered with dronedarone.

Figure 94: Mean verapamil plasma concentrations after repeated oral administration of verapamil alone or coadministration – Day 14

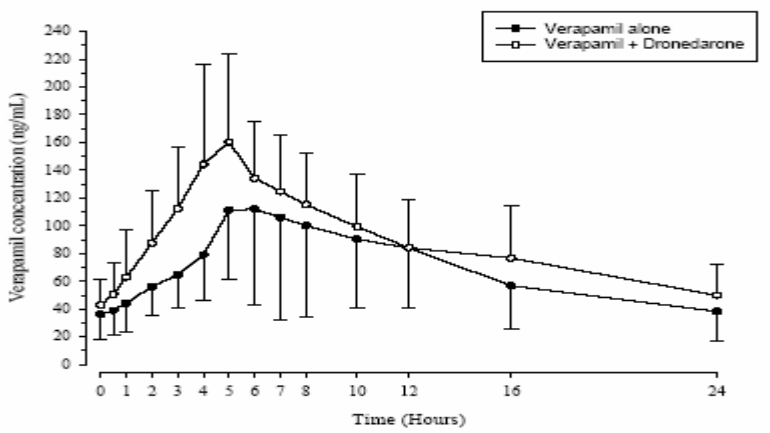


Figure 95: Mean norverapamil plasma concentrations after repeated oral administration of verapamil alone or coadministration – Day 14

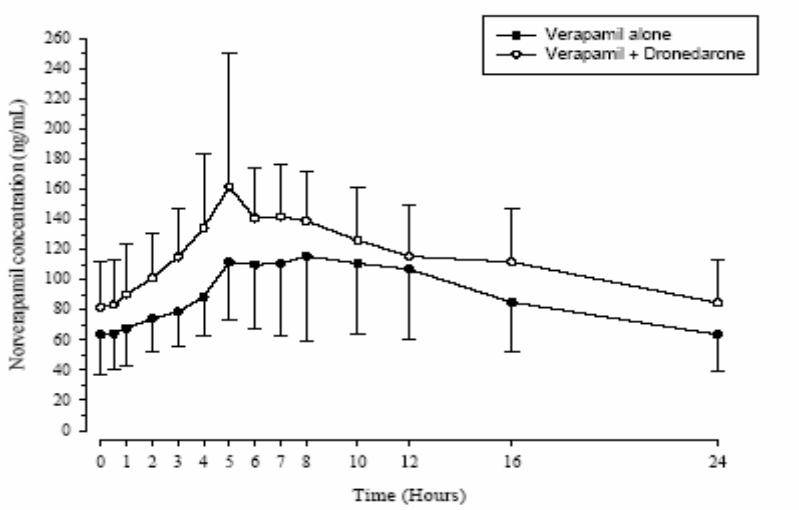


Table 162 shows the PK parameters for verapamil and norverapamil.

Table 162: Mean (CV%) pharmacokinetic parameters of verapamil and norverapamil and their ratio estimates and 90 % CI obtained after repeated administration of verapamil alone or coadministration with dronedarone

PK Parameters	Verapamil Alone[a]	Verapamil + Dronedarone[b]	Ratio Estimates[c] and 90% CI
Verapamil			
C_{max} (ng/mL)	132 (59)	175 (42)	1.40 [1.13 - 1.73]
t_{max} (h)[d]	5.50 [3.02 - 12.0]	5.00 [2.00 - 8.00]	p=0.02
AUC_{0-24} (ng.h/mL)	1670 (46)	2130 (34)	1.30 [1.14 - 1.48]
Norverapamil			
C_{max} (ng/mL)	129 (45)	169 (51)	1.31 [1.08 - 1.59]
t_{max} (h)[d]	6.00 [5.00 - 12.00]	6.00 [5.00 - 10.0]	p=0.83
AUC_{0-24} (ng.h/mL)	2150 (37)	2740 (27)	1.29 [1.15 - 1.44]

[a] n=18
[b] n=17
[c] Ratio verapamil + dronedarone /verapamil, p-value for difference between treatments
[d] Median values [Min – Max]

Statistical analysis reveals that:

- C_{max} and AUC_{0-24} of verapamil after coadministration were increased by 1.4-fold and 1.3-fold respectively, compared with the values observed after verapamil alone; the 90% CI were outside the equivalence interval of 0.80 to 1.25
- C_{max} and AUC_{0-24} of norverapamil after coadministration were increased by 1.31 and 1.29-fold respectively, compared with the values observed after verapamil alone; the 90% CI was outside the equivalence interval of 0.80 to 1.25
- Median value of verapamil time to reach peak plasma concentration (t_{max}) was significantly different after repeated dronedarone alone or after coadministration. For norverapamil, there was no significant difference.

Overall, the increase in verapamil exposure suggests that dronedarone inhibits the metabolism of verapamil.

Pharmacodynamics

The changes in ECG measures from baseline are shown in Table 163.

Table 163: Twelve-lead ECG changes from baseline (Day 1 T-0.5 h) between T0.5-T11.5 on Day 14- pair-wise comparisons for coadministration versus verapamil alone, and versus dronedarone alone, respectively

Change from Baseline in ECG Parameters	Time	Treatment Contrast (Coadministration vs Reference)†	N	Mean[a] Difference [Coadmin. – Reference] (msec)	Coadmin. mean[b] change (msec)	Reference	Reference[c] Mean[b] Change (msec)	95% CI Lower	95% CI Upper
Change QTcB (msec)	-	Coadministration vs Drone	18	11.8	36.2	Dronedarone	24.4	4.3	19.3
		Coadministration vs Vera	18	21.5	36.2	Verapamil	14.7	13.9	29.0
Change QTcF (msec)	-	Coadministration vs Drone	18	13.1	33.2	Dronedarone	20.1	6.5	19.8
		Coadministration vs Vera	18	24.4	33.2	Verapamil	8.8	17.7	31.1
Change PR (msec)*	0.5	Coadministration vs Drone	18	4.9	11.5	Dronedarone	6.6	-3.2	13.1
		Coadministration vs Vera	18	10.5	11.5	Verapamil	1.1	2.3	18.6
	1.0	Coadministration vs Drone	18	1.4	12.3	Dronedarone	10.9	-4.1	6.8
		Coadministration vs Vera	18	14.4	12.3	Verapamil	-2.1	8.8	20.0
	2.0	Coadministration vs Drone	18	6.1	13.1	Dronedarone	7.0	-2.0	14.2
		Coadministration vs Vera	18	13.8	13.1	Verapamil	-0.7	5.7	21.8
	3.0	Coadministration vs Drone	18	7.2	16.4	Dronedarone	9.2	-0.7	15.2
		Coadministration vs Vera	18	18.6	16.4	Verapamil	-2.1	10.6	26.5
	4.0	Coadministration vs Drone	18	11.3	23.6	Dronedarone	12.3	2.1	20.4
		Coadministration vs Vera	18	16.6	23.6	Verapamil	7.0	7.5	25.7
	6.0	Coadministration vs Drone	18	18.8	29.5	Dronedarone	10.7	8.5	29.0
		Coadministration vs Vera	18	11.3	29.5	Verapamil	18.2	1.1	21.5
	8.0	Coadministration vs Drone	18	14.3	18.8	Dronedarone	4.5	7.4	21.2
		Coadministration vs Vera	18	5.9	18.8	Verapamil	12.9	-1.2	12.9
	10.0	Coadministration vs Drone	18	8.5	14.9	Dronedarone	6.4	1.8	15.3
		Coadministration vs Vera	18	4.9	14.9	Verapamil	9.9	-1.8	11.7
	11.5	Coadministration vs Drone	18	7.3	9.9	Dronedarone	2.6	-1.6	16.1
		Coadministration vs Vera	18	2.0	9.9	Verapamil	7.9	-6.8	10.9

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† Coadministration is dronedarone +verapamil; reference is either verapamil or dronedarone

[a] Mean difference = LSM (coadministration) minus LSM (reference)

[b] Mean is LSM (Least Square Means)

[c] Sample size for reference group: n=17 for verapamil alone and n=16 for dronedarone alone for all endpoints.

"-" Overall time; no significant treatment*time interaction

* Significant treatment*time interaction

The analysis of changes from baseline over [T0.5h-11.5h] on Day 14 showed:

- statistically significant treatment-by-time interaction only for PR and statistically significant treatment and time differences for QT effects.
- PR prolongation with a significant change from 0.5 to 6 hours for verapamil vs. verapamil and dronedarone, and for dronedarone vs. coadministration with a significant change from 4 hours to 10 hours.

- QTcB and QTcF also showed statistically significant treatment and time effects resulting in QTcB and QTcF prolongation.

Applicant's Safety Summary
Only one subject experienced TEAEs (treatment emergent adverse events) during coadministration. The incidence of TEAEs was higher in the dronedarone group than in the verapamil group. There were no deaths or SAEs (serious adverse events) in any groups and only one adverse event (maculopapular rash) led to study drug discontinuation during treatment with verapamil alone.

Gastrointestinal disorders were the most frequent TEAEs reported with dronedarone alone. Only one subject had a TEAE (hematuria) during the coadministration period. No deaths or SAEs were reported.

Recommendations/Conclusions
1. Verapamil increased the steady state dronedarone C_{max} and AUC_{0-12} by 1.4-1.5-fold and did not modify steady state exposure of SR35021. Dronedarone and SR35021 t_{max} were not affected by verapamil coadministration compared with dronedarone alone.
2. Dronedarone increased steady state verapamil C_{max} and AUC_{0-24} by 1.4-1.3-fold and steady state norverapamil C_{max} and AUC_{0-24} by 1.3-fold. Verapamil t_{max} was shortened by coadministration of dronedarone and verapamil compared with verapamil alone whereas norverapamil t_{max} was not affected.
3. Coadministration showed statistically significant increases in PR, QTcB, and QTcF compared with dronedarone alone or verapamil alone.

Applicant's Proposed Labeling
Due to the pharmacokinetic interaction and possible pharmacodynamic interaction, calcium antagonists with depressant effects on sinus and atrio-ventricular node such as verapamil and diltiazem should be used concomitantly with dronedarone with caution.

Reviewer Note on Label
The applicant's proposed labeling is acceptable. The increase in dronedarone exposure caused by verapamil does not appear clinically significant. Verapamil dosage can be titrated, therefore, the verapamil dose may be adjusted, if needed, during coadministration with dronedarone.

4.2.25 An interaction study to investigate a potential effect of repeated oral ingestion of grapefruit juice on the pharmacokinetic profile of single and repeated oral doses of dronedarone in young healthy male subjects (INT4886)

PROTOCOL #	INT4886
INVESTIGATOR	Dr. Thierry Duvauchelle
STUDY SITE	ASTER, 3-5, rue Eugene Millon, 75015 PARIS, France
STUDY PERIOD	March – September 2002

Background Information on Study Drugs (Grapefruit Juice and Dronedarone)

	Grapefruit Juice	Dronedarone (SR33589)
Indication	Used as a beverage.	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic.
Metabolites	N/A	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites.
Metabolic Pathway	N/A	Primarily CYP3A substrate.
CYP Inhibitory Potential	Inhibitor of CYP3A4.	Low to moderate potential to inhibit CYP3A and CYP2D6, as well as PGP.
Highest Recommended Dose/Studied Dose	One regular strength glass daily with breakfast.	400 mg BID.

Objectives (per applicant)

- Primary: to assess the effect of repeated oral ingestion of grapefruit juice (GFJ) on the single dose pharmacokinetics (PK) of dronedarone and, its metabolite, SR35021 in fasted and fed conditions; to assess the effect of repeated oral ingestion of GFJ on repeated dose PK of dronedarone and, its metabolite, SR35021 in fed conditions.
- Secondary: to assess the clinical and biological tolerability of dronedarone given alone versus dronedarone co-administered with GFJ.

Study Design

This was a randomized, open-label, non placebo-controlled, two treatment (dronedarone + GFJ or dronedarone + water), 2-period crossover study, with at least a 10 day washout between periods.

There were three treatment phases in each of the two treatment arms:

- Phase 1: 300 mL GFJ was taken three times daily on Days 1-7, with a single dronedarone dose of 400 mg on Day 4 in fasted conditions.
- Phase 2: 300 mL GFJ was taken three times per day continuing on Days 8-10, with a single dose of dronedarone (400 mg) on Day 8 in fed conditions.
- Phase 3: 300 mL GFJ was taken three times daily on days 11-20, with repeated dronedarone doses of 400 mg twice a day in fed conditions. On day 20, there was only a morning drug administration.

(Non-carbonated water was substituted for GFJ in the second treatment arm.)

Reviewer Note on Study Design
The study design was consistent with the FDA-recommended drug-drug interaction Guidance; doses of both compounds were relevant to clinical use.

Subject Demographics
All subjects were Caucasian males between the ages of 18 and 39, as shown in Table 164:.

Table 164: Subject Demographics (INT4886)

Parameter	Statistics/ Category	Total (N=24)
Age (yrs)	N Mean (SD) Minimum - Maximum	24 27.9 (4.9) 18 - 39
Weight (kg)	N Mean (SD) Minimum - Maximum	24 68.22 (9.19) 53.6 – 86.2
Height (cm)	N Mean (SD) Minimum - Maximum	24 176.0 (6.0) 165 - 189
BMI (kg/m2)	N Mean (SD) Minimum - Maximum	24 21.96 (2.36) 18.2 – 25.0
Gender	Male	24 (100%)
Race	Caucasian	24 (100%)

Pharmacokinetic sampling times
The following pharmacokinetic blood samples were drawn at the given times for dronedarone and SR35021:

- Day 4: before dosing and then 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 36, and 48 hours after dosing
- Day 8: before dosing and then 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 36, and 48 hours after dosing
- Days 17, 18, and 19: before morning administration
- Day 20: before dosing and then 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 hours after dosing

Formulation
Dronedarone: 400 mg tablets, batch number CL-04794

- GFJ: double strength reconstituted, batch numbers U1121 and U1323. The main components were bergamotin, 6',7' dihydroxybergamotin, and naringin

Bioanalytical methods
Plasma concentrations of dronedarone and SR35021 were determined using a validated liquid chromatography-mass spectrometry method, DOH0239. The assay method was acceptable as illustrated in Table 165.

Table 165: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.500 to 300 ng/mL range; $R^2 >$ 0.980	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	All individual QC values were within 15% of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.500 to 300 ng/mL range; $R^2 >$ 0.991	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	All individual QC values were within 15% of nominal concentration	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms were provided in the validation report indicating assay specificity.

Pharmacokinetics

The following pharmacokinetic (PK) parameters were measured for dronedarone and SR35021:

- Day 4 and Day 8: C_{max}, t_{max}, AUC_{last}, AUC, R_{met}, and $t_{1/2}$
- Day 20: C_{trough}, C_{min}, C_{max}, t_{max}, AUC_{0-12}, and R_{met}

Statistical methods

PK parameters for dronedarone and SR35021 were summarized by descriptive statistics. Standard statistical methods were used to evaluate PK drug-drug interactions. Occurrence of steady state was assessed using C_{trough} values.

Results

Dronedarone Pharmacokinetics

As shown in Figure 96, Figure 97, and Figure 98, the mean plasma concentrations of dronedarone were increased after concomitant, repeated, oral ingestion of GFJ 300 mL TID with both dronedarone single dose in fasted or fed conditions, and with dronedarone repeated doses in fed conditions.

Dronedarone steady state was reached after seven days of repeated oral administration alone, or co-administered with repeated ingestion of double strength GFJ.

Figure 96: Mean dronedarone plasma concentrations observed after a single 400 mg oral administration under fasted conditions, alone or co-administered with GFJ

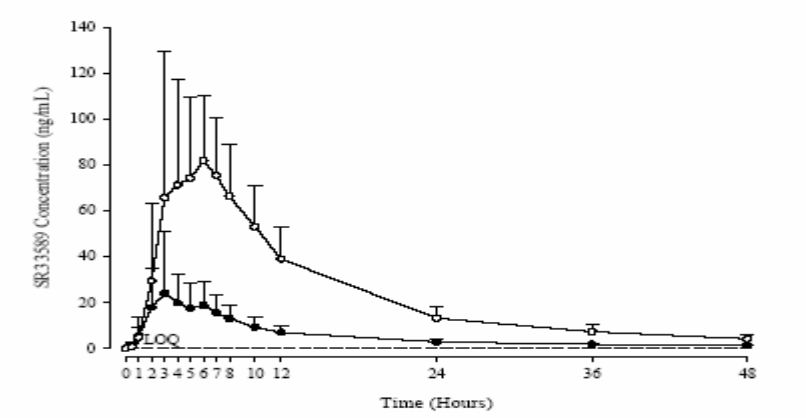


Figure 97: Mean dronedarone plasma concentrations observed after a single 400 mg oral administration under fed conditions, alone or co-administered with GFJ

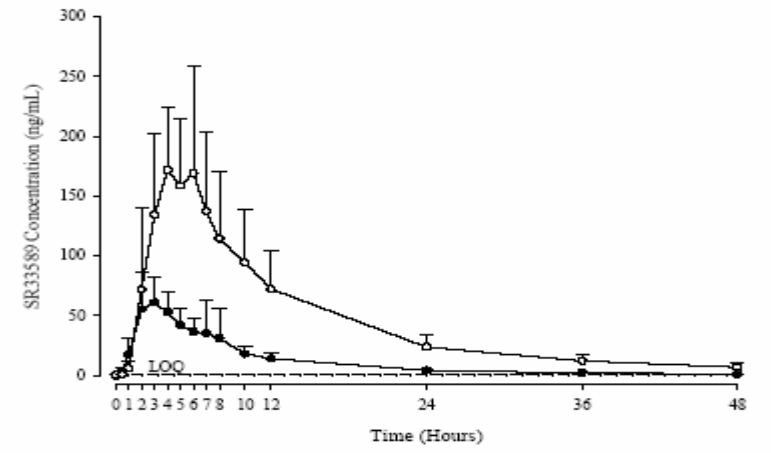
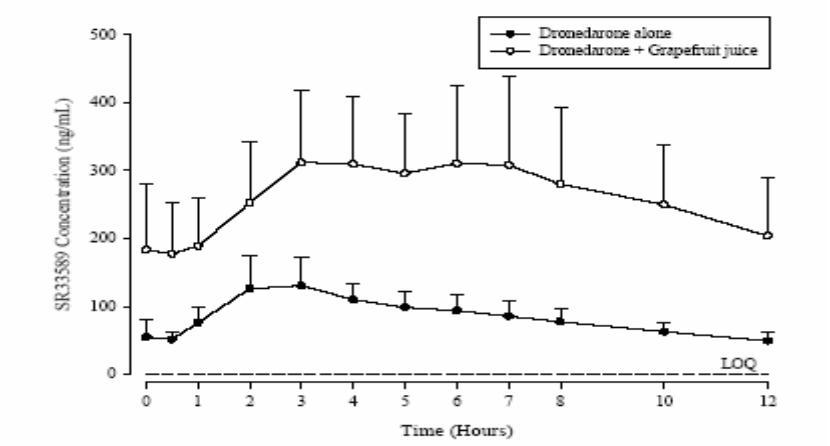


Figure 98: Mean dronedarone plasma concentrations observed after a 10 day repeated 400 mg BID oral administration under fed conditions, alone or co-administered with GFJ



Dronedarone PK measures are summarized in Table 166.

Table 166: Mean (coefficient of variation [CV%]) PK parameters of dronedarone and their ratio estimates and 90% confidence interval (CI) obtained after dronedarone oral administrations, alone or co-administered with GFJ (n=20)

PK Parameter Mean (CV%)	Dronedarone alone	Dronedarone+ grapefruit juice	Ratio estimates[b] and 90% CI
SR33589			
Single administration under fasted conditions			
C_{max} (ng/mL)	29.3 (91)	102 (49)	3.89 [3.03, 4.99]
t_{max} (h)[a]	3	6	1.50 [0.50, 2.50][c]
AUC_{last} (ng.h/mL)	268 (46)	1153 (37)	4.36 [3.62, 5.26]
$t_{1/2z}$ (h)	18.1 (26)[d]	14.3 (16)	-
AUC (ng.h/mL)	304 (42)[d]	1244 (38)	4.11 [3.42, 4.93]
Single administration under fed conditions			
C_{max} (ng/mL)	74.2 (41)	204 (43)	2.77 [2.35, 3.27]
t_{max} (h)[a]	3	4	1.50 [0.99, 2.50][c]
AUC_{last} (ng.h/mL)	564 (29)	2189 (36)	3.83 [3.39, 4.32]
$t_{1/2z}$ (h)	12.9 (21)	12.9 (14)	-
AUC (ng.h/mL)	588 (29)	2320 (36)	3.87 [3.44, 4.36]
Repeated b.i.d. administration under fed conditions			
C_{max} (ng/mL)	147 (31)	364 (33)	2.48 [2.16, 2.84]
t_{max} (h)[a]	3	4	2.00 [1.00, 2.50][c]
AUC_{0-12} (ng.h/mL)	1028 (21)	3186 (34)	3.00 [2.68, 3.36]

As shown in Table 166, relative to dronedarone alone, concomitant, repeated, oral ingestion of double strength GFJ:

- increased dronedarone C_{max} and AUC obtained after a single oral administration of dronedarone in fasted conditions, by approximately 4 fold.
- increased dronedarone C_{max} and AUC obtained after a single oral administration of dronedarone in fed conditions, by approximately 3 fold and 4 fold, respectively.
- increased dronedarone C_{max} and AUC_{0-12} obtained after repeated oral administration of dronedarone BID in fed conditions, by approximately 3 fold.

Time to reach peak plasma concentration (t_{max}) was delayed by 1.5 to 2 hours after concomitant, repeated, oral ingestion of GFJ, compared to that observed after dronedarone alone.

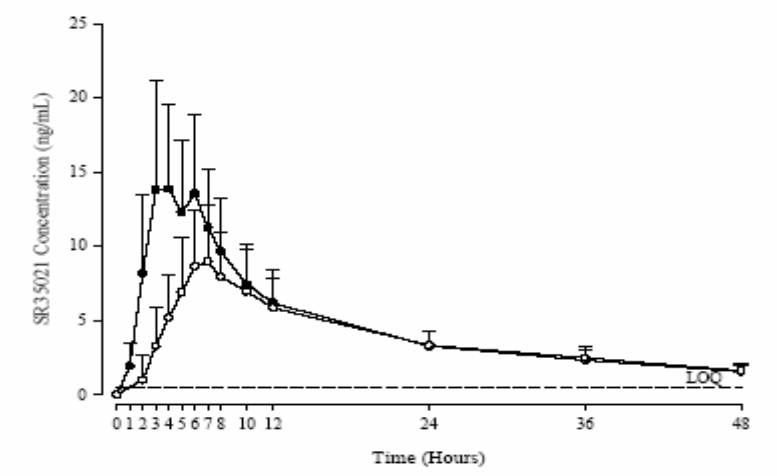
Reviewer Comment on Dronedarone PK Results

The most clinically relevant results are those of repeated administration of dronedarone BID under fed conditions, because this is the way the drug is intended to be taken.

<u>SR35021 Pharmacokinetics</u>

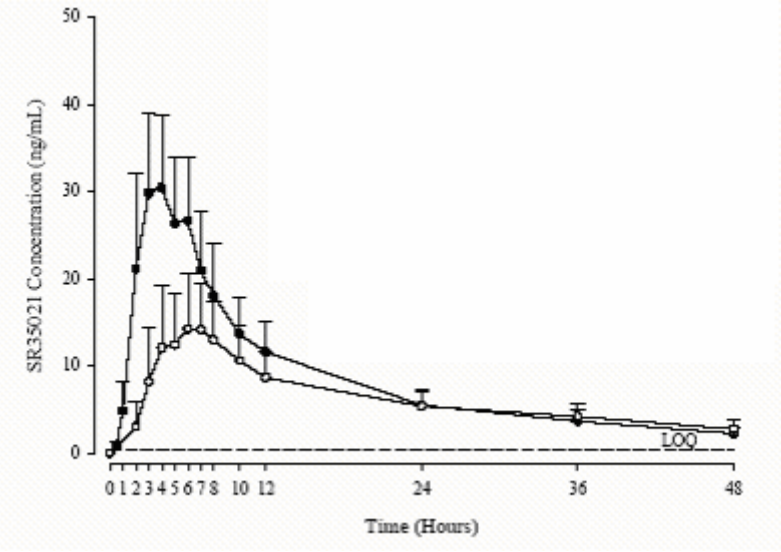
The mean SR35021 plasma concentration time profiles observed after a single dronedarone 400 mg oral administration under fasted conditions, alone or co-administered with GFJ are depicted in Figure 99. In the figure the curve with the filled in symbols refers to dronedarone alone and the open symbol is dronedarone + grapefruit.

Figure 99: Mean SR35021 plasma concentrations observed after a single dronedarone dose under fasted conditions, alone or coadministered with GFJ



The mean SR35021 plasma concentrations observed after a single dronedarone 400 mg oral administration under fed conditions, alone or co-administered with GFJ are depicted in Figure 100. In the figure the curve with the filled in symbols refers to dronedarone alone and the open symbol is dronedarone + grapefruit.

Figure 100: Mean SR35021 plasma concentrations observed after a single dronedarone dose under fed conditions, alone or coadministered with GFJ



The mean SR35021 plasma concentrations observed after a 10-day repeated dronedarone 400 mg BID oral administration under fed conditions, alone or co-administered with GFJ are depicted in Figure 101.

Figure 101: Mean SR35021 plasma concentrations observed after a 10 day repeat dronedarone BID dose under fed conditions, alone or coadministered with GFJ

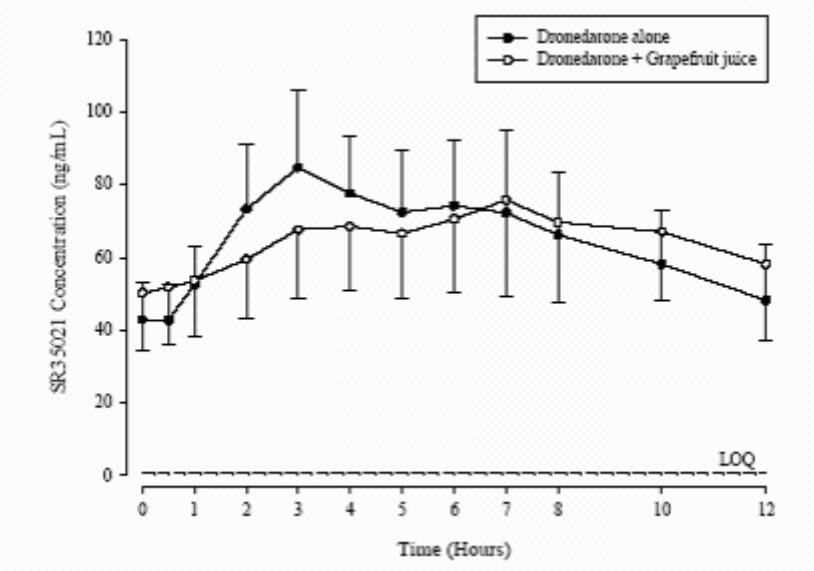


Table 167: Mean (CV%) PK parameters of SR35021 and their ratio estimates and 90% CI obtained after dronedarone oral administrations, alone or co-administered with GFJ (n=20)

PK Parameter Mean (CV%)	Dronedarone alone	Dronedarone + grapefruit juice	Ratio estimates[b] and 90% CI
SR35021			
Single administration under fasted conditions			
C_{max} (ng/mL)	16.7 (39)	9.41 (41)	0.56 [0.47, 0.67]
t_{max} (h)[a]	3	6.5	2.50[c] [1.50, 3.50]
AUC_{last} (ng.h/mL)	224 (30)	181 (29)	0.82 [0.72, 0.92]
$t_{1/2z}$ (h)	21.3 (23)	23.0[d] (19)	-
AUC (ng.h/mL)	273 (27)	241[e] (26)	0.90 [0.80, 1.00]
$R_{met}(C_{max})$	0.68 (28)	0.11 (67)	0.14 [0.11, 0.19]
R_{met}(AUC)	0.95[d] (23)	0.23[e] (53)	0.22 [0.19, 0.26]
Single administration under fed conditions			
C_{max} (ng/mL)	34.2 (25)	16.0 (41)	0.45 [0.37, 0.54]
t_{max} (h)[a]	3.5	6	2.50[c] [1.50, 3.00]
AUC_{last} (ng.h/mL)	416 (26)	299 (32)	0.71 [0.62, 0.81]
$t_{1/2z}$ (h)	19.2 (31)	25.9 (44)	-
AUC (ng.h/mL)	497[d] (24)	393[f] (32)	0.82 [0.74, 0.91]
$R_{met}(C_{max})$	0.51 (37)	0.09 (62)	0.16 [0.12, 0.21]
R_{met}(AUC)	0.86[d] (27)	0.21[f] (37)	0.23 [0.20, 0.28]
Repeated b.i.d. administration under fed conditions			
C_{max} (ng/mL)	87.8 (24)	79.5 (32)	0.89 [0.79, 0.99]
t_{max} (h)[a]	3	6	2.00[c] [1.50, 3.00]
AUC_{0-12} (ng.h/mL)	790 (23)	784 (28)	0.98 [0.89, 1.08]
$R_{met}(C_{max})$	0.64 (26)	0.23 (33)	0.36 [0.32, 0.40]
$R_{met}(AUC_{0-12})$	0.78 (20)	0.26 (32)	0.33 [0.29, 0.36]

The SR35021 PK measures obtained following administration of dronedarone with or without grapefruit are summarized in Table 167.

SR35021 C_{max} and AUC_{0-12} obtained after repeated oral administration of dronedarone 400 mg BID in fed conditions, co-administered with repeated oral ingestion of double strength GFJ, were similar to those observed after dronedarone alone. In all cases, median values of SR35021 time to reach peak plasma concentration (t_{max}) was delayed by 2 to 2.5 hours after concomitant, repeated, oral ingestion of GFJ compared to that observed after dronedarone alone.

SR35021 exposures, observed after a single, oral administration of dronedarone in fasted and in fed conditions, and after repeated oral administration of dronedarone in fed conditions, tended to be lower than dronedarone exposures; the metabolic ratio (R_{met} = ratio of the AUC or C_{max} of the metabolite to the parent drug) ranged from 0.51 to 0.95. R_{met} decreased when dronedarone was co-administered with the repeated ingestion of GFJ. These findings support the observation that GFJ inhibits dronedarone metabolism because less SR35021 is formed in the presence of GFJ than in the absence of GFJ.

Applicant's Safety Summary

Safety assessments included recording of adverse events (AEs), ECG, vital signs (BP and HR), hematology, biochemistry, and urinalysis. There was only one serious adverse event (SAE) reported (first degree AV block). No deaths were reported. Three subjects reported adverse events while on dronedarone, including dizziness, somnolence, and headache. Five other subjects reported adverse events while on dronedarone and GFJ, including first degree AV block, palpitations, abnormal liver function, hypotension, and other minor events. The first degree AV block and abnormal liver function led to discontinuation.

Recommendations/Conclusions

The following PK information generated in this study is acceptable for labeling purposes, as appropriate.

1. Grapefruit juice (GFJ) inhibited dronedarone metabolism; consequently dronedarone plasma concentrations were increased by repeated ingestion of 300 mL of GFJ (double strength) three times per day, relative to dronedarone alone. Dronedarone C_{max} and AUC increased ~2.5 to 3 fold following repeated administration twice a day under fed conditions.
2. SR35021 C_{max} and AUC obtained after repeated administration of dronedarone with GFJ were not significantly changed under fed conditions.

Applicant's Proposed Labeling

Drug Interactions: Repeat doses of double strength 300 mL grapefruit juice three times daily resulted in a 3 fold increase in dronedarone exposure. As grapefruit juice increases dronedarone exposure, patients should be warned to avoid grapefruit juice beverages while taking dronedarone.

Reviewer Note on Label

The sponsor adequately states a warning regarding consuming GFJ while taking dronedarone. The labeling is acceptable, considering the fact that GFJ inhibits dronedarone metabolism.

4.2.26 Pharmacokinetic interaction of repeated oral 400 mg BID dronedarone for 10 days on repeated oral 0.25 mg QD digoxin in healthy young male subjects - Randomized, double-blind, placebo-controlled, two-sequence, two-treatment, crossover study (INT5189)

PROTOCOL #	INT5189
INVESTIGATOR	Dr. Evelyne Guenole
STUDY SITE	Therapharm Recherches, 5, Boulevard Henri Becquerel, F – 14052 Caen Cedex 4 France
STUDY PERIOD	May – September 2004

Background Information on Study Drugs (Digoxin and Dronedarone)

	Digoxin	Dronedarone (SR33589)
Indication	Cardiac Glycoside; Inhibits sodium/potassium ATPase; For the treatment of mild to moderate heart failure, and control of ventricular response rate in patients with chronic atrial fibrillation.	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic.
Metabolites	3 β-digoxigenin, 3-keto- digoxigenin, and their glucuronide and four sulfate conjugates.	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites.
Metabolic Pathway	Not dependent on CYP450; Substrate of P-glycoprotein (PGP)	Primarily CYP3A substrate.
CYP Inhibitory Potential	Does not inhibit or induce CYP450.	Low to moderate potential to inhibit CYP3A and CYP2D6, as well as PGP.
Highest Recommended Dose/Studied Dose	Available in tablets, capsules, elixir, and injection. The dose can range from 125 to 500 mcg depending on the indication and can be titrated.	400 mg BID.

Background Information

A previous dronedarone/digoxin interaction study (INT2634) performed in healthy young male subjects at the dosage of 400 mg once daily (QD) for dronedarone and 0.25 mg digoxin QD (with a loading dose of 0.75 mg) showed that dronedarone increased the digoxin AUC0-24 by 27%. In addition, a pharmacodynamic interaction was observed with a slight increase in heart rate (HR) (64.2 vs. 61.6 bpm) and a slight prolongation of QTc (395 vs. 381 msec) after seven days digoxin + dronedarone coadministration vs. digoxin alone (Emax analysis). These changes were not considered to be of clinical significance.

The proposed dronedarone dose is 400 mg BID, as opposed to the 400 mg QD used in the previous study. The current study used the proposed dronedarone dosage.

Objectives (per applicant)

- Primary: to assess the effect of repeated oral doses of 400 mg twice daily dronedarone on the pharmacokinetic (PK) profile of digoxin after repeated oral doses of 0.25 mg QD digoxin
- Secondary: to assess the clinical and laboratory safety of dronedarone coadministered with digoxin as compared to that of digoxin coadministered with placebo in healthy young male subjects

Study Design
This was a randomized, double-blind, placebo-controlled, repeat dose, two-sequence, two-treatment, and two-period crossover study with a minimum 10-day washout between periods. The treatments were:

- Treatment A - digoxin + placebo of dronedarone:
  - loading dose of 0.75 mg digoxin on Day 1 (0.50 mg in the morning and 0.25 mg in the evening, with 12 hours between the two administrations)
  - Day 2 – 10: a daily maintenance dose of 0.25 mg digoxin in the morning
  - Day 1 – 10: digoxin coadministered with placebo BID
- Treatment B - digoxin + dronedarone:
  - same as Treatment A, except placebo replaced by 400 mg BID dronedarone

Reviewer Note on Study Design
The study design was consistent with the FDA recommended Drug-Drug Interaction Guidance. The doses of digoxin and dronedarone used in the study were within the range of those used in normal clinical practice. However it is unclear why only males were included in the study.

Subject Demographics
Subject demographic characteristics are shown in Table 168.

Table 168: Summary of subject demographic data (INT5189)

		Dronedarone+Digoxin/ Placebo+Digoxin (N=10)	Placebo+Digoxin/ Dronedarone+Digoxin (N=10)	Overall (N=20)
Age (years)	N	10	10	20
	Mean (SD)	22.4 (2.5)	25.3 (6.8)	23.9 (5.2)
	Min - Max	19 - 27	18 - 39	18 - 39
Weight (kg)	N	10	10	20
	Mean (SD)	67.4 (5.9)	68.6 (4.2)	68.0 (5.0)
	Min - Max	60 - 77	62 - 74	60 - 77
Height (cm)	N	10	10	20
	Mean (SD)	173.9 (3.3)	177.5 (5.9)	175.7 (5.0)
	Min - Max	171 - 180	169 - 186	169 - 186
BMI (kg/m^2)	N	10	10	20
	Mean (SD)	22.30 (2.17)	21.78 (1.37)	22.04 (1.78)
	Min - Max	18.9 - 26.3	19.6 - 23.6	18.9 - 26.3
Gender [n (%)]	Male	10 (100)	10 (100)	20 (100)
Race [n (%)]	Caucasian	9 (90.0)	9 (90.0)	18 (90.0)
	Black	1 (10.0)	1 (10.0)	2 (10.0)

Pharmacokinetic sampling times
Plasma and urine samples were collected at scheduled times.

- Dronedarone and SR35021 samples were collected:
  - On Days 1, 2, 3, 5, 7, 9, and 10 – before morning administration
  - On Day 10 – at 0.5, 1, 2, 3, 4, 6, 8, and 12 hours after morning administration in both periods
- Digoxin plasma samples were collected:
  - On Days 1, 2, 3, 5, 7, 9, and 10 – before administration
  - On Day 10 – at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after last administration in both periods

- Digoxin urine samples were collected:
  - On Day 1 – before first digoxin administration
  - On Day 10 – in the 0-24 hour interval in both periods

Formulation

- Dronedarone: 400 mg tablet (2E3), batch number CL-04530
- Digoxin: 0.25 mg tablet, batch number 386127
- Placebo: 0 mg, batch number CL-04404

Bioanalytical methods

Dronedarone and SR35021: Plasma concentrations were determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method (DOH0292). The assay method was acceptable as illustrated in Table 169.

Table 169: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.50 to 300 ng/mL range; $R^2 > 0.995$	Satisfactory
Between day Precision	CVs were not provided.	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers.	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the to 0.50 to 300 ng/mL range; $R^2 >$ 0.995	Satisfactory
Between day Precision	CVs were not provided.	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers.	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms were provided in the validation report indicating assay specificity.

Digoxin: Plasma concentrations were determined by a validated radio-immuno assay method. The assay performance was acceptable as illustrated in Table 170.

Table 170: Performance of Digoxin Assays

Parameter	Measure	Reviewer Comment
	Digoxin Assay	
Linearity	The assay was linear over the 0.05 to 8.0 ng/mL range for plasma. The assay was linear over the 0.1 to 8.0 ng/mL range for urine.	Satisfactory
Between day Precision	CV was < 11% for plasma. CV was < 10% for urine.	Satisfactory
Accuracy	QC samples were between 1.25% to 11.25% of nominal concentrations for plasma. QC samples were between 1.43% and 19% of nominal concentrations for urine.	Satisfactory Not acceptable
LLOQ	0.2 ng/mL in plasma and 0.5 ng/mL in urine	Satisfactory
Specificity	Radio-immuno assay does not yield chromatograms.	Cannot be assessed

* Chromatograms were provided in the validation report indicating assay specificity.

Pharmacokinetics

- The following pharmacokinetic (PK) parameters were measured for dronedarone and SR35021: C_{trough}, C_{max}, t_{max}, and AUC_{0-12}.
- The following PK parameters were measured for digoxin: C_{trough}, C_{max}, t_{max}, AUC_{0-24}, Ae_{0-24} (cumulative amount excreted in the urine), fe_{0-24} (fraction of the dose excreted in the urine), and CL_{R0-24} (renal clearance).

Statistical methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. The time to reach steady state was assessed graphically from plots of C_{trough}.

Results

Dronedarone and SR35021

Mean (SD) dronedarone and SR35021 plasma concentration versus time profiles after repeated administration of dronedarone 400 mg BID for 10 days are shown in Figure 102.

Figure 102: Mean (SD) dronedarone and SR35021 plasma concentration versus time profiles on Day 10 after a 10-day repeated administration of dronedarone with digoxin

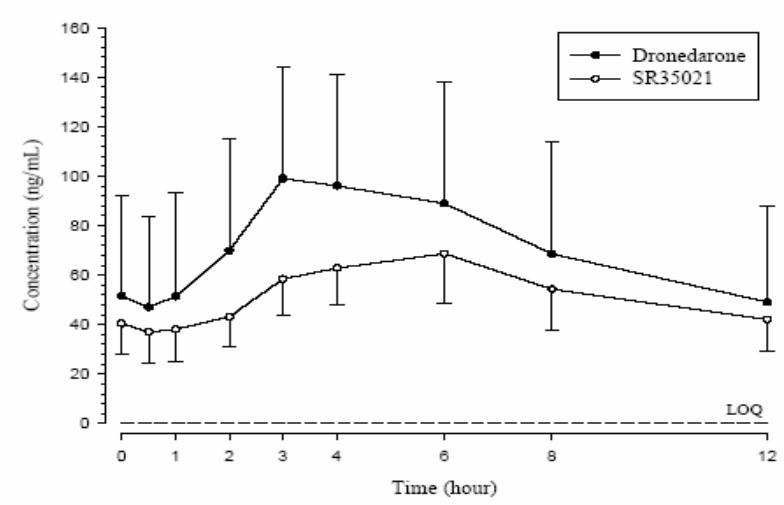


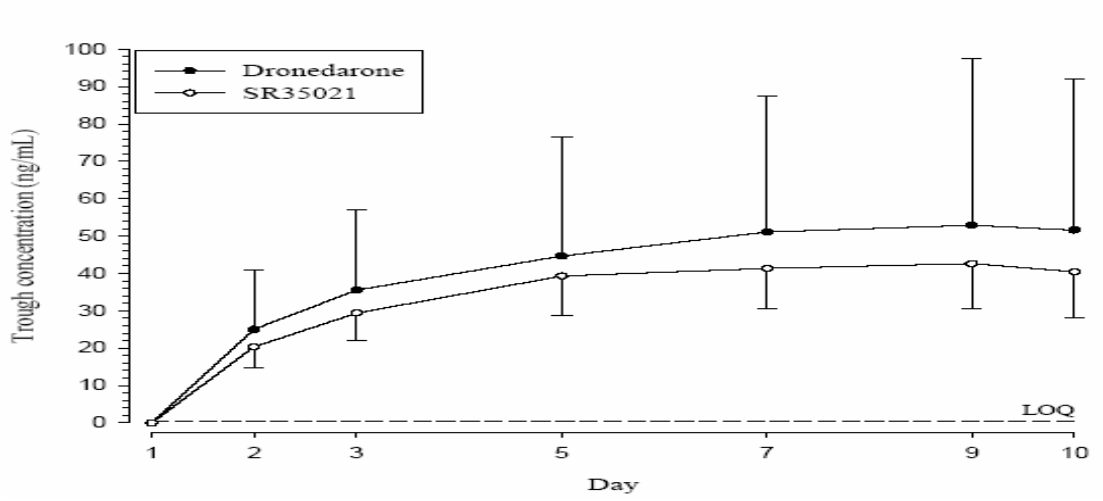
Table 171 shows the dronedarone and SR35021 PK parameters.

Table 171: Summary of dronedarone and SR35021 plasma PK parameters obtained on Day 10 after a 10-day repeated 400 mg BID administration of dronedarone

Parameter	Dronedarone	SR35021
C_{max} (ng/mL)		
Mean (CV%)	109 (44)	70.8 (28)
Min - Max	48.3 - 256	47.9 - 130
t_{max} (hour)		
Median	3.0	6.0
Min - Max	2.0 - 6.0	3.0 – 6.0
AUC_{0-12} (ng.h/mL)		
Mean (CV%)	868 (59)	636 (27)
Min - Max	380 - 2760	392 – 1120

Mean trough plasma concentrations of dronedarone and SR35021 from Day 1 to Day 10 during a 10-day repeated BID 400 mg oral dose of dronedarone and digoxin are graphically summarized in Figure 103.

Figure 103: Mean dronedarone and SR35021 C_{trough} (ng/mL) from Day 1 to Day 10 after a 10 day repeated BID 400 mg oral dose of dronedarone and digoxin

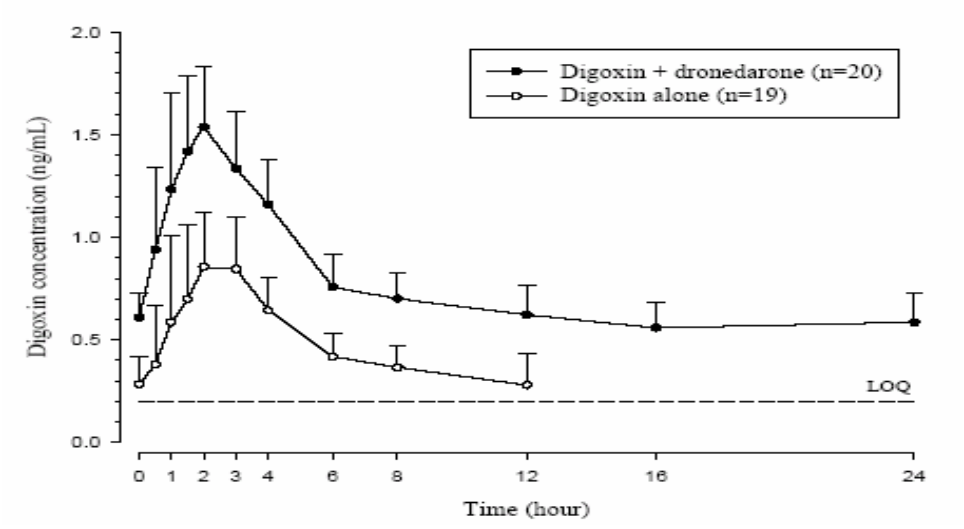


When coadministered with digoxin, average steady state of dronedarone and SR35021 was reached after four treatment days of repeated BID administration of dronedarone. Individual steady state was reached after five treatment days for dronedarone and four treatment days for SR35021.

Digoxin

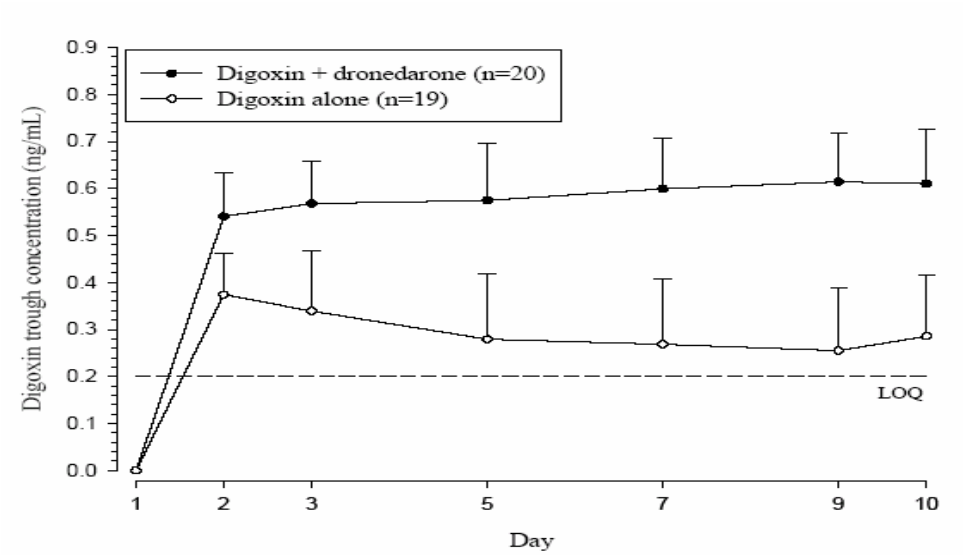
Figure 104 shows the mean (SD) digoxin plasma concentration versus time profiles observed on Day 10 after digoxin was administered for 10 days alone or with dronedarone.

Figure 104: Mean (SD) digoxin plasma concentrations on Day 10 after digoxin 0.25 mg QD administered alone or with dronedarone 400 mg BID



Mean (SD) digoxin C_{trough} observed from Day 1 to Day 10 after a 0.75 mg loading dose on Day 1 followed by a 0.25 mg dose of digoxin administered alone or with dronedarone are shown in Figure 105.

Figure 105: Mean (SD) digoxin trough plasma concentrations from Day 1 to Day 10 after digoxin 0.25 mg QD administered alone of with dronedarone 400 mg BID



According to the applicant, graphical inspection showed that coadministration of dronedarone did not modify steady state conditions for digoxin which was reached within two-treatment days using a 0.75 mg loading dose. However, based on the graphs, it appears that steady state for digoxin alone was achieved by Day 5, rather than Day 2.

Table 172 shows the plasma and urine PK parameters for digoxin observed on Day 10.

Table 172: Mean (CV%) digoxin plasma and urine PK parameters obtained on Day 10 after digoxin administered for 10 days alone or with dronedarone

Parameter	Digoxin + Dronedarone (n=20)	Digoxin Alone (n=19)	Ratio Estimate[a] [90% CI]
Plasma			
C_{max} (ng/mL)	1.71 (17)	1.02 (33)	1.75 [1.58, 1.93]
t_{max}[c] (hour)	2.0 (1.0 – 3.0)	3.0 (1.0 – 4.0)	-0.5 [-1.00, 0.00][b]
AUC_{0-24} (ng.h/mL)	18.0 (18)	7.73 (45)	2.57 [2.21, 2.98]
Urine			
Ae_{0-24} (mg)	0.139 (28)	0.097 (32)	1.45 [1.19, 1.78]
fe_{0-24} (%)	55.8 (28)	38.8 (32)	NA
CL_{R0-24} (L/h)	7.80 (27)	14.2 (41)	0.57 [0.46, 0.69]

[a] geometric mean ratio: digoxin + dronedarone/digoxin alone
[b] estimate of median difference [90% CI of median difference]
[c] median (minimum-maximum)
NA=not applicable

The analysis performed on digoxin parameters showed that, relative to digoxin alone, a 10-day concomitant administration of dronedarone 400 mg BID and digoxin 0.25 mg QD led to:

- a significant increase in digoxin C_{max} by 1.75-fold
- a significant increase in digoxin AUC_{0-24} by 2.57-fold

- no relevant changes in digoxin t_{max}
- a significant decrease in digoxin renal clearance by 43%
- a significant increase in amount of the digoxin dose excreted in urine by 1.45-fold

Reviewer Note
Based upon the results of this study, it is shown that dronedarone has the potential to inhibit PGP; this increases the levels of digoxin in the body. Digoxin renal clearance is inhibited due to the inhibition of PGP pumps in the kidney, thus there is an increase in the amount of digoxin excreted in the urine.

Applicant's Safety Summary
Overall, the tolerability of dronedarone in coadministration with digoxin was satisfactory. The incidence of any treatment emergent adverse events (TEAEs) was lower in dronedarone + digoxin group compared to placebo + digoxin group. These TEAEs included periorbital hematoma, headache, dysuria, and epistaxis. All TEAEs were of mild to moderate intensity. There were no serious adverse events (SAEs) reported, including deaths. One subject discontinued study drug due to an AE.

Recommendations/Conclusions
This review addresses only the PK interactions between digoxin and dronedarone.

1. Relative to digoxin alone, steady state digoxin C_{max} was significantly increased by 1.75-fold after a 10-day concomitant administration of dronedarone 400 mg BID while t_{max} was not modified. A significant increase in steady state AUCs ranging between 2.03-fold and 2.57-fold was observed.

2. Relative to digoxin alone, concomitant administration of dronedarone led to a significant decrease in digoxin renal clearance by 43%. Steady state Ae_{0-24} was significantly increased by 1.45-fold.

Applicant's Proposed Labeling
Due to the pharmacokinetic interaction and possible pharmacodynamic interaction, digoxin should be used with caution concomitantly with dronedarone and patients should be closely monitored for serum digoxin levels.

Reviewer Note on Label
The sponsor adequately states a caution when using digoxin while taking dronedarone. The labeling is acceptable. A dose adjustment is not required when administering dronedarone along with digoxin, because digoxin dosage can be titrated to optimize digoxin safety and efficacy.

4.2.27 Influence of repeated oral doses of ketoconazole [inhibitor of cytochrome P4503A4 (CYP3A4)] on the pharmacokinetic profile of dronedarone in healthy male subjects (INT3561)

PROTOCOL #	INT3561
INVESTIGATOR	Dr Wolfgang Tetzloff
STUDY SITE	IPHAR GmbH Arnikastrasse 4 85365 Höhenkirchen-Siegertsbrunn, Germany
STUDY PERIOD	March – June, 1999

Rationale for Drug-Drug Interaction Study

Background Information on Study Drugs (Ketoconazole and Dronedarone)

	Ketoconazole	Dronedarone
Indication/Mechanism of Action	Broad spectrum antifungal agent. Indicated for the treatment of some systemic fungal infections	Anti-arrhythmic: proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter.
Metabolites	Forms several inactive metabolites	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	Hepatically metabolized, with bile as the primary elimination route	Primarily CYP3A substrate
CYP Inhibitory Potential	Potent CYP3A inhibitor	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	The recommended initial oral dose is 200 mg QD; however dosage may be increased to 400 mg QD	400 mg BID

Objectives (per applicant)

- Primary: to assess the effect of repeated oral doses of ketoconazole on the pharmacokinetic profile of SR33589 (dronedarone) and its N-debutyl metabolite SR35021 after a single oral ascending dose of dronedarone given under fed conditions.
- Secondary: to assess a potential pharmacodynamic resulting effect, to assess the clinical and biological tolerability of dronedarone, alone and co-administered with ketoconazole and to document plasma concentrations of ketoconazole after repeated doses.

Study Design

This was a non-randomized, open-label, non placebo-controlled and two-period study. The two treatment periods were:

- Period 1: one day dronedarone (100 or 200 mg) alone followed by 5-day washout
- Period 2: seven days ketoconazole (200 mg QD) alone and one day co-administration of dronedarone+ ketoconazole.

There was a 13-day washout period between the 100 and 200 mg dose levels, for a given subject.

Reviewer Note on Study Design

Typically, drug interaction studies with ketoconazole are conducted at 400 mg QD to show the full magnitude of drug interaction. However, the use of a lower ketoconazole dose, 200 mg QD,

is consistent with the FDA-recommended drug-drug interaction Guidance because the safety concerns obviate the need for conducting the study at the highest recommended dose of either ketoconazole or dronedarone.

Subject Demographics
Subject demographics are presented in Table 173. All subjects were Caucasian males.

Pharmacokinetic sampling times
The following pharmacokinetic blood samples were drawn at the given times:

- For dronedarone and SR35021: 35 min before dosing and 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours postdose.
- For Ketoconazole: Day 1 and Day 8 at 35 min before dosing and on Day 8 at 1, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours postdose.

Formulation

- Dronedarone: 100 mg capsules, lot number 98-01946
- Ketoconazole: 200 mg tablets, lot number 98-J28/751 (no additional product information was provided)

Table 173: Subject Demographic Data (INT3561)

Parameter	Statistics	Dronedarone		Total
		100 mg	200 mg	
Age (years)	N	6	6	12
	Mean	27.3	32.5	29.9
	SD	5.0	3.4	4.9
	Min	22	28	22
	Max	35	38	38
Height (cm)	N	6	6	12
	Mean	184.5	181.0	182.8
	SD	3.3	7.3	5.7
	Min	179	173	173
	Max	189	193	193
Weight (kg)	N	6	6	12
	Mean	78.80	81.00	79.90
	SD	7.32	6.07	6.52
	Min	70.1	75.4	70.1
	Max	88.3	91.6	91.6

Bioanalytical methods

<u>Dronedarone and SR35021 Assays</u>
Dronedarone and SR35021 concentrations were determined using a validated electrospray LC-MS/MS method. The assay performance was acceptable:

- Linear range for dronedarone and SR35021 was 0.5 – 50 ng/mL; R^2 for dronedarone > 0.993 for all runs, except one run where R^2 was 0.976; R^2 for SR35021 > 0.992
- QC charts were provided, but no summarized values for CV or relative bias were provided; however, individual QC samples were within 15 % of nominal concentrations, suggesting assay was accurate
- Chromatograms were not provided so specificity could not be assessed, however, the validation report, which includes chromatograms, demonstrates assay specificity

Ketoconazole Assay

Ketoconazole plasma concentrations were determined by a validated HPLC (with ultraviolet detection) method. The assay performance was acceptable as illustrated in Table 174.

Table 174: Performance of Ketoconazole Assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 10 to 5000 ng/mL range; $R^2 > 0.990$	Satisfactory
Between day Precision	CV was < 12 %	Satisfactory
Accuracy	QC samples were between -5 and 13 % of nominal concentration	Satisfactory
LLOQ	10 ng/ml	Satisfactory
Specificity	Chromatograms were provided that demonstrate specificity	Satisfactory

Pharmacokinetics

The following pharmacokinetic (PK) measures were determined after each treatment:

- For dronedarone and SR35021: Cmax, tmax, AUClast, AUC and $t_{1/2}$
- For ketoconazole: Cmax, tmax, Cmin, and AUC_{0-24h}.

Pharmacodynamics

The following pharmacodynamic (PD) measures were determined: heart rate (HR), and PR-, QRS-, QT- and QTc- intervals, T-wave amplitude, hourly average AUC_{0-12}, peak values and time to peak values. Electrocardiogram (ECG) measurements were obtained at the following times:

- Screening
- Period 1: Day 0 at 8:00 am, and Day 1 at 30 minutes before dosing and 2, 4, 6, 8, 12, 24, 48, 72 and 96 hours post dose
- Period 2: Day 1 and Day 7 at 8:00 am
- Period 2: Day 8 at 30 minutes before dosing and 2, 4, 6, 8, 12, 24, 48, 72 and 96 hours post dose

Statistical methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. Dronedarone alone was the reference treatment and dronedarone + ketoconazole was the test treatment. Pharmacodynamic measures were also analyzed using standard statistical approaches.

Results

Dronedarone Pharmacokinetics

The mean plasma concentration-time profiles for dronedarone (100 and 200 mg doses) following administration of dronedarone with or without ketoconazole are depicted in Figure 106.

Dronedarone PK measures are summarized in Table 175. Dronedarone exposure was greatly increased (> 8-fold in Cmax and > 15-fold in AUC) in the presence of ketoconazole (200 mg) at both the 100 and 200 mg dronedarone dose levels (Table 176).

Figure 106: Mean dronedarone plasma concentration-time profiles following administration of dronedarone +/- ketoconazole

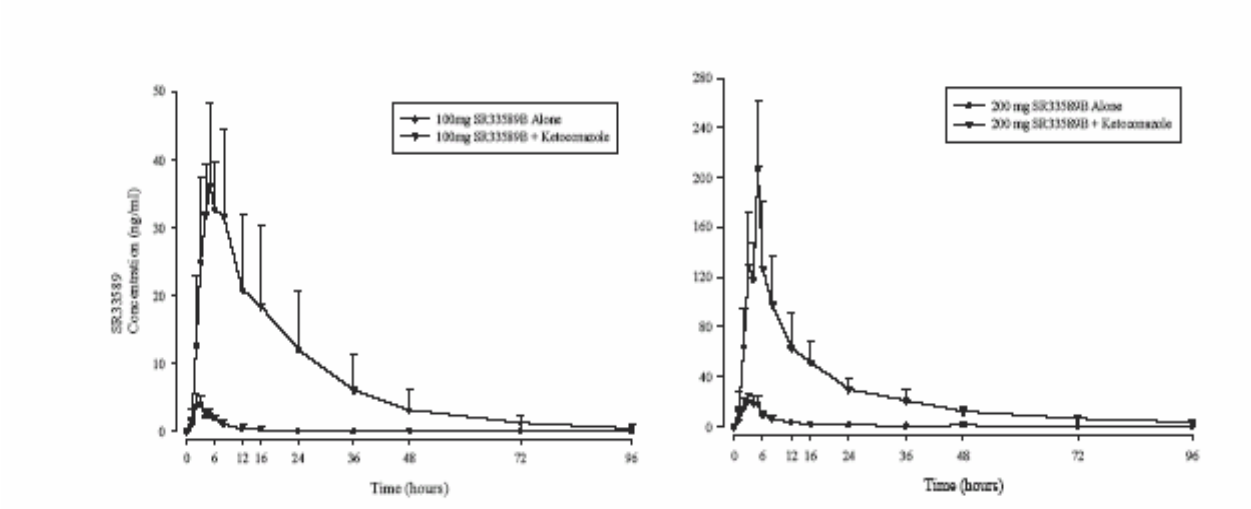


Table 175: Mean (SD) dronedarone PK measures in healthy males following single dose administration with or without ketoconazole (n=6)

Parameter	100 mg dronedarone		200 mg dronedarone	
	Alone (Period 1)	+keto (Period 2)	Alone (Period 1)	+keto (Period 2)
C max (ng/mL)	4.6 (1.1)	43.3 (10.5)	23.8 (4.6)	206.6 (54.1)
t max (h)	2.8 (1.2)	4.7 (1.9)	3.5 (1.1)	5.0 (0.0)
AUClast (ng h/mL)	20 (8)	726 (376)	163 (44)	2559 (677)
AUC (ng h/mL)	30 (7)a	745 (383)	160 (45)a	2692 (714)
t1/2 (h)	4.7 (2.3)a	17.8 (5.6)	16.2 (4.0)a	25.1 (4.6)

a- n = 4; keto = ketoconazole

Table 176: Dronedarone geometric mean ratios and associated 95 % confidence intervals for Cmax and AUC in the presence and absence of 200 mg ketoconazole

Parameter	100 mg dronedarone		200 mg dronedarone	
	Ratio	95% CI	Ratio	95% CI
C_{max} (ng/mL)	9.4	7.5-11.7	8.6	6.9-10.7
AUC_{last} (ng.h/mL)	35.9	26.6-48.4	15.8	11.7-21.3
AUC (ng.h/mL)	25.2	18.7-34.0	16.6	12.3-22.3

There appeared to be a dose dependent increase in AUC. This dose dependency is likely related to the non-linear nature of dronedarone PK. Nevertheless at both dronedarone dose levels there is a significant increase in dronedarone AUC and Cmax (> 8-fold) indicating that ketoconazole strongly inhibits dronedarone metabolism, as expected.

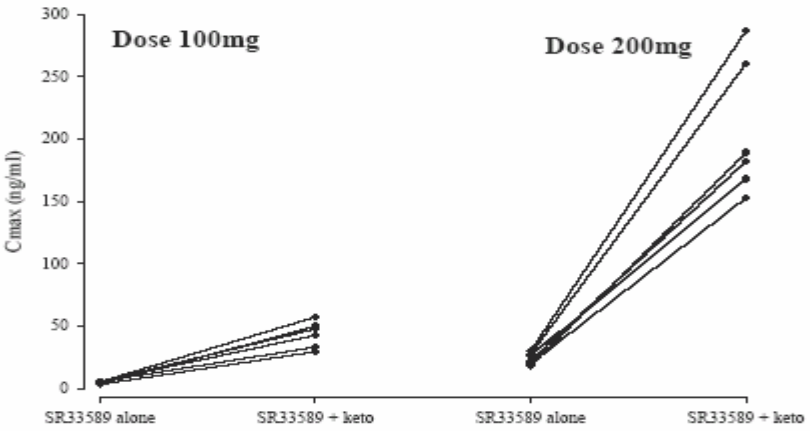
Reviewer Note on Confidence Intervals

For regulatory purposes, 90 % confidence intervals (CIs) are preferred over 95 % CIs. In this study, the type of CI, 90 % or 95 %, and its width is not of consequence, because the geometric

mean ratio is much greater than one and the associated 90 % confidence intervals will be much greater than the default no effect range (0.8 to 1.25 based on 90 % confidence interval).

The match stick plots in Figure 107 further illustrate the observed increase in dronedarone exposure when co-administered with ketoconazole; all subjects had Cmax increases in the presence of ketoconazole.

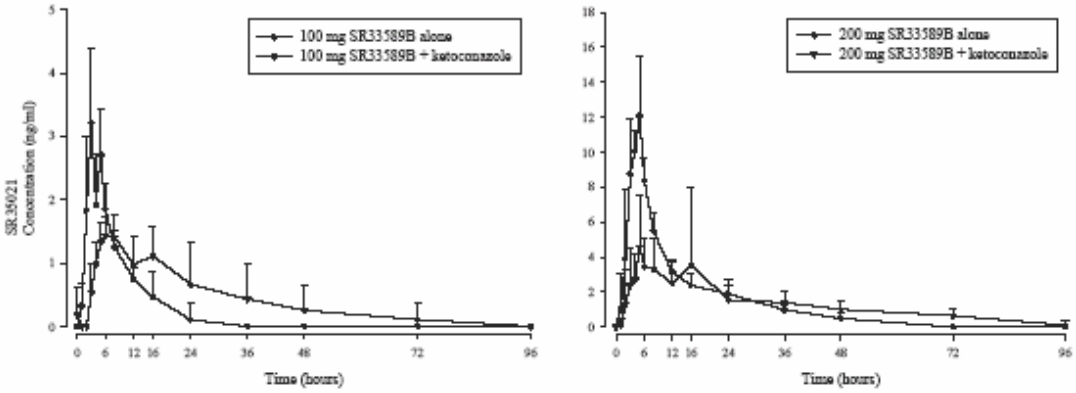
Figure 107: Individual and mean dronedarone Cmax values following administration of dronedarone with our without ketoconazole



SR35021 Pharmacokinetics

The mean SR35021 plasma concentration time profiles following administration of 100 mg or 200 mg with or without ketoconazole are depicted in Figure 108.

Figure 108: Mean SR35021 plasma concentration-time profile following administration of dronedarone with or without ketoconazole



SR35021 PK measures are shown in Table 177.

Table 177: SR30521 PK measures in healthy males following administration of dronedarone in the presence or absence of ketoconazole

Parameter	100 mg dronedarone		200 mg dronedarone	
	Alone(Period 1)	+keto(Period 2)	Alone(Period 1)	+keto(Period 2)
C_{max} (ng/mL)	3.6 (0.8)	1.7 (0.2)	13.6 (1.2)	5.0 (3.8)
t_{max} (h)	3.3 (0.8)	7.3 (4.3)	4.3 (1.0)	7.0 (4.4)
AUC_{last} (ng h/mL)	21 (6)	34 (29)	123 (21)	118 (77)
AUC (ng h/mL)	26 (7)[b]	NC	142 (22)[c]	NC
$T_{1/2}$ (h)	8.2 (5.3)[a]	NC	16.7 (3.8)[c]	43.6 (10.1)[c]

a : n=4 ; b : n=3 ; c : n=5 NC: not calculable keto: ketoconazole

Geometric mean ratios and associated 95% CI of the SR35021 PK measures are presented in Table 178.

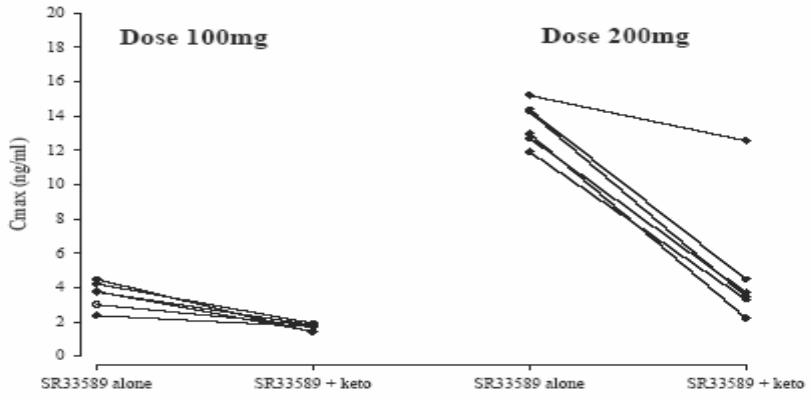
Table 178: SR35021 Geometric mean ratios for Cmax and AUC and associated confidence intervals obtained in dronedarone-ketoconazole drug interaction study

Parameter	100 mg dronedarone		200 mg dronedarone	
	Ratio	95% CI	Ratio	95% CI
Cmax (ng/mL)	0.48	[0.3-0.7]	0.31	[0.2-0.5]
AUClast (ng.h/mL)	1.3	[0.7-2.3]	0.8	[0.5-1.5]

SR35021 Cmax values were significantly decreased, but no statistically significant difference was observed in AUC last values.

The match stick plots in Figure 109 further illustrate the observed decrease in dronedarone Cmax when co-administered with ketoconazole. This finding supports the observation that ketoconazole inhibits dronedarone metabolism because less SR35021 is formed in the presence of ketoconazole than in the absence of ketoconazole.

Figure 109: Matchstick plots showing change in SR35021 for individual subjects following administration of dronedarone +/- ketoconazole



Ketoconazole Pharmacokinetics

The mean(SD) ketoconazole PK values after repeated 8-day of 200 mg ketoconazole dose with 100 mg or 200 mg dronedarone (period 2) are summarized in Table 179.

Table 179: Mean (SD) ketoconazole PK measures following administration of ketoconazole and dronedarone

Dronedarone dose	C_{max} (ng/mL)	t_{max} (h)	C_{min} (ng/mL)	AUC_{0-24h} (ng h/mL)
100 mg	2778 (948)	2.3 (0.8)	21.2 (13.7)	17642 (7464)
200 mg	3233 (1147)	3.2 (1.2)	64.0 (43.1)	23420 (10871)

The ketoconazole PK values are consistent with the values obtained in previous studies, suggesting that single dose administration of dronedarone does not alter ketoconazole exposure.

Pharmacodynamics

The applicant's pharmacodynamic analysis on ECG parameters (Table 180) indicated:

1. PR interval

There was statistically significant PR-prolongation (hourly and peak) when dronedarone (100 mg and 200 mg dronedarone pooled) was co-administered with ketoconazole, compared to dronedarone alone.

2. QTc interval

The average hourly QTc AUC value for dronedarone + ketoconazole was approximately 4 ms greater than dronedarone alone. On the other hand, the increase in peak QTc was not statistically significant.

Figure 110 and Figure 111 depict the mean changes (relative to baseline, T-30 minutes) in PR and QTc values over time (12 hour dosing period). PR-time and QTc-time values exhibited high inter-patient variability. This variability may have been decreased if baseline values were available over the entire sampling period, not just at the initial time point, because ECG measures tend to exhibit a circadian pattern.

Figure 110: Mean Changes in PR* over time following administration of 200 mg dronedarone and 200 mg dronedarone + ketoconazole

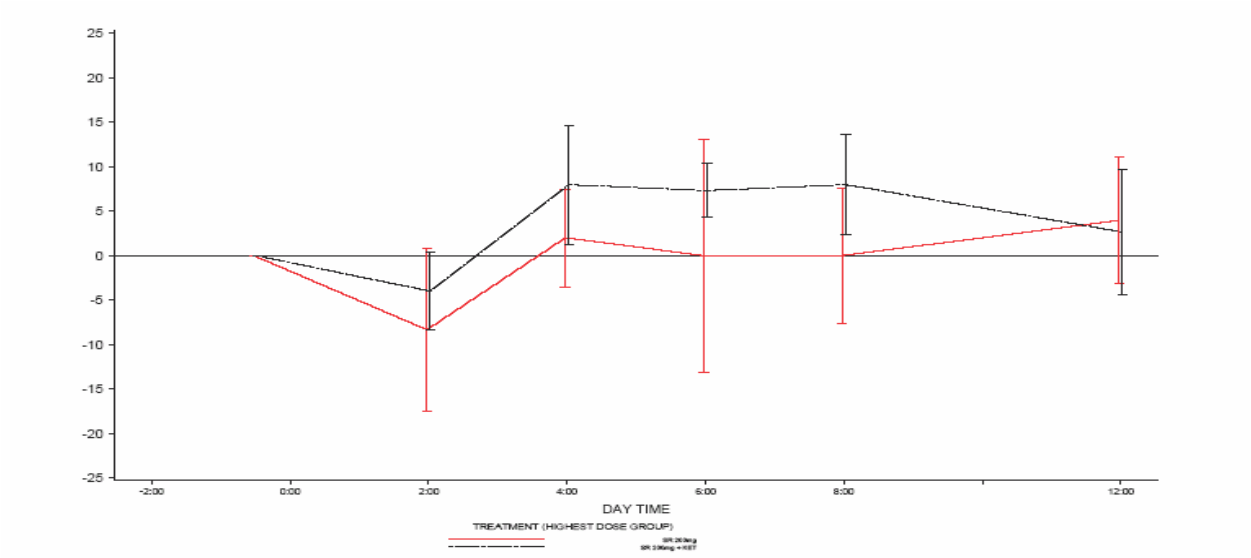
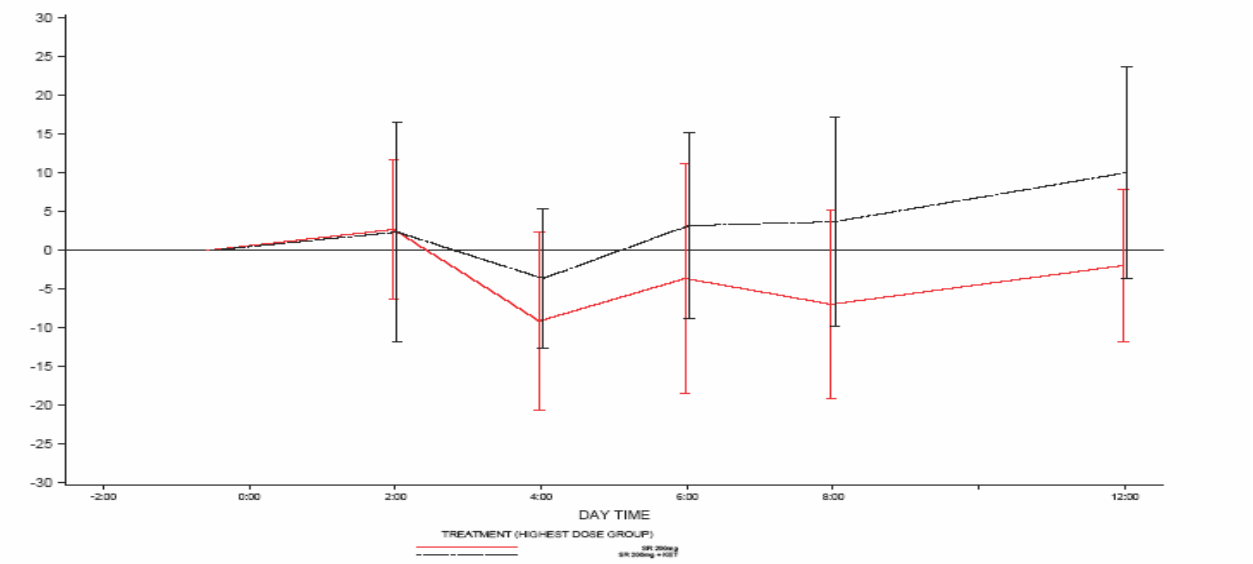


Figure 111: Mean (SD) QTc* changes (baseline corrected) with time after administration of 200 mg alone and 200 mg dronedarone + ketoconazole



* top curves (black lines) represent ketoconazole + dronedarone and lower curves (red lines) represent dronedarone alone

Reviewer Comment on Pharmacodynamic Results

The clinical relevance of the increased PR interval and hourly QTc AUC is not clear. The dronedarone exposures obtained in this study via metabolic inhibition are several folds higher than anticipated clinical exposures.

Table 180: Analysis of PR-interval and QTc values following dronedarone alone and dronedarone + ketoconazole

Parameter	Dronedarone dose	Mean (SD) by treatment		Mean difference (SD)	Difference estimate [95% CI]	p value
		alone	with keto			
PR-interval						
hourly AUC (ms)	100 mg (N=6)	158.3 (19.2)	165.9 (19.0)	7.6 (3.2)		
	200 mg (N=6)	169.5 (17.9)	186.8 (27.6)	17.3 (12.0)		
	pooled (N=12)	163.9 (18.7)	176.3 (25.1)		12.4 [6.8 ; 18.1]	0.0006
peak (ms)	100 mg (N=6)	165.3 (20.0)	174.0 (19.1)	8.7 (5.9)		
	200 mg (N=6)	177.3 (16.7)	194.7 (29.8)	17.3 (16.1)		
	pooled (N=12)	171.3 (18.7)	184.3 (26.2)		13.0 [5.2 ; 20.8]	0.0041
QTc						
hourly AUC (ms)	100 mg (N=6)	399.3 (9.5)	403.0 (10.6)	3.7 (4.4)		
	200 mg (N=6)	395.4 (14.4)	399.5 (18.7)	4.1 (7.3)		
	pooled (N=12)	397.3 (11.8)	401.2 (14.6)		3.9 [0.02 ; 7.7]	0.0488
peak (ms)	100 mg (N=6)	409.0 (8.4)	411.7 (11.2)	2.7 (5.9)		
	200 mg (N=6)	405.7 (13.5)	409.3 (19.6)	3.7 (11.0)		
	pooled (N=12)	407.3 (10.8)	410.5 (15.3)		3.2 [-2.5 ; 8.9]	0.2433

Applicant's Safety Summary

There were no serious adverse events (SAEs), deaths or significant adverse events in this study. A total of four adverse effects were reported in this study, but none occurred during co-administration of dronedarone with ketoconazole. The reported adverse events were mild first

degree AV block on dronedarone alone immediately prior to co-administration and a mild headache on ketoconazole.

Recommendations/Conclusions
The following PK information generated in Study INT3561 is acceptable for labeling purposes, as appropriate.

Pharmacokinetics

- Ketoconazole (200 mg) given once daily over eight days inhibited dronedarone metabolism; consequently dronedarone plasma concentrations were elevated (Cmax increased ~ 9-fold and AUC increased > 16-fold), relative to when dronedarone was given alone.
- The increase in dronedarone exposure showed some dose dependency, particularly with AUC values, which may be reflective of dronedarone's non-linear PK.
- Relative to when dronedarone was given alone, dronedarone + ketoconazole, led to decreased SR35021 formation.

Pharmacodynamics

- Statistically significant PR- prolongation was observed with dronedarone co-administered with ketoconazole compared to dronedarone alone
- Super-therapeutic dronedarone exposures did not appear to alter the QTc interval in a clinically significant manner; the maximum increase in QTc was 4 ms and no QTc value exceeded 450 ms.

Overall the pharmacodynamic changes do not appear clinically relevant.

Labeling
The applicant has proposed to contraindicate potent CYP3A metabolic inhibitors, such as ketoconazole, during dronedarone therapy.

Reviewer's Note on Applicant's Labeling Proposal
The proposal to contraindicate potent inhibitors appears reasonable and will minimize the risk of observing undesirable ECG changes. Additionally, the large increase in dronedarone exposure may have additional undesirable side effects that have been documented in other studies; in general exposures associated with administration of dronedarone doses ≥ 800 mg do not have an acceptable safety profile.

4.2.28 Pharmacokinetic interaction of repeated oral 400 mg BID dronedarone on repeated oral 400 mg BID theophylline in healthy young male subjects: randomized, placebo-controlled, double-blind, 2-sequence, 2-treatment crossover study (INT5084)

PROTOCOL #	INT5084
INVESTIGATOR	Dr Regine Rouzier
STUDY SITE	Center CAP, Clinique Rech, 9, Avenue Charles Flahault, F - 34094 Montpellier Cedex 5
STUDY PERIOD	June – November 2004

Background Information on Study Drugs (Theophylline and Dronedarone)

	Theophylline	Dronedarone
Indication/Mechanism of Action	Bronchodilator used in treatment of chronic Asthma and chronic obstructive pulmonary disease	Anti-arrhythmic: proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter.
Metabolites	Several oxidative metabolites are formed	Several metabolites including, debutylated SR35021* (major), and hydroxy and oxidative metabolites
Metabolic Pathway	CYP1A2 substrate	Primarily CYP3A substrate
CYP Inhibitory Potential	None reported	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Titrated and has a relatively narrow therapeutic index; highest dose is 400 mg	400 mg BID

*SR35021 has minimal potential to inhibit CYP1A2 (Ki = 31 μM)

Objectives (per applicant)

- Primary: To assess the effect of repeated oral 400 mg twice a day (BID) dronedarone on the pharmacokinetic (PK) profile of theophylline after repeated oral 400 mg BID theophylline, both dronedarone and theophylline being given in fed conditions.
- Secondary: To assess the clinical and laboratory safety of dronedarone co-administered with theophylline as compared to that of theophylline co-administered with placebo of dronedarone in healthy young male subjects.

Study Design

This was a single center, randomized, double-blind, placebo-controlled, two-period and two-period crossover study. The two treatment periods were:

- Period 1: 400 mg dronedarone twice daily + 400 mg theophylline twice daily
- Period 2: 400 mg theophylline twice daily + placebo dronedarone

There was a 10-day washout period between treatments.

Subject Demographics

Subject demographics are presented in Table 181. Five subjects did not complete the study: four in theophylline + dronedarone and one in theophylline + placebo.

Table 181: Subject Demographics (Study 5084)

Parameter (unit)	Statistics/Category	Overall Subjects (N=39)
Age (years)	N Mean (SD) Min-Max	39 24.6 (4.5) 18-39
Weight (kg)	N Mean (SD) Min-Max	39 69.08 (5.07) 60.0-80.5
Height (cm)	N Mean (SD) Min-Max	39 176.3 (6.5) 164-192
BMI (kg/m²)	N Mean (SD) Min-Max	39 22.27 (1.72) 18.8-25.7
Gender	Male (N,%)	39 (100)
Race	Caucasian (N,%) Black (N,%) Asian / oriental (N,%) Other (N,%)	34 (87.2) 3 (7.7) 1 (2.6) 1 (2.6)

Pharmacokinetic sampling times

The following pharmacokinetic blood samples were drawn at the given times:

- For dronedarone and SR35021: before morning dose (Ctrough) on Days 1, 3, 5, 7, 9, and 10 and 0.5, 1, 2, 3, 6, 8, 10 and 12 hours after administration on Day 10.
- For theophylline: before morning dose (Ctrough) on Days 1, 3, 5, 7, 9, and 10 and 0.5, 1, 2, 3, 6, 8, 10 and 12 hours after administration on Day 10.

Formulation

- Dronedarone: 400 mg tablets, batch number CL-04530
- Theophylline: 400 mg tablets (Teva LP), batch number 02475
- Dronedarone Placebo: 0 mg tablets, batch number CL-04404

Bioanalytical methods

Dronedarone and SR35021 Assays

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as shown in Table 182.

Table 182: Performance of SR35021 and Dronedarone Assays

Parameter	Measure	Reviewer Comment
	Dronedarone	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.990$	Satisfactory
Between day Precision	CV was not provided	Cannot be assessed
Accuracy	Mean relative bias values were not provided, however, individual QC samples were all within 15 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.993$	Satisfactory
Between day Precision	CV was not provided	Cannot be assessed
Accuracy	Mean relative bias values were not provided, however, individual QC samples were all within 15 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* chromatograms provided in the validation report demonstrate assay specificity

Theophylline Assays

Theophylline plasma concentrations were determined by a validated HPLC method with UV detection. The assay performance was acceptable as illustrated in Table 183.

Table 183: Performance of Theophylline Assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 50 to 20000 ng/mL range; $R^2 > 0.999$	Satisfactory
Between day Precision	CV was < 8 %	Satisfactory
Accuracy	QC samples were between 0 and 2.5 % of nominal concentration	Satisfactory
LLOQ	50 ng/ml	Satisfactory
Specificity	Chromatograms were provided that demonstrate specificity	Satisfactory

Pharmacokinetics

The following pharmacokinetic (PK) measures were determined after each treatment:

- For dronedarone and SR35021: Ctrough before morning administration on Days 1 to 10 and Cmax, tmax, AUC_{0-12} on Day 10
- For theophylline: Ctrough from Day 1 to Day 10 and Cmax, tmax and AUC_{0-12} on Day 10.

Statistical methods

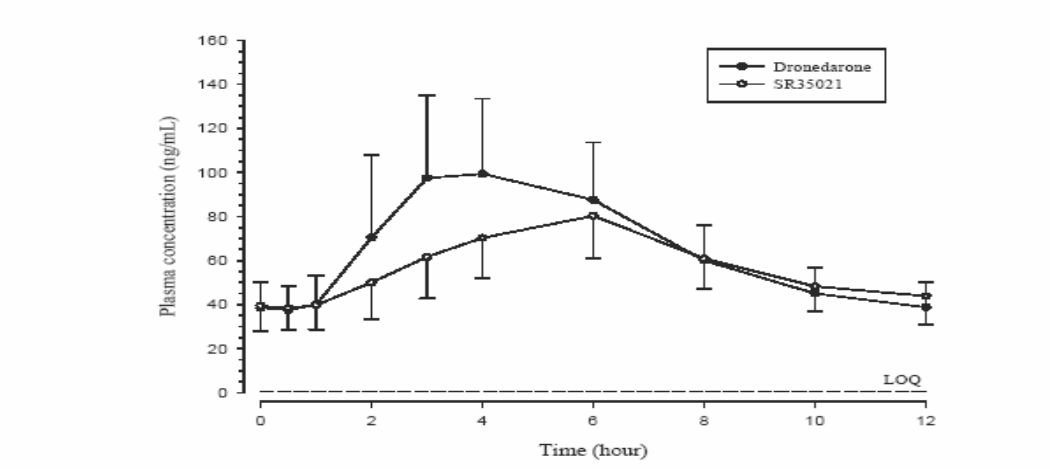
Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. Theophylline + placebo was the reference treatment and dronedarone + theophylline was the test treatment.

Results

Dronedarone Pharmacokinetics

The mean plasma concentration-time profiles for dronedarone and SR35021 are depicted in Figure 112.

Figure 112: Mean dronedarone and SR35021 plasma concentration-time profile under fasted and fed conditions



Dronedarone and SR35021 PK measures are summarized in Table 184.

Table 184: Mean (SD) dronedarone and SR35021 PK measures in healthy males following administration of dronedarone with theophylline(n=33)

Parameter	Dronedarone	SR35021
C_{max} (ng/mL)	117 (31)	82.6 (22)
t_{max} (hour)[a]	3.0 (2.0 – 6.0)	6.0 (2.0 - 8.0)
AUC_{0-12} (ng.h/mL)	799 (25)	699 (22)

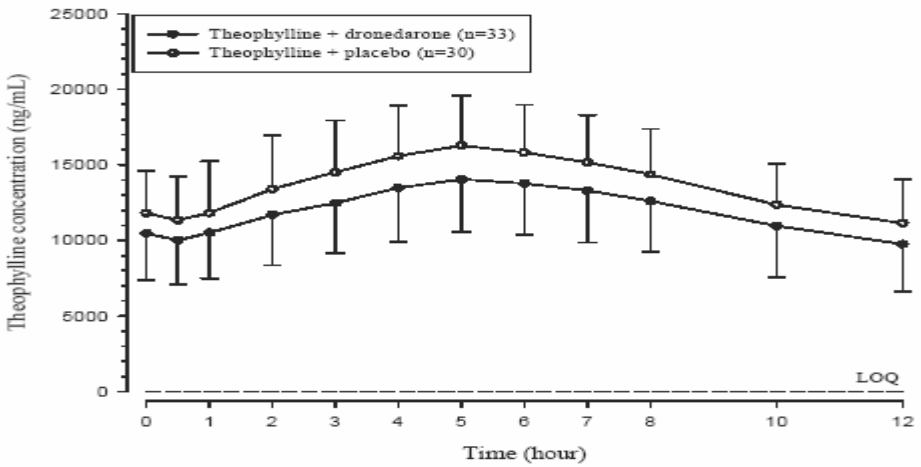
[a]: median (min-max)

The dronedarone and SR35021 PK data are consistent with those obtained in other studies where dronedarone was administered alone; this finding suggests that theophylline does not affect dronedarone PK.

Theophylline PK

The theophylline plasma concentration-time profile is depicted in Figure 113.

Figure 113: Theophylline plasma concentration-time profiles in the presence and absence of dronedarone



Theophylline PK measures and exposure comparisons are summarized in Table 185.

Table 185: Theophylline mean (CV%) and geometric mean ratios and associated 90 % confidence intervals in the presence and absence of 400 mg theophylline

Parameter	Theophylline + dronedarone (n=33)	Theophylline+ placebo (n=30)	Ratio estimate[a] [90% CI]
C_{max} (ng/mL)	14400 (25)	16600 (20)	0.830 [0.800, 0.860]
t_{max}[b] (hour)	5.0 (2.0 – 8.0)	5.0 (3.0 – 8.0)	0 [-0.50, 0.02][c]
AUC_{0-12} (ng.h/mL)	145000 (27)	166000 (22)	0.822 [0.796, 0.850]

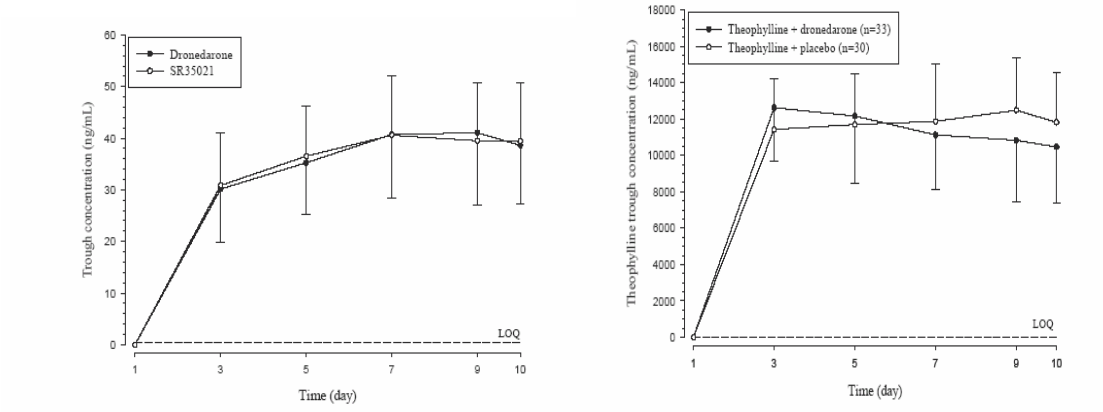
[a]: geometric mean ratio: theophylline + dronedarone/theophylline + placebo
[b]: median (minimum-maximum)
[c]: estimate of median difference [90% CI of median difference]

The confidence intervals indicate that dronedarone decreases theophylline exposure by ~ 20 %; however, this decrease in exposure may not be clinically significant as the decrease is almost entirely within the default no effect confidence interval region (0.80 -1.25).

Attainment of Steady State

Dronedarone steady state was achieved on Day 7 (Figure 114). The time to reach steady state (Tss) for theophylline was delayed in the presence of dronedarone: theophylline + placebo: Tss = three days vs. theophylline + dronedarone Tss steady state = nine days

Figure 114: Time to achieve dronedarone, SR35021, and theophylline steady state



Applicant's Safety Summary

No deaths or serious AEs (SAEs) occurred during the study. Initial insomnia, nausea, and headache were the most frequently reported treatment emergent (TE) AEs in both treatments. Three subjects discontinued study drug due to TEAEs: TEAEs were mainly GI-related (n = 3). The report indicates that six subjects discontinued study drug due to hypertheophyllinemia (theophylline concentrations > 20 µg/mL), but the five of these subjects were on placebo treatment. It is noted that hypertheophyllinemia was not considered an AE.

Dronedarone presence caused an increase in QTc values, relative to the QTc values obtained with theophylline alone: QTc > 450 ms were observed in 5/36 subjects during theophylline + placebo and 10/36 during theophylline + dronedarone treatment.

Recommendations/Conclusions

The following PK information generated in Study INT3561 is acceptable for labeling purposes, as appropriate:

After a 10-day concomitant administration of dronedarone 400 mg BID with 400 mg BID theophylline, relative to theophylline alone, there was approximately a 20 % decrease in steady state of theophylline AUC_{0-12}. These changes may not be clinically significant as the AUC change was just outside the no-effect default lower boundary, whereas the Cmax was within the default no-effect range.

Labeling

The applicant's proposed labeling is acceptable as it adequately reflects the study findings. A dosage adjustment does not appear warranted based on the study findings. Theophylline dosage may be titrated upwards, if needed.

4.2.29 Study on the interaction between a single oral dose of warfarin and repeated oral doses of SR33589B in healthy male subjects (INT3353)

PROTOCOL #	INT3353
INVESTIGATOR	Dr. W. Tetzloff
STUDY SITE	IPHAR - Institut für Klinische Pharmakologie GmbH - Arnikastrasse 4 - D- 85635 Höhenkirchen- Siegerstsbrunn
STUDY PERIOD	March – May 1998

Background Information on Study Drugs (Warfarin and Dronedarone)

	Warfarin	Dronedarone
Indication/Mechanism of Action	Anticoagulant used for several indications including treatment of thromboembolic complications associated with atrial fibrillation	Anti-arrhythmic: proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter.
Metabolites	Several metabolites formed including hydroxylated and reduced (alcohol) species. These metabolites have minimal activity.	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	Undergoes stereo-selective metabolism (S-isomer is five times as active as R-isomer and primarily responsible for clinical effectiveness). Multiple CYP enzymes but CYP2C9 appears predominant	Primarily CYP3A substrate
CYP Inhibitory Potential	None reported	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Dose titrated to achieve adequate anticoagulation based on international normalized ratio	400 mg BID

Objectives (per applicant)

Primary: To assess the effect of repeated oral doses of SR33589B (dronedarone) on the pharmacokinetic profile of warfarin given as a single oral dose.

Secondary

- To assess the pharmacodynamic effects of both warfarin alone and warfarin co-administered with dronedarone
- To estimate the effect of a single oral dose of warfarin on the pharmacokinetics of SR33589 at steady- state
- To assess the tolerability of dronedarone administered both alone and with warfarin.

Study Design

This was an open-labeled, randomized, two-period cross-over study with a 21-day wash out between two warfarin administrations. The following two sequences were followed, where warfarin was given as a single dose on each occasion:

1. warfarin/dronedarone+ warfarin sequence- Day 1, warfarin alone and 14 consecutive days of dronedarone with warfarin concomitantly administered on Day 8

2. dronedarone + warfarin /warfarin sequence- fourteen consecutive days of dronedarone with warfarin concomitantly administered on the Day 8, and one day of warfarin administration alone.

The warfarin dose was 30 mg and the dronedarone dose was 600 mg BID.

Reviewer's Note on Previously Conducted Warfarin-Dronedarone Drug Interaction Study

In a previous study a sequence effect was observed with warfarin administration; however, results obtained in that study are qualitatively and quantitatively similar to the current study. The source of the sequence effect is unclear.

Subject Demographics

Key subject demographic characteristics are as follows:

- Sex: all male subjects
- Race: all Caucasian
- Weight (Range): 69.9 – 86.0 kg
- Age (range): 26 – 45 years

All subjects, except one (Subject 002), completed the study.

Formulation

- Dronedarone: 200 mg capsules, batch number 96-00198
- Warfarin: 10 mg tablets, batch number 7002 (commercially available source)

Pharmacokinetic sampling times

The following pharmacokinetic blood samples were drawn at the given times:

- R- and S- warfarin: before warfarin administration then 1, 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours after administration
- Dronedarone and SR35021: before the morning administration of dronedarone on Days 1, 3, 5, 7, 8, 9, 10, 11, 12 and 14 of dronedarone treatment.
- Dronedarone and SR35021: On Days 7 and 8 of dronedarone administration, samples were taken 1, 2, 3, 4, 5, 6, 8 and 12 hours after the morning administration of dronedarone.

Pharmacokinetics

The following pharmacokinetic (PK) measures were determined after each treatment:

- R-warfarin and S-warfarin: Cmax, tmax, AUClast, AUC and $t_{1/2}$ after single administration of warfarin alone or with repeated administration of dronedarone.
- Dronedarone and SR35021:
    - Cmax, tmax and AUC_{0-12} after repeated administration of dronedarone alone or with a single administration of warfarin
    - Ctrough on Day 3, 5, 7, 8, 9, 10, 11, 12 and 14 days after repeated administration.

Activity/Pharmacodynamics

The pharmacodynamic effects, prothrombin time (%) and international normalized ratio (INR), of warfarin alone and co-administered with dronedarone were determined.

Bioanalytical methods

Dronedarone and SR35021 Assays

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as shown in Table 186.

Table 186: Dronedarone and SR35021 assay performance

Parameter	Measure	Reviewer Comment
	Dronedarone	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day Precision	CV was < 6 %	Satisfactory
Accuracy	QC samples were between -1 and 3 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Satisfactory
	SR35021	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day Precision	CV was < 6 %	Satisfactory
Accuracy	QC samples were between -3 and 4 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Satisfactory

* chromatograms provided in validation report that indicate assay specificity

R- and S-Warfarin concentrations were determined by HPLC with UV detection. The assay performance was acceptable as shown in Table 187.

Table 187: Performance of Warfarin Assay

Parameter	Measure	Reviewer Comment
	R-warfarin Assay	
Linearity	The assay was linear over the 10 to 2000 ng/mL range	Satisfactory
Between day Precision	CV was < 7 %	Satisfactory
Accuracy	QC samples were within 7 % of nominal concentration	Satisfactory
LLOQ	10 ng/ml	Satisfactory
Specificity	Chromatograms were not provided	Cannot be assessed
	S-warfarin Assay	
Linearity	The assay was linear over the 10 to 2000 ng/mL range	Satisfactory
Between day Precision	CV was < 7 %	Satisfactory
Accuracy	QC samples were within 6 % of nominal concentration	Satisfactory
LLOQ	10 ng/ml	Satisfactory
Specificity	Chromatograms were not provided	Cannot be assessed

Statistical methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. The reference treatments were dronedarone alone and warfarin alone and the test treatment was warfarin + dronedarone.

PD measures were analyzed using ANOVA and 95 % confidence intervals for the differences in the treatment means were determined. Variables included in the analyses were INR and percentage prothrombin time (PT), overall hourly average PT, maximum INR, the time of maximum INR (rank transformed), minimum PT (percentage) and the time of the minimum PT (rank transformed). These variables are further defined in the following table.

Parameter	Calculated Measure	Calculation
Prothrombin INR	Overall hourly average	AUC[f]/168[+]
	Maximum	Largest increase from T_0
	Time of maximum	Time of largest increase from T_0
Prothrombin Time (%)	Overall hourly average	AUC[f]/168[+]
	Minimum	Largest decrease from T_0
	Time of minimum	Time of largest decrease from T_0

f AUC = Area Under the Curve calculated using the trapezoidal rule.
\+ 168 hours is the overall time interval

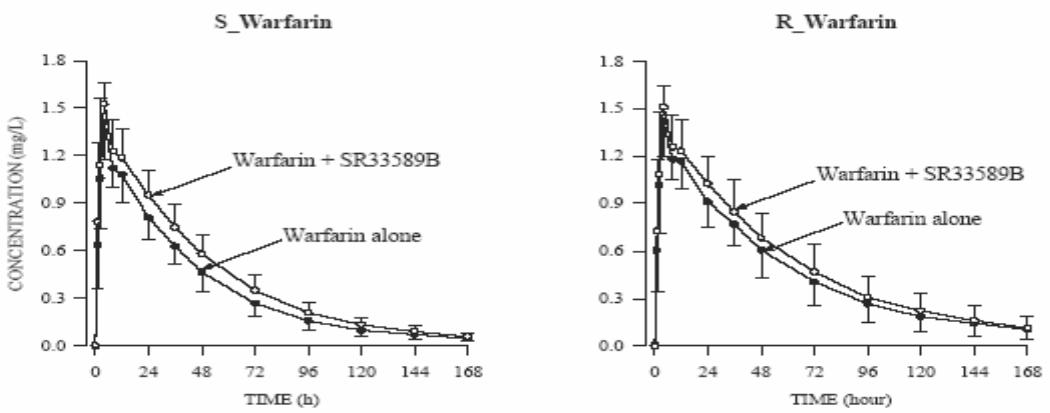
Reviewer Note on PD Statistical Analyses
INR is the most commonly used warfarin PD measure, therefore, this review focuses on INR results.

Results

Warfarin Pharmacokinetics

The plasma concentration-time profiles for S- and R-warfarin are depicted in Figure 115.

Figure 115: S- and R-warfarin plasma concentration-time profiles following single dose administration of warfarin and dronedarone (multiple dose for eight days before warfarin)



The mean (± SD) and CV% of R- and S- warfarin plasma pharmacokinetic parameters obtained after a single 30 mg administration of warfarin (n = 16) alone or with dronedarone are shown in Table 188.

Table 188: Mean (CV %) S- and R-warfarin PK measures following administration of warfarin +/- dronedarone

Parameter	S-warfarin		R-warfarin	
	warfarin alone	warfarin + SR33589B	warfarin alone	warfarin + SR33589B
C_{max} (mg/L)	1.44 (0.20) 14%	1.54 (0.13) 9%	1.45 (0.17) 12%	1.51 (0.13) 9%
t_{max} (h)	4.37 (2.43) 56%	4.00 (1.26) 32%	5.24 (2.79) 53%	4.49 (2.35) 52%
AUC_{last} (mg.h/L)	60.1 (11.2) 19%	71.7 (13.0) 18%	76.8 (18.6) 24%	85.5 (21.1) 25%
AUC (mg.h/L)	63.0 (12.2) 19%	75.0 (14.3) 19%	84.9 (24.1) 28%	94.3 (28.5) 30%
$t_{½}$ (h)	40.4 (4.8) 12%	38.1 (4.3) 11%	49.1 (9.5) 19%	46.8 (12.2) 26%

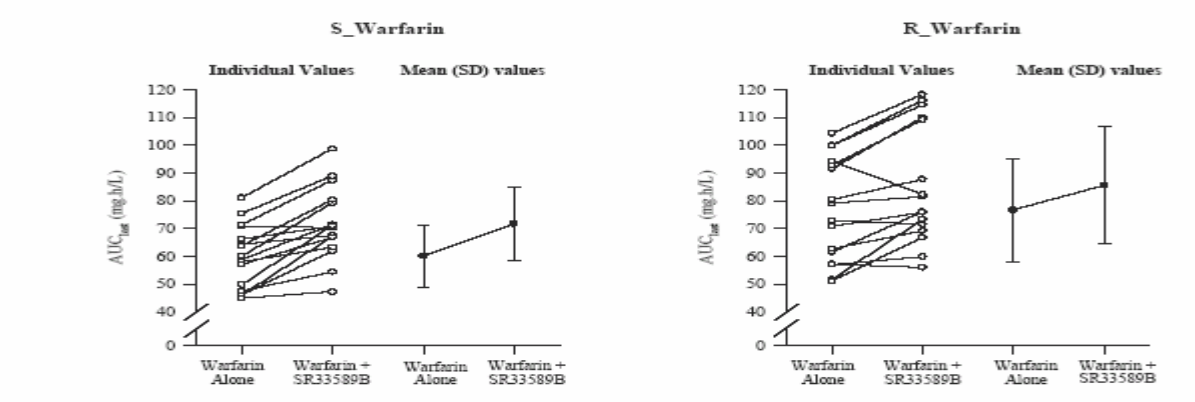
The ratio estimates and 90% confidence intervals (CIs) calculated for Cmax and AUC treatment effect (warfarin + dronedarone versus warfarin alone) of S- and R-warfarin and R- warfarin are shown in Table 189.

Table 189: S- and R- warfarin geometric mean ratios and associated 90 % CIs in the presence and absence of 400 mg dronedarone

Parameter	S-warfarin		R-warfarin	
	Ratio	90% CI	Ratio	90% CI
C_{max}	1.07	[1.00 , 1.14]	1.04	[0.98 , 1.11]
AUC_{last}	1.19	[1.13 , 1.26]	1.11	[1.06 , 1.18]
AUC	1.19	[1.13 , 1.26]	1.11	[1.05 , 1.18]

Most subjects had increased warfarin exposure in the presence of dronedarone as indicated from Table 189 and Figure 116. However, the increase in exposure is generally within the default no effect CI range, suggesting that co-administration of dronedarone with warfarin does not result in a clinically significant PK interaction.

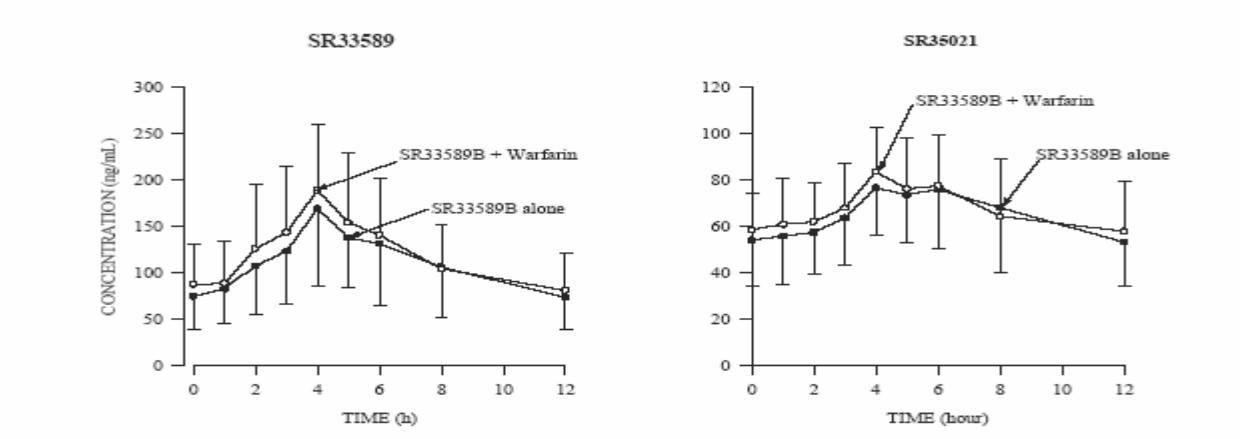
Figure 116: Individual and mean S- and R- warfarin AUCs following administration of warfarin +/- dronedarone



Dronedarone PK

The mean plasma concentration-time profiles for dronedarone are depicted in Figure 117.

Figure 117: Dronedarone plasma concentration-time profiles following administration of dronedarone +/- single dose administration of warfarin



Dronedarone and SR35021 PK measures are summarized in Table 190 and Table 191.

Table 190: Mean (CV %) dronedarone and SR35021 PK measures following administration of warfarin +/- dronedarone

Parameter	SR33589		SR35021	
	SR33589B alone	SR33589B + warfarin	SR33589B alone	SR33589B + warfarin
C_{max} (ng/mL)	175 (79) 45%	191 (72) 38%	86.0 (23.4) 27%	86.5 (19.4) 22%
t_{max} (h)	4.13 (1.36) 33%	3.81 (0.75) 20%	5.31 (1.58) 30%	4.97 (1.40) 28%
AUC_{0-12h} (ng.h/mL)	1312 (581) 44%	1424 (630) 44%	775 (247) 32%	802 (227) 28%

Table 191: S- and R- warfarin geometric mean ratios and associated 90 % confidence intervals in the presence and absence of 400 mg dronedarone

Parameter	SR33589		SR35021	
	Ratio	90% CI	Ratio	90% CI
C_{max}	1.13	[1.05 , 1.22]	1.02	[0.96 , 1.09]
AUC_{0-12h}	1.08	[1.02 , 1.15]	1.04	[0.99 , 1.10]

The dronedarone and SR35021 PK data indicate that warfarin does not alter dronedarone or SR35021 PK significantly.

Activity (Pharmacodynamics)

The PD (INR) results are summarized in the following figures and tables. The PD data related to INR, the most clinically relevant parameter, indicate the following:

- overall hourly average INR for subjects co-administered dronedarone and warfarin was 7 % greater than that for subjects receiving warfarin alone (p= 0.007)
- maximum INR for warfarin alone and warfarin + dronedarone was similar (p = 0.096)
- time of maximum INR overlapped in the two treatment groups
- no statistically significant effects were observed for INR at T0, suggesting that prothrombin times had returned to T0 levels at the end of the wash out period.
- there were no sequence or period effects

Figure 118: Effects of warfarin +/- dronedarone administration on INR

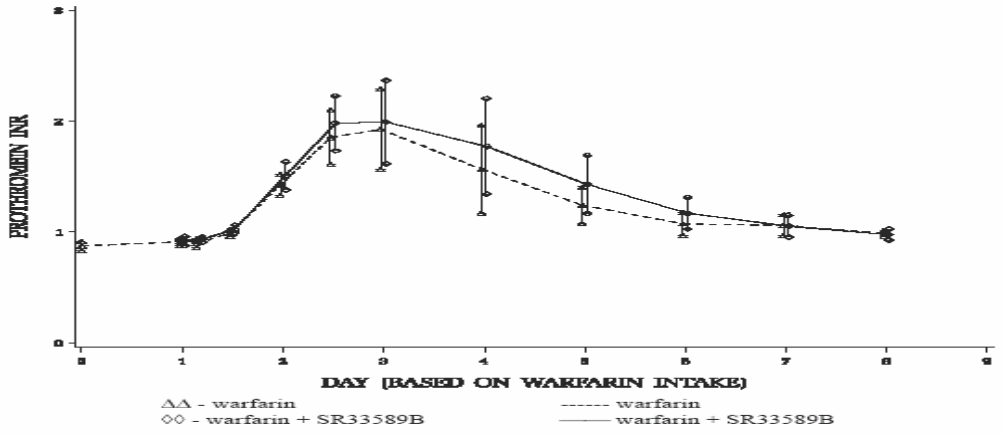


Table 192: INR values following administration of warfarin +/- dronedarone

Prothrombin Time	Parameter	Statistic	Warfarin	SR33589B + warfarin	(S+W)/W estimate (approx. 95% CI)[a]
INR	Overall Hourly Average	Mean (SD)	1.32 (0.31)	1.41 (0.37) *	107.0% (102.3%, 111.7%)
	Maximum	Mean (SD)	1.99 (0.68)	2.10 (0.73)	105.8% (98.8%, 112.8%)
	Time of Maximum	Median (Min-Max)	1.75 (1.00-3.00)	1.50 (1.50-3.00)	NA

* Significantly different from warfarin, $p < 0.01$.
[a] 95 % confidence intervals (CI) were calculated for the differences in treatment means
NA – Not applicable.

Table 193: Analysis of prothrombin time

Prothrombin Time	Parameter	P-Values		
		Sequence	Period	Treatment
INR	PT at T0	0.7494	0.1229	0.6749
	Overall Hourly Average	0.5904	0.0206	0.0065
	Maximum	0.4983	0.0569	0.0959
	Time of Maximum (Ranks)	0.3770	0.6109	0.6109

Applicant's Safety Summary

Overall, concomitant administration of dronedarone with warfarin was well tolerated. Four subjects each experienced a single adverse event (AE) in this study, only one of which led to the withdrawal of a subject. The AEs were as follows: asymptomatic non-sustained ventricular tachycardia (n = 2), second degree atrioventricular block type 1 (n =1) and headache (n = 1).

Recommendations/Conclusions

The following findings from study INT3353 are acceptable for labeling as appropriate:

- Co-administration of a single dose of warfarin with dronedarone does not alter the PK of dronedarone or SR35021
- Relative to administration of warfarin alone (single dose), administration of dronedarone at 600 mg BID for seven days followed by concomitant administration of a single dose of warfarin, increases warfarin AUC by 11 % but has no effect on Cmax. The AUC increase does not appear clinically relevant based on PK measures, as the confidence intervals are generally within the default no effect range.
- Relative to administration of warfarin alone, co-administration of warfarin +/- dronedarone did not alter the INR maximum value or time of maximum value; however, the overall hourly average prothrombin time for subjects co-administered dronedarone and warfarin was significantly greater for INR (7 % increase) when subjects received the warfarin dose alone. However, this INR increase does not appear clinically significant.

Labeling

The labeling should reflect the study findings. A dosage adjustment does not appear warranted based on the study findings. However, precautionary language may be included indicating that INR time may increase (resulting in increased bleeding) when warfarin is co-administered with dronedarone, relative to when warfarin is administered alone. This effect may result from the increased warfarin exposure. It is noted that the warfarin dosage can be titrated to modulate this undesirable effect, if needed.

4.2.30 Interaction study between repeated oral doses of dronedarone and repeated oral doses of nisoldipine in healthy male subjects - randomized, open-labeled, 3 treatments, crossover study (INT4881)

PROTOCOL #	INT4881
INVESTIGATOR	Mark Allison, M. D.
STUDY SITE	MDS Pharma Services, 4639 South 36th Street, Phoenix, AZ 85040,
STUDY PERIOD	January – April 2002

Background Information on Study Drugs (Nisoldipine and Dronedarone)

	Nisoldipine	Dronedarone
Indication/Mechanism of Action	Calcium channel blocker commonly prescribed in cardiac patients	Anti-arrhythmic: proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter.
Metabolites	Hydroxylated active metabolite (activity 1/10th that of parent)	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	CYP3A substrate with low oral bioavailability	Primarily CYP3A substrate
CYP Inhibitory Potential	None reported	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Therapy initiated at 20 mg QD and drug titrated	400 mg BID

Objectives (per applicant)

Primary

- To assess the effect of repeated oral doses of dronedarone on the pharmacokinetic (PK) profile of nisoldipine after repeated oral doses of 20 mg once daily (QD)
- To assess the effect of repeated oral doses of nisoldipine on the PK profile of dronedarone after repeated oral doses of 400 mg twice daily (BID)

Secondary

- To assess the clinical and biological tolerability of dronedarone given alone, of nisoldipine given alone, and of dronedarone co-administered with nisoldipine
- To assess the potential pharmacodynamic (PD) effect of dronedarone when co-administered with nisoldipine

Study Design

This was an open-label, non-placebo-controlled, repeated oral doses, randomized, 3-treatment, 3-period and crossover study. The washout period was seven to 13 days. The three treatments were

- dronedarone 400 mg BID alone for 14 days
- nisoldipine 20 mg QD alone for 14 days
- dronedarone and nisoldipine co-administration for 14 days

Reviewer Note on Nisoldipine Dose
The nisoldipine dose is not the highest recommended dose (60 mg). Use of a dose lower than the highest recommended dose is acceptable, if driven by safety concerns.

Subject Demographics
Subject demographics are summarized in Table 194.

Table 194: Subject demographics (Study 4881)

Parameter	Statistics/ Category	Total (N=28)
Age (yrs)	N Mean (SD) Min - Max	28 26.0 (4.2) 19 - 34
Weight (kg)	N Mean (SD) Min - Max	28 74.21 (9.19) 57.7 – 89.7
Height (cm)	N Mean (SD) Min - Max	28 175.1 (7.1) 164 - 193
BMI (kg/m^2)	N Mean (SD) Min - Max	28 24.21 (2.86) 18.8 – 27.9
Gender	Male (N,%)	28 (100%)
Race	Caucasian (N,%) Black (N,%) Hispanic (N,%)	25 (89.3%) 2 (7.14%) 1 (3.57%)

Formulation
- Dronedarone: 400 mg tablet, batch number CL-04141
- Nisoldipine (Sular) 20 mg tablets, batch number 4548F

Pharmacokinetic sampling times
The following pharmacokinetic blood samples were drawn at the given times:
- Dronedarone and SR35021: pre-morning dose on Days 1, 2, 4, 8, 10, 12 and 14
- Dronedarone and SR35021: 0.5, 1, 2, 3, 4, 6, 8, 10, 12 hours after dosing on Day 14
- Nisoldipine: before administration on Days 1, 2, 4, 8, 10, 12 and 14
- Nisoldipine: 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours after dosing on Day 14, for each period of treatment.

Pharmacokinetics
The following PK measures were determined:
- Dronedarone and SR35021- Ctrough, Cmax , tmax, AUC_{0-12}, and Rmet (SR35021 AUC_{0-12}/SR33589 and AUC_{0-12} ratio)
- Nisoldipine- Ctrough, Cmax, tmax, AUC_{0-24}.

Activity/Pharmacodynamics
The following primary pharmacodynamic (PD) variables were determined: heart rate, electrocardiogram (ECG) intervals (PR- interval and corrected QT value calculated with the Bazett formula [QTc]). The secondary PD variables were QRS- and QT-interval.

Statistical Methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. The reference treatments were dronedarone alone and nisoldipine alone and the test treatment was nisoldipine + dronedarone. Standard statistical methods were used to evaluate pharmacodynamics.

Bioanalytical methods

Dronedarone and SR35021 Assays

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method (DOH0239). The assay performance was acceptable as shown in Table 195.

Table 195: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day Precision	CV values were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided, however, the majority of individual QC samples were within 15 % of nominal concentration.	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided	Satisfactory
	SR35021	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.993$	Satisfactory
Between day Precision	CV value was not provided	Cannot be assessed
Accuracy	Relative bias values were not provided, however, the majority of individual QC samples were within 15 % of nominal concentration.	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity*	Chromatograms were not provided	Cannot be assessed

* assay validation report includes chromatograms that indicate assay specificity

Nisoldipine concentrations were determined by a validated LC-MS/MS method. The assay performance was acceptable as shown in Table 196.

Table 196: Performance of Nisoldipine Assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 0.10 to 25 ng/mL range; $R^2 > 0.993$	Satisfactory
Between day Precision	CV was < 9 %	Satisfactory
Accuracy	QC samples were between -1.9 and – 3.4 % of nominal concentration	Satisfactory
LLOQ	0.10 ng/ml	Satisfactory
Specificity	Chromatograms were not provided	Cannot be assessed

Results

PK data were available from 26 subjects; two subjects were withdrawn from the study.

Dronedarone and SR35021 Pharmacokinetics

The dronedarone and SR35021 plasma concentration-time curves are depicted in Figure 119 and Figure 120, respectively.

The pharmacokinetic measures of dronedarone and SR35021 after dronedarone administration with or without nisoldipine are summarized in Table 197.

Figure 119: Dronedarone plasma concentration-time profiles following administration of dronedarone +/- nisoldipine

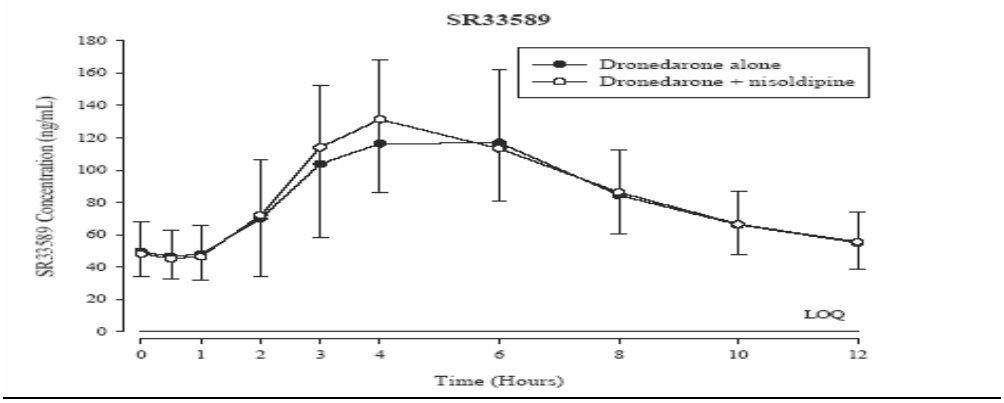


Figure 120: SR35021 plasma concentration-time profiles following administration of dronedarone +/- nisoldipine

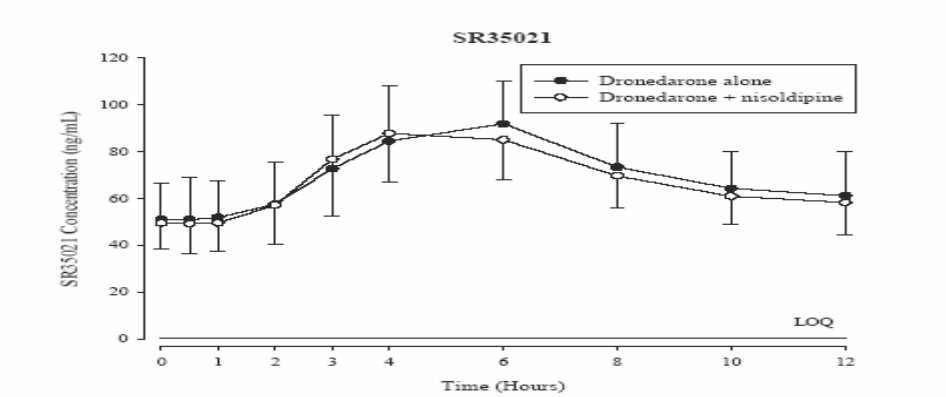


Table 197: Dronedarone and SR35021 PK Measures following administration of dronedarone +/- nisoldipine

PK Parameters	Dronedarone Alone	Dronedarone + Nisoldipine	Ratio Estimates[b] and 90% CI
		SR33589	
C_{max} (ng/mL)	134 (38)	144 (32)	1.12 [1.02; 1.22]
t_{max} (h)[a]	5	4	p=0.188
AUC_{0-12} (ng.h/mL)	1008 (34)	1039 (28)	1.07 [1.01; 1.12]
		SR35021	
C_{max} (ng/mL)	95.7 (21)	93.8 (20)	1.00 [0.94; 1.06]
t_{max} (h)[a]	6	4	p=0.02
AUC_{0-12} (ng.h/mL)	852 (23)	828 (18)	0.99 [0.94; 1.04]
R_{acc} (AUC_{0-12})	0.90 (26)	0.84 (24)	-

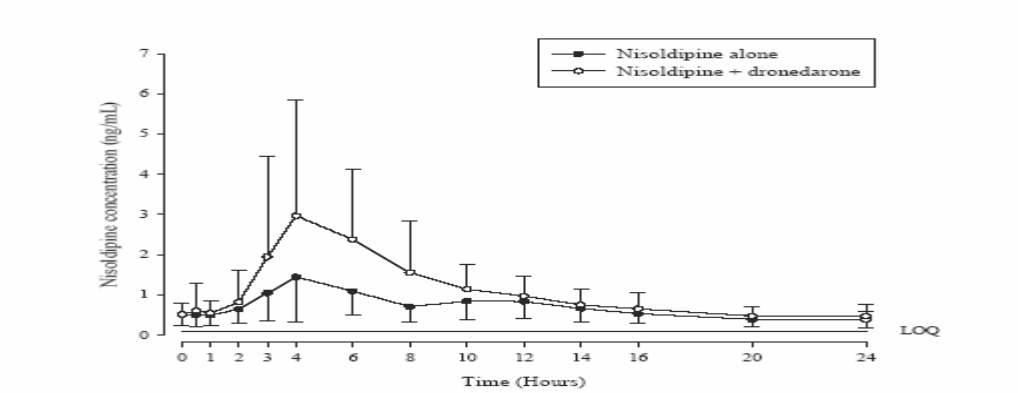
[a] Median values
[b] ratio dronedarone + nisoldipine / dronedarone, p-value for difference between treatments

The data indicate that nisoldipine does not alter dronedarone PK in a clinically significant manner (confidence interval within no effect range).

Nisoldipine Pharmacokinetics

The nisoldipine plasma concentration-time profiles following administration of nisoldipine with or without dronedarone are depicted in Figure 121.

Figure 121: Nisoldipine plasma concentration time profile in the presence and absence of dronedarone



The nisoldipine PK measures obtained following administration of nisoldipine with or without dronedarone are presented in Table 198.

Table 198: Nisoldipine PK Measures following administration of nisoldipine +/- dronedarone (n = 26)

PK Parameter Mean (CV%)	Nisoldipine Alone	Nisoldipine + Dronedarone	Ratio Estimates[b] and 90% CI
C_{max} (ng/mL)	1.76 (60)	4.10 (74)	2.13 [1.55; 2.93]
t_{max} (h)[a]	4	4	p=0.377
AUC_{0-24} (ng.h/mL)	16.8 (41)	26.4 (51)	1.50 [1.08; 2.10]

[a] Median values
[b] ratio nisoldipine + dronedarone / nisoldpine, p-value for difference between treatment

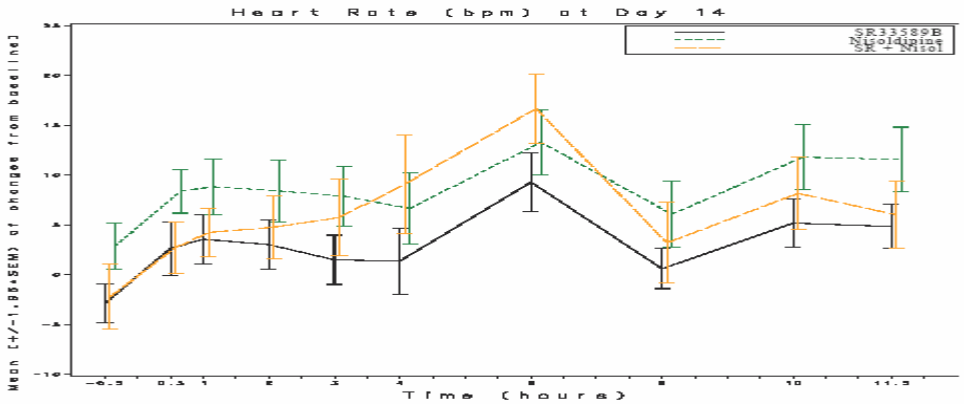
Co-administration of dronedarone increased mean nisoldipine Cmax and AUC_{0-24} by 2.1- fold and 1.5- fold, respectively. This finding suggests dronedarone inhibited nisoldipine metabolism.

Pharmacodynamics

The pharmacodynamic (PD) data for the nisoldipine-dronedarone interaction are graphically illustrated in the following figures and Table 199. Each PD measure is discussed in turn.

- Heart rate

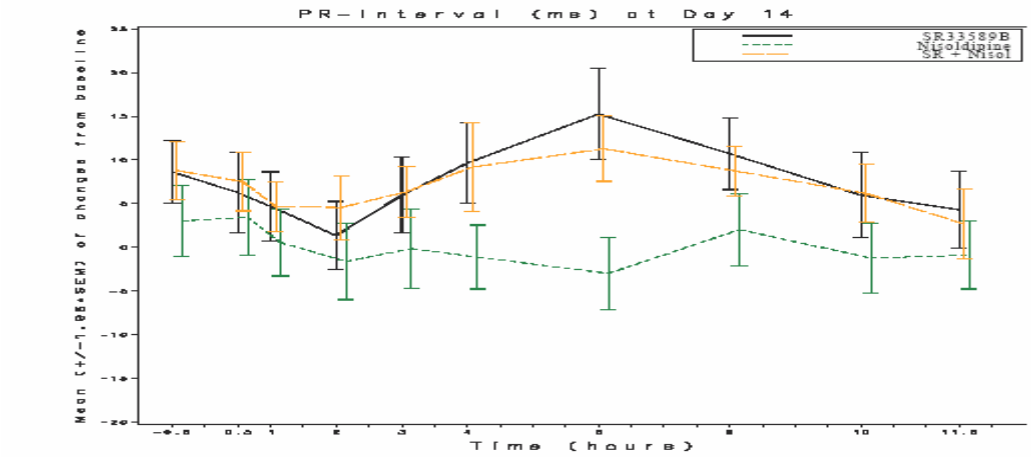
Figure 122: Changes in Heart Rate (Day 14 vs. Baseline) following administration of dronedarone alone, nisoldipine alone and nisoldipine + dronedarone



After 14 days of treatment, the change from baseline HR for nisoldipine alone was greater than that of dronedarone alone. However, there was no difference between the co-administration treatment and either treatment given alone, suggesting that there was no PD interaction on HR.

- PR Interval

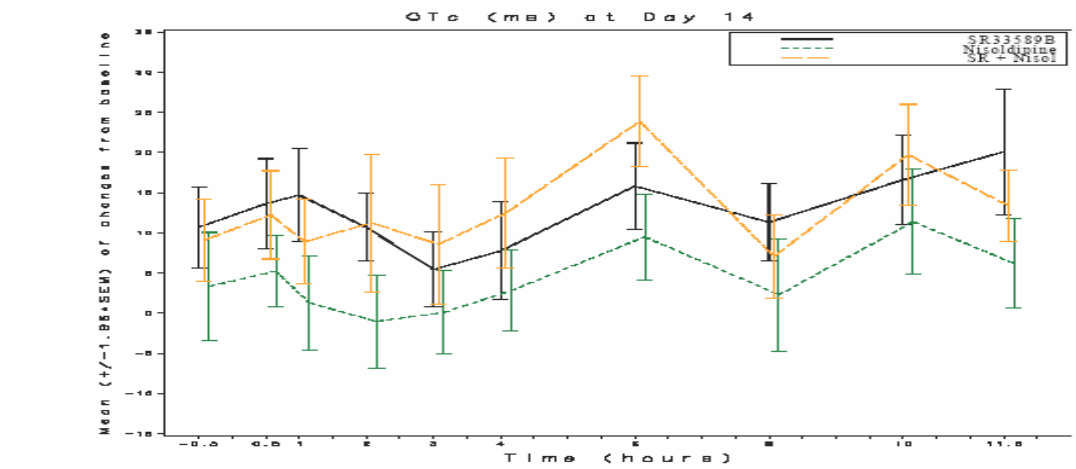
Figure 123: Changes in PR interval (Day 14 vs. Baseline) following administration of dronedarone or nisoldipine alone and nisoldipine + dronedarone



A statistically significant difference in mean change from baseline (Day 1 pre-dose) PR-interval over 12 hours on Day 14 was seen between the co-administration and the nisoldipine alone treatments. However, the mean increases in PR-interval were similar after repeated doses of dronedarone given alone or in combination with nisoldipine. The data suggest that there was no PD interaction on PR-interval, and the observed significant difference in PR- interval after repeated co-administration versus nisoldipine alone was probably due to the dronedarone effect.

- QTc

Figure 124: Changes in QTc interval (Day 14 vs. Baseline) following administration of dronedarone or nisoldipine alone and nisoldipine + dronedarone



A statistically significant difference in mean change from baseline (Day 1 pre-dose) QTc over 12 hours on Day 14 was seen between the co-administration and the nisoldipine alone treatments. However, the mean increases in QTc were similar after repeated doses of dronedarone given alone or in co-administration with nisoldipine. The data suggest that there was no PD interaction on QTc and the observed significant difference in QTc after repeated co-administration versus nisoldipine alone was probably due to the dronedarone effect.

Table 199: Pharmacodynamic data of the Day 14 mean difference estimates in averaged changes from baseline over 12 hours

Parameter (Unit)	Estimates of Mean Differences [95% CI]		
	Nisol. – Drone. (N = 26)	Co-admin. – Nisol. (N = 26)	Co-admin. – Drone. (N = 26)
Heart rate (bpm)	5.61 [2.17, 9.05]	-2.68 [-6.11, 0.76]	2.93 [-0.52, 6.39]
PR-interval (ms)	-7.38 [-11.21, -3.55]	6.60 [2.77, 10.43]	-0.78 [-4.62, 3.07]
QTc (ms)	-8.73 [-14.05, -3.42]	8.46 [3.15, 13.78]	-0.27 [-5.61, 5.07]

Applicant's Safety Summary

No deaths or serious adverse events were reported during the study. All reported treatment-emergent adverse events (TEAEs) were mild in severity. TEAEs were almost twice as common in the dronedarone + nisoldipine treatment group compared to the dronedarone or nisoldipine alone treatment groups. The most common TEAEs were dizziness, headache, palpitations, nausea, and vomiting. Vital signs and ECG measures were comparable between treatment groups.

Recommendations/Conclusions

The following findings from study INT4881 are acceptable for labeling as appropriate:

- co-administration of nisoldipine (20 mg QD) and dronedarone (400 mg BID) increased nisoldipine Cmax and AUC_{0-24} by 2.1-fold and 1.5-fold, respectively, relative to nisoldipine alone
- dronedarone exposure was not altered by nisoldipine
- there did not appear to be a pharmacodynamic interaction between dronedarone and nisoldipine with respect to their effect on PR, QTc or HR.

Labeling Comments

The applicant's labeling proposal is acceptable as it reflects the study findings. A dosage adjustment does not appear warranted during nisoldipine and dronedarone co-administration although nisoldipine exposure is increased. The therapeutic dosage range is approximately 10 to 60 mg; therefore, initiating therapy at 20 mg (typical initial dosage) with dronedarone, will lead to nisoldipine exposures that fall within therapeutic range. Subsequently, the nisoldipine dosage can be titrated, as needed depending on the safety and effectiveness of the nisoldipine-dronedarone regimen. In sum, precautionary language should be included in the label to indicate that patients receiving dronedarone and nisoldipine as part of therapy may have an increase in nisoldipine concentrations that may exacerbate adverse events associated with high nisoldipine exposure.

Reviewer's Note on Applicant's Labeling

The applicant's labeling is satisfactory although it does not provide specific precautionary language with regard to the consequences of increased nisoldipine concentrations. This omission is acceptable because the increase in nisoldipine concentration is only 50 % and nisoldipine dosage is routinely titrated during therapy.

4.2.31 Dose escalation study of the tolerability and pharmacodynamic effects of dronedarone on top of metoprolol in healthy male volunteers (PDY3828)

PROTOCOL #	PDY3828
INVESTIGATOR	Henri Caplain, MD
STUDY SITE	Aster Clinical Research Center, 3 and 5 rue Eugène Millon, 75015 Paris, France,
STUDY PERIOD	May – October, 1999

Background Information on Study Drugs (Metoprolol and Dronedarone)

	Metoprolol	Dronedarone
Indication/Mechanism of Action	Beta blocker used in the treatment of hypertension, angina pectoris and heart failure	Anti-arrhythmic: proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter.
Metabolites	Several metabolites are formed; exhibits stereo-selective metabolism (S and R). Metabolites are inactive	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	CYP2D6 substrate	Primarily CYP3A substrate
CYP Inhibitory Potential	None reported	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Initial dosage varies depending on indication; subsequently dosage is titrated. Dose range: 12.5 to 200 mg daily	400 mg BID

Objectives (per applicant)

- to assess the tolerability and the pharmacodynamic effects in particular on myocardial contractility of escalating doses of dronedarone on top of metoprolol in healthy male volunteers
- to assess other pharmacodynamic effects of study drug and to assess effects of dronedarone on the pharmacokinetics (PK) of metoprolol at steady state.

Study Design

This was a randomized, double-blind, placebo-controlled, repeated dose and dose-escalating study. The following treatments were given over a 13 day period: five days metoprolol followed by eight days metoprolol + dronedarone. The metoprolol dosage was 200 mg once daily (QD) and dronedarone 400, 600, or 800 mg twice daily (BID) or placebo under fed conditions.

Subject Demographics

Subject demographics are summarized in Table 200. Forty-nine subjects were treated; however 39 subjects were evaluable for pharmacokinetics and 44 for pharmacodynamics.

Formulation

- Dronedarone: 200 mg tablets, batch number 98-01499
- Dronedarone placebo: batch number 99-02198
- Metoprolol: 200 mg tablets, batch number 99-02197

Table 200: Subject demographics (PDY3828)

Parameter	Statistics/ Category	Placebo	800 mg	1200 mg	1600 mg	All
Age (years)	N	13	6	9	21	49
	Mean	28.3	31.2	30.2	29.1	29.4
	SD	3.22	4.17	5.07	3.98	4.02
	Min	25	27	24	24	24
	Max	36	38	39	40	40
Height (cm)	N	13	6	9	21	49
	Mean	176.8	179.3	178.1	177.9	177.8
	SD	6.35	7.61	7.10	7.11	6.79
	Min	168	165	167	163	163
	Max	188	187	187	189	189
Weight (kg)	N	13	6	9	21	49
	Mean	71.49	75.13	72.72	70.19	71.60
	SD	8.701	5.474	10.18	7.858	8.230
	Min	56.5	69.2	59.1	57.8	56.5
	Max	82.4	83.2	89.0	85.7	89.0
Gender [n (%)]	Male	13 (100%)	6 (100%)	9 (100%)	21 (100%)	49(100%)
Race [n (%)]	Caucasian	13 (100%)	6 (100%)	9 (100%)	21 (100%)	49 (100%)

Pharmacokinetic sampling times

The following pharmacokinetic blood samples were drawn at the given times:

- Dronedarone and SR35021
  - Day 6 before administration, and Days 7, 9, 11 at Time 0 (T0)
  - Day 13 at T0 and 1, 2, 3, 4, 5, 6, 8, 10, and 12 h after dosing.
- Metoprolol and alpha-hydroxy-metoprolol
  - Day 0, 5, 7, 9, 11 and 13 before treatment
  - Days 5 and 13 at T0, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h post dose

Bioanalytical methods

Dronedarone and SR35021 Assays

Dronedarone and SR35021 concentrations were determined by LC-MS/MS (DOH0151). The assay performance was acceptable as shown in Table 201.

Table 201: Performance of Dronedarone and SR35021 Assay

Parameter	Measure	Reviewer Comment
	Dronedarone	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.995$	Satisfactory
Between day Precision	CV < 12 %	Acceptable
Accuracy	QC samples were between -1.8 and 3.3 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Satisfactory
	SR35021	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.982$	Satisfactory
Between day Precision	CV was < 18 % for low QC sample (close to LLOQ) and CV < 10 % for mid and high QC samples	Satisfactory
Accuracy	QC samples were between -2.8 and 1.7 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Satisfactory

* chromatograms were included in the assay validation report that demonstrate specificity

Metoprolol and alpha-hydroxy-metoprolol

Metoprolol and alpha-hydroxy-metoprolol concentrations were determined by HPLC. The assay performance was acceptable as shown in Table 202.

Table 202: Performance of Warfarin Assay

Parameter	Measure	Reviewer Comment
	Metoprolol Assay	
Linearity	The assay was linear over the 5 to 1000 ng/mL range; $R^2 > 0.999$	Satisfactory
Between day Precision	CV was < 8 %	Satisfactory
Accuracy	QC samples were between 2.5 and 4.2 % of nominal concentration	Satisfactory
LLOQ	5 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory
Parameter	Measure	Reviewer Comment
	alpha-hydroxy-metoprolol Assay	
Linearity	The assay was linear over the 5 to 1000 ng/mL range; $R^2 > 0.999$	Satisfactory
Between day Precision	CV was < 10 %	Satisfactory
Accuracy	QC samples were between 2.3 and 7.0 % of nominal concentration	Satisfactory
LLOQ	5 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Pharmacokinetics

The following PK measures were determined:

- For Dronedarone and SR35021- Cmax, tmax, Cmin, and $AUC_{0\text{-}12h}$
- For metoprolol and alpha-hydroxy-metoprolol- Cmax, tmax, Cmin, and $AUC_{0\text{-}24h}$

Activity/Pharmacodynamic Endpoint

The primarily and secondary endpoints were measured by a variety of techniques including, Doppler echocardiography, phonocardiogram, carotidogram and transthoracic electrical impedance cardiogram. The primary endpoints were mean velocity of endocardial circumferential fiber shortening (Vcfmean), left ventricular ejection fraction (LVEF), and cardiac output (CO); secondary endpoints were HR, stroke volume, systolic time interval corrected to HR (electromechanical systole [QS 2i]), and cardiac index.

Statistical Methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. The reference treatment was metoprolol alone and metoprolol + dronedarone was the test treatment.

The pharmacodynamic analyses were based on the change in Day 5 and Day 13 measurements (CHG Day13- 5), using a one-way ANOVA model with term for dose.

Results

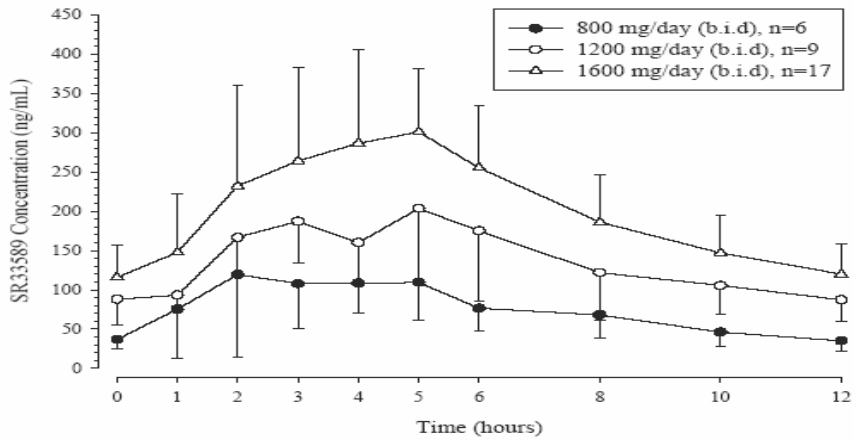
<u>CYP2D6 metabolic status</u>

Initial genotyping indicated that 2 out of the 44 available subjects were poor metabolizers (PMs: Subjects No. 2 and No. 5 in dronedarone 800 mg/day (BID) group). A more sophisticated analysis that allowed characterization of rare or unknown mutations indicated that three subjects initially identified as extensive metabolizers (EM) were PM (Subjects 28 and 32 in dronedarone 1600 mg/day BID group and subject 13 in placebo group). The report indicates that eight subjects did not undergo genotyping. According to the applicant the PK profile of these eight subjects were consistent with the results obtained for the 39 EM subjects, thus, they were considered EM in the analysis.

Reviewer Note on CYP2D6 status
The applicant correctly indicates that the evaluation of dronedarone's CYP2D6 inhibition potency is not possible, if the enzyme is not expressed (such as with PMs), therefore the statistical analyses would be performed using the results of the 39 remaining EM subjects. This approach is reasonable however all data could have been analyzed to make the study findings globally applicable because the general population includes PM, EM and other CYP2D6 metabolizers.

Dronedarone Pharmacokinetics
The dronedarone plasma concentration-time curves obtained following administration of dronedarone with metoprolol are depicted in Figure 125.

Figure 125: Dronedarone plasma concentration-time profiles following administration of dronedarone with metoprolol



The dronedarone PK measures are summarized in Table 203; based on a comparison to historical data, metoprolol does not appear to alter dronedarone PK.

Table 203: Dronedarone PK Measures following administration of dronedarone with metoprolol

Mean (SD) Parameters	SR33589B Treatment		
	800 mg/day (b.i.d.) n=6	1200 mg/day (b.i.d.) n=9	1600 mg/day (b.i.d.) n=17
C_{min} (ng/mL)	33.3 (12.0)	74.5 (27.4)	106.0 (36.9)
C_{max} (ng/mL)	167.1 (77.8)	240.7 (65.9)	348.5 (100.3)
t_{max} (h) *	4.0	4.0	4.0
AUC_{0-12h} (ng.h/mL)	912 (347)	1657 (449)	2455 (734)

a: median values

SR35021 Pharmacokinetics
The SR35021 plasma concentration-time curves following dronedarone administration with metoprolol are depicted in Figure 126.

The SR35021 PK measures are summarized in Table 204; based on a comparison to historical data, metoprolol does not appear to alter SR35021 PK.

Figure 126: SR35021 plasma concentration-time profiles following administration of dronedarone +/- metoprolol

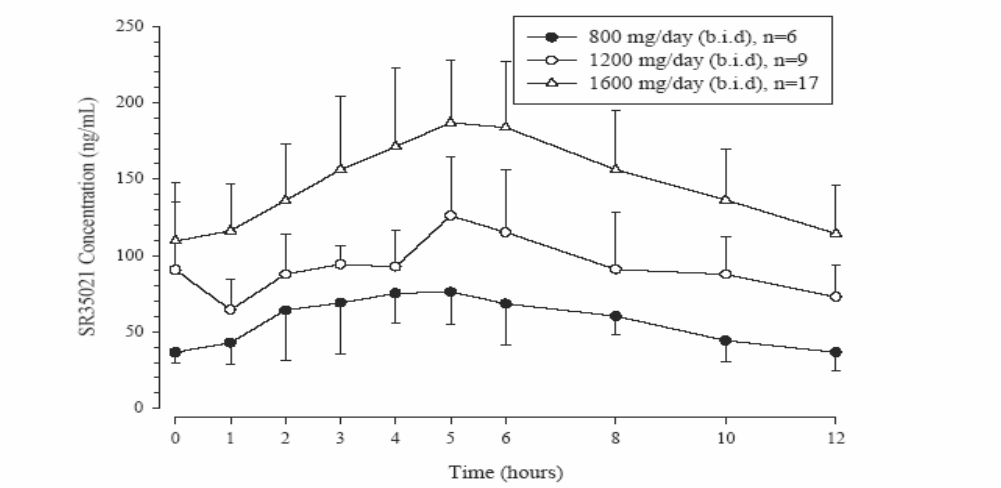


Table 204: SR35021 PK Measures following administration of dronedarone + metoprolol

Mean (SD) Parameters	SR33589B Treatment		
	800 mg/day (b.i.d.) n=6	1200 mg/day (b.i.d.) n=9	1600 mg/day (b.i.d.) n=17
C_{min} (ng/mL)	33.5 (8.8)	58.6 (17.8)	102.6 (28.7)
C_{max} (ng/mL)	88.2 (29.0)	155.9 (38.5)	198.3 (45.1)
t_{max} (h) *	5.5	5.0	5.0
AUC_{0-12h} (ng.h/mL)	689 (187)	1111 (249)	1794 (398)

a: median values

Metoprolol Pharmacokinetics

The metoprolol plasma concentration-time curves following co-administration of metoprolol with varying dronedarone doses and placebo are depicted in Figure 127.

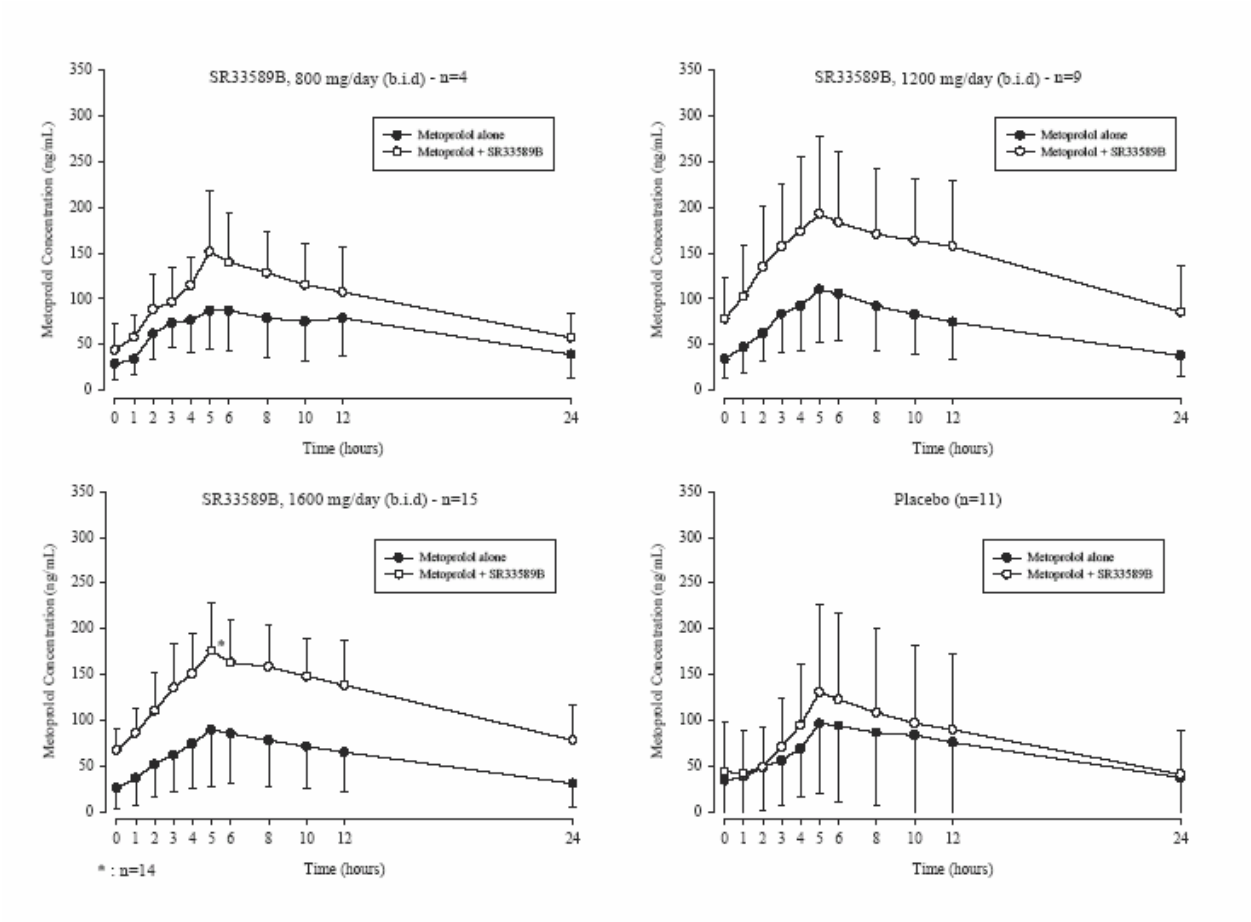
The metoprolol PK measures obtained following administration of metoprolol with or without dronedarone are presented in Table 205.

Table 205: Metoprolol PK Measures following administration of metoprolol +/- dronedarone (n = 26)

Parameters	SR33589B/Placebo Treatment			
	Placebo (n=11)	*800 mg/day (b.i.d.) n=4*	*1200 mg/day (b.i.d.) n=9*	*1600 mg/day (b.i.d.) n=15*
Metoprolol alone (day 5)				
C_{min} (ng/mL)	30.3 (43.4)	27.9 (17.5)	31.8 (18.4)	23.1 (20.4)
C_{max} (ng/mL)	100.6 (86.4)	92.7 (39.8)	111.4 (56.5)	96.2 (61.8)
t_{max} (h)*	5.0	4.0	5.0	5.0
AUC_{0-24h} (ng.h/mL)	1541 (1563)	1555 (803)	1662 (863)	1386 (909)
Metoprolol + SR33589B (day 13)				
C_{min} (ng/mL)	36.3 (44.5)	41.8 (26.6)	76.0 (44.6)	62.3 (27.2)
C_{max} (ng/mL)	134.1 (96.8)	162.6 (55.5)	195.8 (86.8)	180.9 (51.3)
t_{max} (h)*	5.0	5.0	5.0	5.0
AUC_{0-24h} (ng.h/mL)	1862 (1689)	2318 (846)	3361 (1534)	2980 (948)

*: median values

Figure 127: Metoprolol plasma concentration time profile in the presence and absence of dronedarone



The Cmax data (Table 206) indicate that administration of dronedarone resulted in increased metoprolol exposure (Day 13 vs. Day 5) relative to administration of metoprolol alone; this increase was dependent to some extent on the dronedarone dose (numerically, the 1600 mg dose produced a greater increase in metoprolol exposure than the 800 and 1200 mg doses. The applicant's analysis indicates that on Day 13 there was a significant difference between metoprolol Cmax obtained after placebo and after dronedarone treatment for the 1600 mg/day treatment (p= 0.0044). This difference was not significant for the other dronedarone treatments (800 mg/day and 1200 mg/day).

Table 206: Metoprolol Cmax comparisons for dronedarone-metoprolol drug interaction evaluation

	Contrast Day 13 / Day 5			
	Placebo (n=11)	SR33589B 800 mg/day (b.i.d.) (n=4)	SR33589B 1200 mg/day (b.i.d.) (n=9)	SR33589B 1600 mg/day (b.i.d.) (n=15)
Ratio	1.34	1.84	1.78	2.23
90% CI	[1.08-1.66]	[1.29-2.64]	[1.40-2.26]	[1.86-2.69]
95% CI	[1.03-1.73]	[1.20-2.84]	[1.34-2.37]	[1.79-2.79]

The findings for $AUC_{0\text{-}24h}$ data (Table 207) were qualitatively similar to the Cmax findings: Day 13 metoprolol exposure was 1.6- to 2.5-fold greater than Day 5 exposure. At Day 13 a

significant difference was observed between metoprolol AUC_{0-24h} obtained after placebo treatment and after dronedarone treatment, for the 1200 mg/day treatment (p= 0.0118), and for the 1600 mg/day treatment (p= 0.0078). For the 800 mg/day treatment this difference was not significant.

Table 207: Metoprolol AUC comparisons for dronedarone-metoprolol drug interaction evaluation

	Contrast Day 13/Day 5			
	Placebo (n=11)	**SR33589B 800 mg/day (b.i.d.) (n=4)**	**SR33589B 1200 mg/day (b.i.d.) (n=9)**	**SR33589B 1600 mg/day (b.i.d.) (n=15)**
Ratio	1.29	1.63	2.08	2.53
90% CI	[1.08-1.55]	[1.21-2.20]	[1.70-2.54]	[2.17-2.95]
95% CI	[1.04-1.61]	[1.14-2.34]	[1.63-2.64]	[2.10-3.05]

Overall the data indicate, metoprolol's metabolism is inhibited by dronedarone.

<u>α-hydroxy-metoprolol pharmacokinetics</u>

The plasma concentration time profile of α-hydroxy-metoprolol following administration of metoprolol alone or metoprolol co-administered with dronedarone is shown in Figure 128; PK measures for α-hydroxy-metoprolol are presented in Table 208.

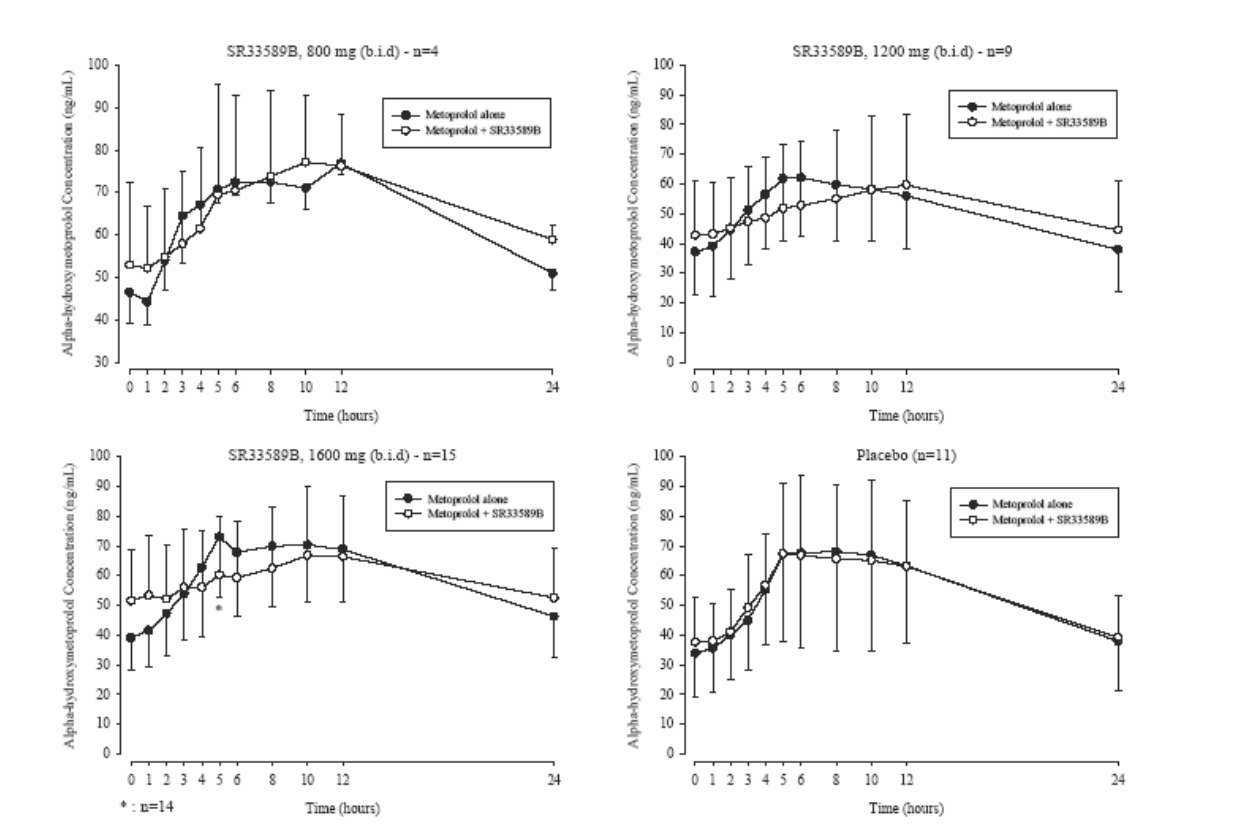
Table 208: Alpha-hydroxy-metoprolol PK measures obtained following administration of metoprolol +/- dronedarone

Mean (SD) Parameters	**SR33589B/Placebo Treatment**			
	Placebo (n=11)	***800 mg/day (b.i.d.) n=4***	***1200 mg/day (b.i.d.) n=9***	***1600 mg/day (b.i.d.) n=15***
Metoprolol alone (day 5)				
C_{min} (ng/mL)	31.9 (13.9)	43.6 (5.0)	34.4 (13.0)	37.6 (11.4)
C_{max} (ng/mL)	72.2 (33.2)	77.4 (1.5)	64.1 (21.5)	75.1 (22.4)
t_{max} (h)*	10.0	12.0	6.0	8.0
AUC_{0-24h} (ng.h/mL)	1294 (526)	1541 (38)	1216 (395)	1421 (376)
Metoprolol + SR33589B (day 13)				
C_{min} (ng/mL)	34.7 (14.3)	49.5 (17.3)	42.0 (17.6)	46.6 (17.0)
C_{max} (ng/mL)	70.7 (26.7)	81.7 (16.6)	60.4 (24.8)	70.6 (22.4)
t_{max} (h)*	5.1	10.9	12.0	12.0
AUC_{0-24h} (ng.h/mL)	1309 (453)	1615 (298)	1247 (492)	1428 (443)

*: median values , a: n=15

Administration of dronedarone with metoprolol did not appear to alter α-hydroxymetoprolol's PK, relative to when metoprolol was administered alone; geometric mean ratios and 90 % confidence intervals were not provided.

Figure 128: alpha-hydroxy metoprolol plasma concentration time profiles following administration of metoprolol +/- varying dronedarone doses or placebo



Pharmacodynamics

Three sets of PD parameters were assessed: Doppler echocardiography (DEC), contractility and cardiac impedance.

Reviewer Note on Study Design (Sample size)

The applicant notes that they intentionally increased sample size for the 1600 mg group relative to the other dronedarone dose groups to test the protocol hypotheses. Consequently, findings in the 1600 mg group must be considered as the most robust; the opposite is true for the 800 mg group because of the sample size differences. According to the applicant subjects were included in the lower dose groups mainly to verify good tolerability, thus allowing dose-escalation to the 1600 mg daily target. It is noted that the proposed clinical dosage of dronedarone is 400 mg BID.

DEC parameters (Primary PD Endpoints)

The statistical analyses for DEC parameters are summarized in Table 209.

Table 209: DEC comparisons

Parameter (unit)	Comparison SR33589B Versus Placebo	Mean Difference Estimate	95% CI Lower Bound	95% CI Upper Bound	P-value
VCFMean (sec-1)	800 mg	-0.03	-0.20	0.14	0.7563
	1200 mg	-0.11	-0.26	0.04	0.1509
	1600 mg	-0.28	-0.41	-0.14	0.0002
FS	800 mg	-0.01	-0.06	0.04	0.7911
	1200 mg	-0.03	-0.07	0.02	0.1892
	1600 mg	-0.07	-0.10	-0.03	0.0011
LVEF (%)	800 mg	-10.89	-21.02	-0.76	0.0358
	1200 mg	-2.13	-11.06	6.81	0.6334
	1600 mg	-9.37	-17.01	-1.73	0.0175
HR (bpm)	800 mg	-2.92	-7.72	1.88	0.2265
	1200 mg	-3.25	-7.48	0.98	0.1285
	1600 mg	-3.68	-7.30	-0.06	0.0463
CO (L/min)	800 mg	-1.12	-1.92	-0.32	0.0075
	1200 mg	-0.00	-0.71	0.70	0.9937
	1600 mg	-0.44	-1.07	0.18	0.1555

Overall, there was a trend toward statistically significant difference between the 1600 mg dose group versus placebo (Day 5 vs. Day 13). Dronedarone dosages that produced statistically significant differences from placebo are summarized below:

- For Vcfmean, only 1600 mg group
- For FS, only 1600 mg group
- For LVEF, both 800 and 1600 mg group, where 800 mg produced larger change
- For HR, only 1600 mg group
- For CO, only 800 mg group

Contractility parameters(Secondary PD Endpoints)

The difference estimates for phonocardiogram parameters are summarized in Table 210.

Results on secondary contractility parameters, assessed by phonocardiogram/carotidogram and impedance cardiogram showed similar trends in all dose groups with QS 2i showing the most significant changes.

Table 210: Contractility parameters

Parameter (unit)	Comparison SR33589B Versus Placebo	Mean Difference Estimate	95% CI Lower Bound	95% CI Upper Bound	P-value
QS2i (ms)	800 mg	10.39	1.49	19.29	0.0233
	1200 mg	12.97	5.12	20.82	0.0018
	1600 mg	20.36	13.65	27.07	0.0000
LVETi (ms)	800 mg	-4.57	-15.27	6.14	0.3929
	1200 mg	2.96	-6.52	12.44	0.5314
	1600 mg	12.90	4.53	21.28	0.0035
PEPi (ms)	800 mg	13.92	1.91	25.93	0.0243
	1200 mg	9.11	-1.53	19.75	0.0910
	1600 mg	7.10	-2.30	16.49	0.1343
RR (ms)	800 mg	79.83	-42.31	201.97	0.1940
	1200 mg	14.06	-93.66	121.77	0.7933
	1600 mg	35.46	-56.64	127.56	0.4411

For all cardiac impedance parameters, HR, stroke volume, and cardiac index, the changes of largest magnitude were observed in the 800 mg and 1600 mg groups (Table 211).

Table 211: Cardiac Impedance Parameters expressed as change from Day 5 to Day 13 (Mean differences between Dronedarone and Placebo)

Parameter (unit)	Comparison SR33589B Versus Placebo	Mean Difference Estimate	95% CI Lower Bound	95% CI Upper Bound	P-value
HR (bpm)	800 mg	-5.33	-9.65	-1.02	0.0168
	1200 mg	-3.22	-7.03	0.58	0.0946
	1600 mg	-5.19	-8.59	-1.80	0.0037
Stroke Volume (mL)	800 mg	-13.42	-30.67	3.83	0.1239
	1200 mg	-12.92	-28.13	2.30	0.0939
	1600 mg	-13.29	-26.30	-0.28	0.0455
Cardiac Index (L/min/m2)	800 mg	-0.68	-1.22	-0.15	0.0138
	1200 mg	-0.55	-1.02	-0.08	0.0240
	1600 mg	-0.71	-1.12	-0.31	0.0009

- For HR, the differences versus placebo were statistically significant in the 800 mg and 1600 mg groups
- For stroke volume, the difference versus placebo was statistically significant in only the 1600 mg group
- For cardiac index, the differences versus placebo for all dronedarone dose groups were statistically significant

PD Summary

The PD findings suggest that combining dronedarone with metoprolol may alter cardiac parameters; however, the effect appears more dependent on the dronedarone dose than on an interaction between metoprolol and dronedarone per se. Consistent changes were observed only with the 1600 mg dose; this may be a function of larger sample size for this dose group compared the other dose groups, allowing the effect to be statistically realized. It is noted that the 1600 mg daily dose is double the proposed clinical dose, therefore the effects observed may not be applicable to the proposed dronedarone clinical usage.

Applicant's Safety Summary

No serious adverse events (SAEs) or deaths were reported. There was a trend towards increased AE reporting as dronedarone dose increased. Other salient safety highlights include:

- more heart rate and rhythm disorders were reported in placebo subjects (~ 90 %) relative to dronedarone (16.7% of 800 mg subjects, 77.8% of 1200 mg subjects, and 75% of 1600 mg subjects).
- GI system disorders were reported in all treatment groups; the incidences of GI disorders increased with dronedarone dose (16.7% in the 800 mg group, 22.2% in the 1200 mg group, and 50% in the 1600 mg group). These GI incidences were higher than in both the metoprolol alone (4.1%) and placebo (7.7%) groups.

Four subjects discontinued from study due to AEs, 3 of which were heart rate and rhythm disorders and the remaining due to severe rash. All subjects recovered without corrective treatment except in the case of rash, which was treated with cetirizine. High increases in alanine

aminotransferase (ALT) and/or aspartate aminostranferase (AST) values at Day 13 or Day 20 were observed in some subjects; the investigator considered the increases at the 1600 mg dose clinically relevant. Exercise tolerance was good and the same workload could be reached with a lower heart rate during submaximal exercise. Holter monitoring showed a dose related heart rate-lowering effect and no evidence of proarrhythmia.

Recommendations/Conclusions
The findings from this study should be viewed within the context that the proposed clinical dosage is 400 mg BID vs. 1600 mg/day, the dose at which most clinical effects were observed. The following information from study PDY3828 is acceptable for labeling as appropriate:

Pharmacokinetics

- Relative to administration of metoprolol alone, metoprolol exposure was increased by 1.6 to 2.5- fold (AUC and Cmax) after concomitant administration of dronedarone for eight days; this finding suggests that dronedarone inhibits metoprolol metabolism. The PK interaction appeared dose-dependent, particularly with respect to the AUC measure.
- Dronedarone does not alter alpha-hydroxy-metoprolol exposure when dronedarone is co-administered with metoprolol

Pharmacodynamics
Relative to administration of placebo (metoprolol alone)

- Vcfmean was significantly reduced when co-administered with dronedarone 1600 mg daily; this finding indicates a reduction in myocardial contractility. Results on other contractility parameters using a different technique show a similar trend.
- QS2i increased with all dronedarone doses supporting the hypothesis of a decrease in contractility induced with dronedarone, particularly as dose increased.
- Cardiac index decreased after the addition of dronedarone (all dronedarone doses), with the 1600 mg dose yielding the greatest decrease

Labeling
The applicant's labeling proposal is acceptable: states results of study and mentions potential pharmacodynamic effects with beta blockers, such as metoprolol.

4.2.32 Influence of repeated oral doses of nifedipine and of repeated oral doses of diltiazem (inhibitors of cytochrome P450 3A4) on the pharmacokinetic profile of dronedarone in healthy male subjects, preliminary study (INT4074)

PROTOCOL #	INT4074
INVESTIGATOR	Dr Wolfgang Tetzloff
STUDY SITE	Phoenix International Iphar, Arnikastrasse 4, D- 85635 Höhenkirchen- Siegertsbrunn, Germany
STUDY PERIOD	January – May 2000

Rationale for Drug-Drug Interaction Study

Table 212: Background Information on Study Drugs (Diltiazem and Nifedipine and Dronedarone)

	Diltiazem and Nifedipine	Dronedarone
Indication/Mechanism of Action	Calcium channel blockers used as antihypertensive and for angina	Anti-arrhythmic: proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter.
Metabolites	Diltiazem: two major metabolites (desacetyl and demethyl) and other metabolites Nifedipine: numerous metabolites	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	Diltiazem: Extensively metabolized by liver Nifedipine: extensively metabolized; appears to be metabolized by CYP3A	Primarily CYP3A substrate
CYP Inhibitory Potential	Nifedipine: CYP3A (Ki = 10 -22 μM) and PGP inhibitor Diltiazem: CYP3A and PGP inhibitor, and metabolites have inhibitory activity	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Diltiazem: dosage varies depending on indication; range of doses is 120 to 540 mg QD (initial for hypertension 120 to 240 mg) and dosage is titrated Nifedipine: Usual maintenance dose is 30 to 60 mg QD (initial 30 mg) and is titrated to a maximum of 90 mg QD	400 mg BID

Objectives (per applicant)

Primary

To assess the effect of repeated oral doses of nifedipine and of repeated oral doses of diltiazem, separately, on the pharmacokinetic profile of SR33589 and its N-debutyl metabolite SR35021 after a single oral ascending dose of dronedarone given in fed conditions.

Secondary

- to assess a potential pharmacodynamic resulting effect of each co-administration on electrocardiogram (ECG) parameters, heart rate (HR) and blood pressure
- to assess the clinical and biological tolerability of dronedarone given alone, and co-administered with nifedipine or with diltiazem
- to document plasma concentrations of nifedipine during and after repeated doses
- to document plasma concentrations of diltiazem during and after repeated doses

Study Design
This was a non-randomized, open-label, non-placebo-controlled, sequential design, and 2-period study. The treatments over the two periods follow.

- Period 1: a single dose of dronedarone alone (400, 800, 1200 and 1600 mg)
- Period 2: From Day 1 to day 4, 20 mg BID repeated oral doses of nifedipine. On Day 5 a single oral dose of dronedarone co-administered with a single oral dose of 20 mg nifedipine in the morning and a single oral dose of nifedipine alone.

Alternatively in Period 2, diltiazem 240 mg BID was administered according to the same schedule as nifedipine, except on Day 5 only a morning dose was given (no evening dose).

There was a 4-day washout period between Period 1 and Period 2.

Reviewer Note on Study Design (Evaluated Dronedarone Doses)
For dronedarone administered with nifedipine, only the 400 and 1600 mg dronedarone dose groups were studied because, no effect was seen at the 400 mg dose level. For dronedarone administered with diltiazem, the 1600 mg dose was substituted with the 1200 mg dose to avoid potential safety issues associated with high dronedarone exposure. The selected dronedarone doses appear reasonable.

It should be noted that neither diltiazem nor nifedipine were studied at their highest approved doses, 540 mg QD and 90 mg QD, respectively; the Drug Interaction Guidance recommends using the highest approved dose, unless there are safety concerns. This study should have been conducted at higher diltiazem and nifedipine doses to determine maximal interaction, particularly with respect to pharmacodynamic interaction potential.

Subject Demographics
Subject demographics are summarized in Table 213.

Table 213: Subject demographics (Study 4074)

Parameter	Statistics	Dronedarone				Total
		400 mg	800 mg	1200 mg	1600 mg	
Age (years)	N	12	6	6	6	30
	Mean	26.8	36.7	31.3	33.3	31.0
	SD	3.3	3.7	8.1	5.0	6.1
	Min	20	31	23	25	20
	Max	33	40	39	39	40
Height (cm)	N	12	6	6	6	30
	Mean	179.3	181.2	181.5	177.2	179.7
	SD	4.2	6.3	5.5	4.4	5.0
	Min	174	171	174	171	171
	Max	187	189	187	182	189
Weight (kg)	N	12	6	6	6	30
	Mean	78.7	73.2	82.0	77.5	78.0
	SD	7.2	5.5	7.6	7.9	7.3
	Min	67.7	65.5	73.9	65.0	65.0
	Max	91.8	81.0	94.2	88.6	94.2
BMI (kg/m^2)	N	12	6	6	6	30
	Mean	24.5	22.3	24.9	24.8	24.2
	SD	2.01	1.15	2.43	3.32	2.37
	Min	20.2	21.1	21.4	19.8	19.8
	Max	28.7	24.3	27.5	29.3	29.3

Formulation

- Dronedarone: 200 mg tablet, batch number 98-01645
- Nifedipine: 20 mg slow release tablet (Adalat®, Bayer, Germany); batch number Ch-B:CAUUN1
- Diltiazem: 240 mg slow release capsules (Dilzem®, Goedexke, Germany; batch number Ch-B:0323079

Pharmacokinetic sampling times

The following pharmacokinetic blood samples were drawn at the given times:

- Day 1 (period 1)- samples were collected at predose (5 minutes before dosing) and 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72 and 96 hours post dose
- For nifedipine (period 2)- samples were collected predose on Day 1, predose on Day 1 before second dose, on Day 2 before first dose, on Day 3 before second dose, on Day 3 before second dose, on Day 4 before dosing and Day 4 before second dose
- For diltiazem (period 2)- samples were collected predose on Day 1, on Day 2 before first dose, on Day 3 before second dose, and on Day 4 before dosing

Pharmacokinetics

The following PK measures were determined:

- SR33589 and SR35021: Cmax, tmax, AUClast, AUC, $t_{1/2z}$ on Day 1 (Period 1) and on Day 5 (Period 2);
- Nifedipine: trough levels from Day 1 to Day 4, and Cmax, Cmin, tmax, $AUC_{0\text{-}12h}$ on Day 5 (Period 2);
- Diltiazem: trough levels from Day 1 to Day 4, and Cmax, Cmin, tmax, $AUC_{0\text{-}24h}$ on Day 5 (Period 2).

Activity/Pharmacodynamics

The following PD measures were determined:

- Vital signs (Heart rate or HR and blood pressure or BP)
- ECG parameters (PR-, QRS-, QT- and QTc intervals) were determined

Reviewer Note on PD Assessment

Ideally a placebo group should have been included to offer a more objective assessment of PD effects and safety.

Statistical Methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. The reference treatment was dronedarone alone and the test treatments were dronedarone + diltiazem or nifedipine. Pharmacodynamics were assessed by standard methods.

Bioanalytical methods

<u>Dronedarone and SR35021 Assays</u>

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as shown in Table 214.

Table 214: Performance of Dronedarone and SR35021 Assay

Parameter	Measure	Reviewer Comment
	Dronedarone	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.989$	Satisfactory
Between day Precision	CV was < 13 %	Satisfactory
Accuracy	QC samples were between -2.7 and 4.0 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Satisfactory
Parameter	Measure	Cannot be assessed
	SR35021	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.994$	Satisfactory
Between day Precision	CV was < 10 %	Satisfactory
Accuracy	QC samples were between -4.6 and 1.6 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms were provided in assay validation report that indicate assay specificity

Nifedipine Assay

Nifedipine concentrations in plasma were determined by gas chromatography with electronic capture detection. The assay performance was acceptable as shown in Table 215.

Table 215: Performance of Nifedipine Assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 1.0 to 500 ng/mL range; $R^2 > 0.999$	Satisfactory
Between day Precision	CV was < 11 %	Satisfactory
Accuracy	QC samples were between 10 and 15 % of nominal concentration	Satisfactory
LLOQ	1 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Diltiazem and diltiazem metabolites

The concentration of diltiazem and its metabolites in plasma samples were determined by HPLC. The assay performance was acceptable as shown in Table 216.

Table 216: Performance of Diltiazem Assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 5 to 500 ng/mL range; $R^2 > 0.999$	Satisfactory
Between day Precision	CV was < 4 %	Satisfactory
Accuracy	QC samples were between -6 and 2 % of nominal concentration	Satisfactory
LLOQ	5 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Results

Dronedarone and SR35021 Pharmacokinetics (+/- diltiazem)

The dronedarone and SR35021 plasma concentration-time profiles are depicted in Figure 129.

The mean (CV%) pharmacokinetic parameters of dronedarone and SR35021 after dronedarone administration with or without diltiazem are summarized in Table 217 and Table 218.

Figure 129: Dronedarone and SR35021 plasma concentration-time profiles following administration of dronedarone +/- diltiazem

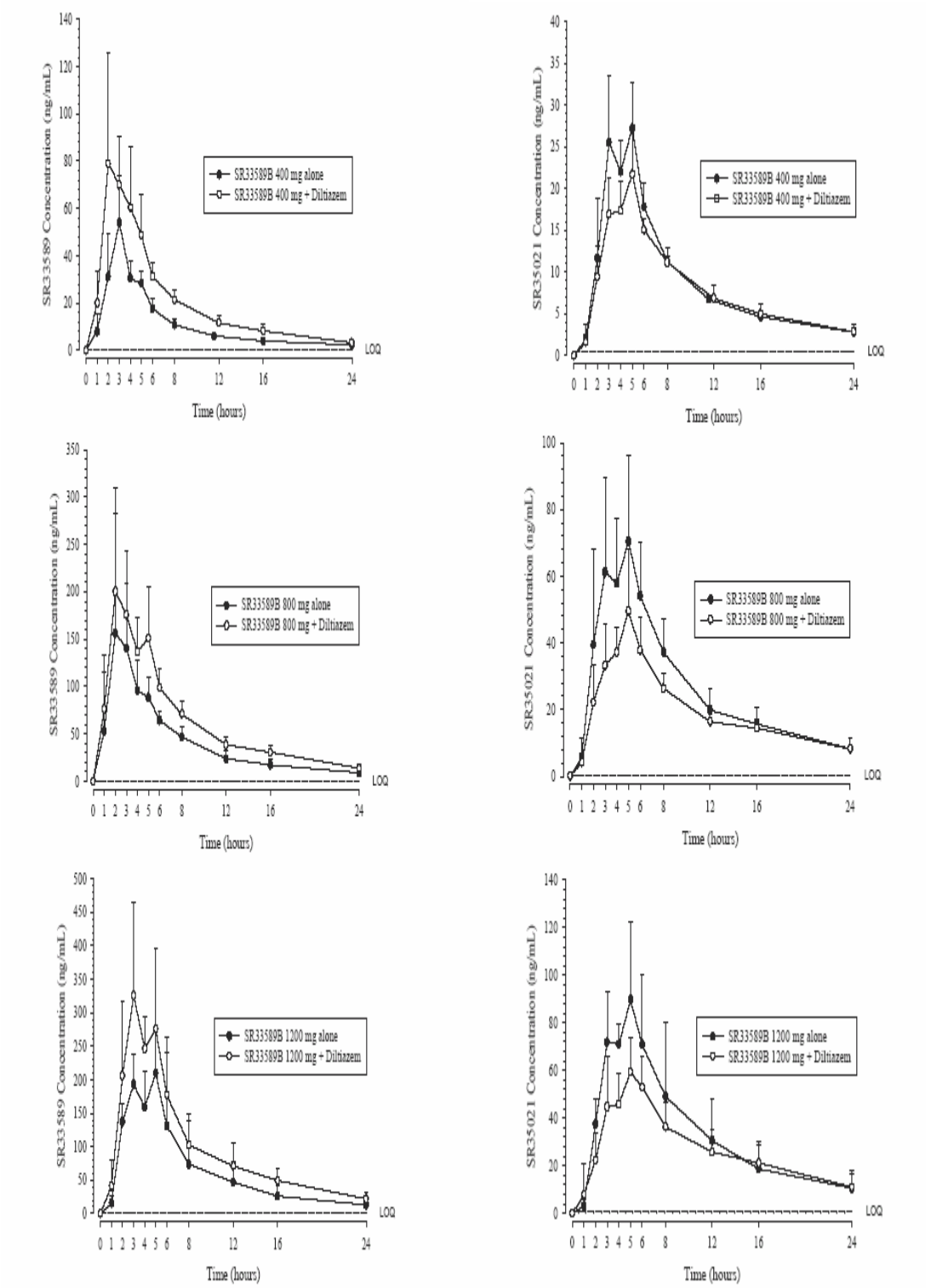


Table 217: Dronedarone PK Measures following administration of dronedarone +/- diltiazem

Mean (SD)	Dronedarone 400 mg (n=6)		Dronedarone 800 mg (n=6)		Dronedarone 1200 mg (n=6)	
Parameters	*alone*	*+diltiazem*	*alone*	*+diltiazem*	*alone*	*+diltiazem*
C_{max} (ng/mL)	56.6 (18.6)	93.9 (35.7)	187.1 (111.4)	225.6 (90.0)	258.0 (161.8)	387.5 (122.1)
t_{max} (h)[a]	3.0	2.0	3.0	2.5	3.0	3.0
t_{last} (h)	50.0 (11.8)	64.0 (19.6)	80.1 (19.7)	92.0 (9.8)	92.0 (9.8)	96.0 (0.0)
AUC_{last} (ng.h/mL)	304 (80)	559 (132)	1183 (464)	1790 (489)	1814 (1042)	2808 (786)
$t_{1/2z}$ (h)	15.2 (4.8)	14.4 (2.6)[b]	19.6 (4.1)	21.3 (5.1)	22.5 (2.5)	27.5 (3.7)
AUC (ng.h/mL)	320 (86)	581 (145)[b]	1213 (462)	1823 (497)	1852 (1072)	2885 (825)

Table 218: Dronedarone and SR35021 PK Measures following administration of dronedarone +/- diltiazem

Mean (SD)	Dronedarone 400 mg (n=6)		Dronedarone 800 mg (n=6)		Dronedarone 1200 mg (n=6)	
Parameters	*alone*	*+diltiazem*	*alone*	*+diltiazem*	*alone*	*+diltiazem*
C_{max} (ng/mL)	31.2 (4.8)	22.1 (4.4)	74.3 (26.0)	49.7 (18.6)	94.4 (32.0)	59.9 (13.4)
t_{max} (h)[a]	3.0	5.0	5.0	5.0	4.0	5.0
t_{last} (h)	72.0 (0.0)	64.0 (12.4)	96.1 (0.2)	92.0 (9.8)	88.0 (12.4)	96.0 (0.0)
AUC_{last} (ng.h/mL)	292 (14)	263 (32)	877 (224)	701 (157)	1070 (560)	950 (314)
$t_{1/2z}$ (h)	21.9 (4.9)	23.4 (6.8)	21.1 (2.4)	23.8 (2.9)	19.2 (4.4)	21.3 (4.6)
AUC (ng.h/mL)	314 (19)	298 (55)	904 (226)	739 (165)	1100 (584)	988 (340)

Consistent with previous studies, dronedarone exposure increased in a greater than dose proportional manner from the 400 to 1200 mg dose levels.

The applicant's statistical analyses revealed that there was no significant dose-by-treatment effect for any of the PK measures, therefore, drug-drug interaction analyses were pooled across dronedarone dose groups. Table 219 summarizes the drug-drug interaction results.

Table 219: Dronedarone Drug interaction results following administration of dronedarone +/- diltiazem

PK Measure	Dronedarone + diltiazem /dronedarone alone
Cmax	1.51 (1.31 -1.75)
AUClast	1.69 (1.55 – 1.85)

The interaction results indicate that diltiazem increased dronedarone AUC and Cmax by ~ 60 %, suggesting that diltiazem inhibited dronedarone metabolism. This finding is expected because dronedarone is a CYP3A substrate and diltiazem is a moderate CYP3A inhibitor.

SR35021 exposure was decreased in the presence of diltiazem, relative to when dronedarone was administered alone, which is consistent with CYP3A metabolic inhibition.

<u>Dronedarone and SR35021 Pharmacokinetics (+/- nifedipine)</u>
The dronedarone and SR35021 plasma concentration-time curves are depicted in Figure 130.

The mean (CV%) pharmacokinetic parameters of dronedarone and SR35021 after dronedarone administration with or without nifedipine are summarized in Table 220 and Table 221.

Figure 130: Dronedarone and SR35021 plasma concentration-time profiles following administration of dronedarone +/- nifedipine

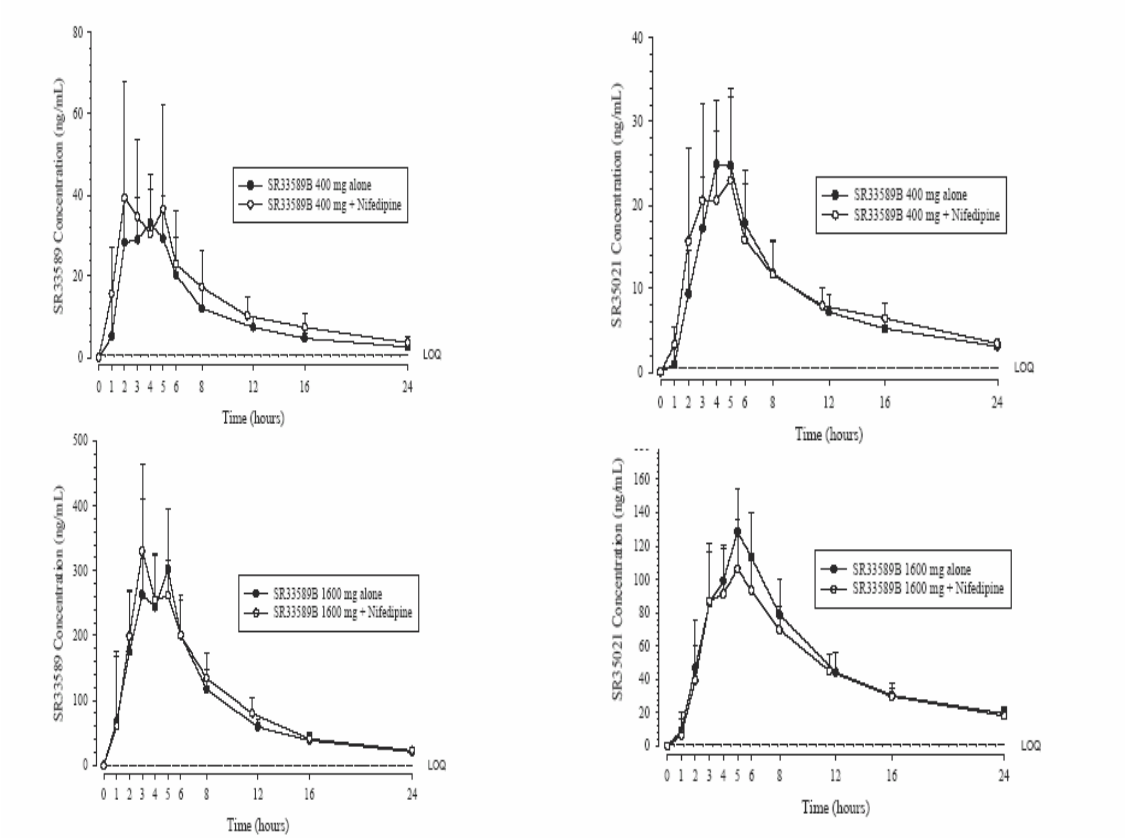


Table 220: Dronedarone PK Measures following administration of dronedarone +/- nifedipine

Mean (SD)	Dronedarone 400 mg (n=6)		Dronedarone 1600 mg (n=6)	
Parameters	*alone*	*+ nifedipine*	*alone*	*+ nifedipine*
C_{max} (ng/mL)	38.4 (9.7)	55.1 (20.9)	348.9 (125.2)	338.0 (124.2)
t_{max} (h)[a]	2.5	2.0	5.0	3.0
t_{last} (h)	50.0 (11.8)	64.0 (12.4)	96.0 (0.0)	96.0 (0.0)
AUC_{last} (ng.h/mL)	297 (85)	412 (186)	2664 (722)	2943 (856)
$t_{1/2z}$ (h)	14.5 (3.6)	19.4 (6.8)	20.1 (4.6)	22.9 (3.4)
AUC (ng.h/mL)	312 (88)	432 (189)	2700 (741)	2995 (883)

Table 221: SR35021 PK Measures following administration of dronedarone +/- nifedipine

Mean (SD)	Dronedarone 400 mg (n=6)		Dronedarone 1600 mg (n=6)	
Parameters	*alone*	*+ nifedipine*	*alone*	*+ nifedipine*
C_{max} (ng/mL)	26.6 (6.5)	26.9 (10.7)	128.6 (25.6)	106.5 (28.7)
t_{max} (h)[a]	4.5	3.0	5.0	5.0
t_{last} (h)	76.0 (9.8)	76.0 (9.8)	96.0 (0.0)	96.0 (0.0)
AUC_{last} (ng.h/mL)	288 (76)	317 (87)	1713 (379)	1606 (343)
$t_{1/2z}$ (h)	24.3 (5.7)	26.1 (10.5)	17.6 (1.8)	20.2 (3.1)
AUC (ng.h/mL)	310 (72)	345 (83)	1746 (382)	1655 (353)

The applicant's statistical analyses revealed that there was no significant dose-by-treatment effect for any of the dronedarone PK measures (nifedipine interaction), therefore, drug-drug interaction analyses were pooled across dronedarone dose groups. Table 222 summarizes the drug-drug interaction results.

Table 222: Dronedarone Drug interaction results following administration of dronedarone +/- nifedipine

PK Measure	Dronedarone + nifedipine/ dronedarone alone
Cmax	1.15 (0.96 – 1.37)
AUClast	1.20 (1.07 – 1.34)

Relative to dronedarone alone, nifedipine did not change dronedarone Cmax, but AUClast was increased ~ 20 %; this finding suggests nifedipine marginally inhibits dronedarone metabolism.

There was a statistically significant dose-by-treatment effect for SR35021 AUClast and AUC during nifedipine co-administration with dronedarone; therefore, the dose groups were analyzed separately. No statistically significant treatment effect was observed for SR35021 Cmax.

Table 223: Dronedarone Drug interaction results following administration of dronedarone +/- nifedipine

Measure	Geometric Mean ratio and 90 % CI for Dronedarone + nifedipine/dronedarone alone	
	Dronedarone 400 mg	Dronedarone 1600 mg
Cmax	0.67 [0.63 – 0.72]	0.89 [0.77 – 1.02]
AUClast	1.10 [0.99-1.22]	0.94 [0.86-1.02]

Diltiazem Pharmacokinetics

The diltiazem, desacetyl diltiazem and N-demethyl desacetyl diltiazem plasma concentration-time profiles following administration of diltiazem with varying dronedarone doses are depicted in the following three figures.

Reviewer Note: Exclusion of Subject 30

The applicant notes that Subject Number 30 in the dronedarone 1200 mg dose group, was considered an outlier: 5-fold higher in N-demethyl desacetyl diltiazem plasma concentrations and 2.6-fold higher in desacetyl diltiazem plasma concentrations, as compared to other subjects. The diltiazem plots do not include Subject 30; including Subject 30 had a major impact on the mean results. Overall, exclusion of this subject's results appears reasonable, however the applicant should have determined why Subject 30 had different results from the other subjects.

Figure 131: Diltiazem plasma concentration time profile following administration of diltiazem and dronedarone

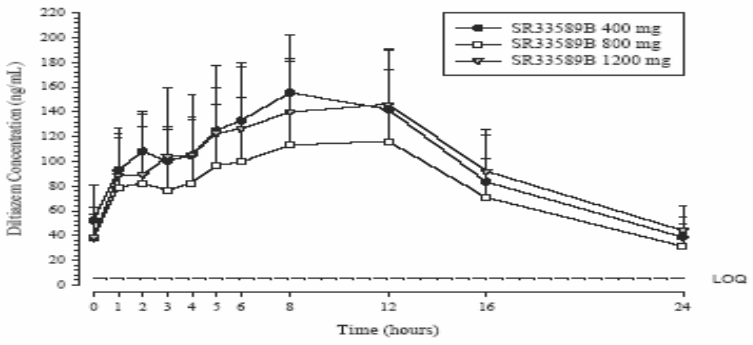


Figure 132: Desacetyl Diltiazem plasma concentration time profile following administration of diltiazem and dronedarone

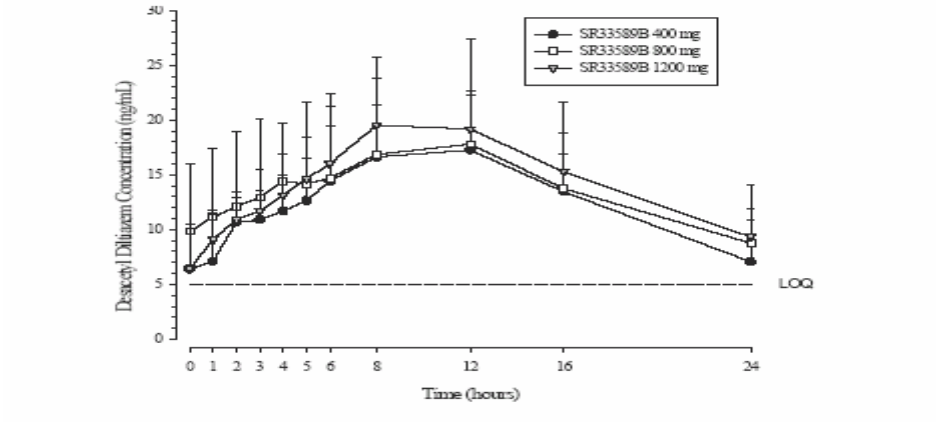
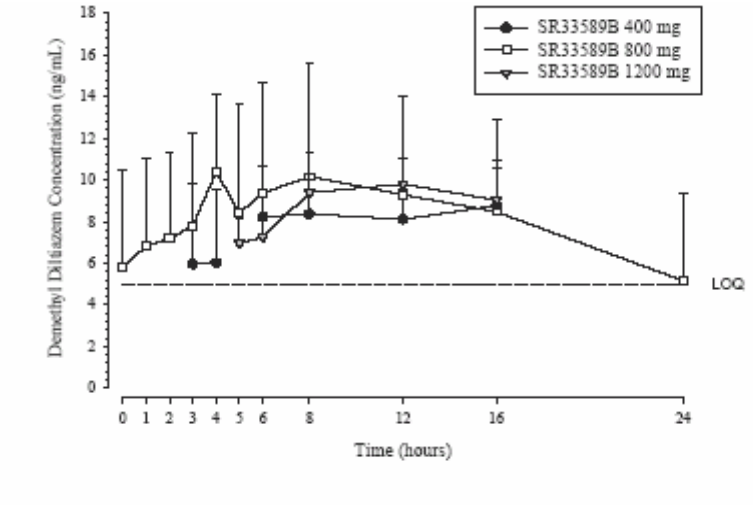


Figure 133: Demethyl desacetyl plasma concentration time profile following administration of diltiazem and dronedarone



The mean (CV%) pharmacokinetic parameters of diltiazem and its two major metabolites following administration of dronedarone and diltiazem are summarized in Table 224 and Table 225.

Table 224: Diltiazem PK Measures following administration of dronedarone +/- diltiazem

Mean (SD)	Dronedarone treatment		
Parameters	*400 mg (n=6)*	*800 mg (n=6)*	*1200 mg (n=6)*
C_{min} (ng/mL)	36.6 (10.2)	30.8 (23.9)	37.7 (19.8)
C_{max} (ng/mL)	163.8 (38.7)	121.2 (70.1)	150.6 (43.1)
t_{max} (h) [a]	8.0	10.0	10.0
AUC_{0-24h} (ng.h/mL)	2445 (533)	1936 (1222)	2449 (874)

a: median values

PK of diltiazem and its metabolites did not appear dependent on dronedarone dose, especially, when Subject 30 was omitted from the PK analysis.

Table 225: PK Measures of diltiazem metabolites following administration of dronedarone +/- diltiazem

Mean (SD) Parameters	Dronedarone treatment			
	400 mg (n=6)	*800 mg (n=6)*	*1200 mg (n=6)*	*1200 mg (n=5) Without No.30*
Desacetyl diltiazem				
C_{min} (ng/mL)	6.0 (3.3)	7.5 (6.2)	11.6 (13.2)	6.4 (4.0)
C_{max} (ng/mL)	18.4 (5.6)	18.8 (7.5)	26.4 (15.9)	20.1 (3.8)
t_{max} (h)[a]	10.0	12.0	10.0	8.0
AUC_{0-24h} (ng.h/mL)	298 (98)	330 (180)	493 (356)	351 (79)
N-Demethyl desacetyl diltiazem				
C_{min} (ng/mL)	BLQ (NC)	BLQ (NC)	17.7 (40.4)	BLQ (NC)
C_{max} (ng/mL)	9.9 (2.0)	11.8 (3.8)	35.3 (61.4)	10.2 (1.5)
t_{max} (h)[a]	12.0	8.0	14.0	12.0
AUC_{0-24h} (ng.h/mL)	141 (48)	192 (110)	692 (1307)	159 (66)

a: median values
BLQ: Below the LOQ, NC: Not calculable

Nifedipine Pharmacokinetics

The nifedipine plasma concentration-time profiles following administration of nifedipine with dronedarone are depicted in Figure 134.

Figure 134: Nifedipine plasma concentration time profiles following administration of nifedipine and dronedarone

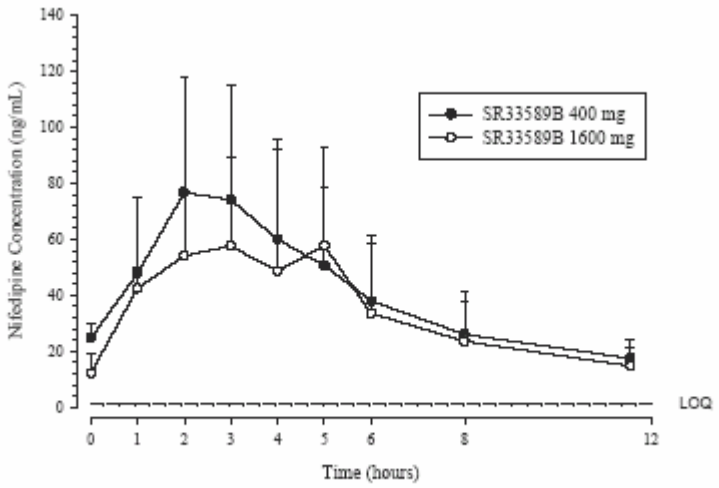


Table 226: Performance of Nifedipine Assay

Mean (SD) Parameters	Dronedarone treatment	
	400 mg (n=6)	*1600 mg (n=6)*
C_{min} (ng/mL)	6.7 (5.6)	6.7 (2.4)
C_{max} (ng/mL)	47.6 (18.3)	47.8 (13.1)
t_{max} (h)[a]	2.5	3.5
AUC_{0-12h} (ng.h/mL)	274 (128)	256 (71)

a: median values

PK of nifedipine did not appear dependent on dronedarone dose.

Pharmacodynamics

ECG Data

The ECG data obtained during dronedarone alone and dronedarone with diltiazem or nifedipine are presented in Table 227.

Table 227: ECG data of the Day 5 (co-administration) vs. Day 1 (dronedarone alone) mean difference in averaged changes from baseline over 12 hours (only statistically significant contrasts reported)

Parameter	Significant contrasts ($p < 0.05$)	Estimate [95% CI]
PR (ms)	SR+diltiazem vs SR alone	
	- overall doses (N = 18)	14.37 [12.15 ; 16.59]
	- 400 mg (N = 6)	19.22 [15.37 ; 23.07]
	- 800 mg (N = 6)	12.44 [8.60 ; 16.29]
	- 1200 mg (N = 6)	11.44 [7.60 ; 15.29]
	- at T2	17.56 [12.11 ; 23.00]
	- at T4	12.44 [7.00 ; 17.89]
	- at T6	14.00 [8.56 ; 19.44]
	- at T8	16.22 [10.78 ; 21.66]
	- at T12	21.33 [15.89 ; 26.78]
QRS (ms)	SR+nifedipine vs SR alone	
	- 1600 mg (N = 6)	1.78 [0.29 ; 3.27]
QT (ms)	SR+nifedipine vs SR alone	
	- overall doses (N = 12)	-4.39 [-8.30 ; -0.47]
	SR+diltiazem vs SR alone	
	- overall doses (N = 18)	5.79 [2.71 ; 8.87]
	In the diltiazem group only :	
	- 800 mg vs 400 mg	19.89 [0.84 ; 38.94]
	- 1200 mg vs 400 mg	26.38 [7.32 ; 45.43]
QT_c (ms)	SR+diltiazem vs SR alone	
	- overall doses (N = 18)	3.80 [1.85 ; 5.74]

Diltiazem

For Diltiazem co-administration, PR- interval, QT- interval and QTc values were significantly changed by the addition of diltiazem to dronedarone.

- PR- interval: the co-administration effect was detected to be statistically significant
  - overall doses (p= 0.0001)
  - between doses (p- value for dose by administration interaction= 0.0101)
  - between time points (p-value for administration by time interaction= 0.0012).

It is noted that there was significantly lower PR prolongation in the 1200 mg dronedarone dose group than in the 400 mg dronedarone dose group.

- QT- intervals were also significantly prolonged after addition of diltiazem to dronedarone
  - overall doses
  - significantly prolonged in the 800 mg and 1200 mg dronedarone dose groups compared to the 400 mg dose group, suggesting a dose-response may exist; however data were highly variable (wide confidence interval)
- QTc interval was significantly prolonged after addition of diltiazem to dronedarone; however : the prolongation was ~ 4 ms over all doses. The QTc prolongation due to diltiazem was not significantly different between dronedarone dose groups or between time points.

Nifedipine
For nifedipine, only QRS- and QT- intervals values were significantly changed by the addition of nifedipine to dronedarone.

- QRS- interval was prolonged only in the highest dronedarone dose group (1600 mg)
- QT- interval, showed a statistically significant overall effect of the co-administration (p-value = 0.0283); there was a decrease in QT interval

Vital Signs
The changes in vital signs (Dronedarone + co-administered drug vs. Dronedarone alone) are summarized in Table 228.

Table 228: Vital Sign data of the Day 5 (co-administration) vs. Day 1 (dronedarone alone) mean difference in averaged changes from baseline over 12 hours (only statistically significant contrasts reported)

Parameter	Significant contrasts ($p < 0.05$)	Estimate [95% CI]
HR (bpm)	In the diltiazem group only	
	- 800 mg vs 400 mg	-7.57 [-13.18 ; -1.96]
	- 1200 mg vs 400 mg	-8.04 [-13.65 ; -2.43]
SBP (mmHg)	SR+nifedipine vs SR alone	
	- overall doses (N = 12)	-3.25 [-5.42 ; -1.07]
	SR+diltiazem vs SR alone	
	- overall doses (N = 18)	-1.92 [-3.67 ; -0.16]
	- at T12 (N = 18)	-8.22 [-12.51 ; -3.94]
	In the diltiazem group only	
	- 800 mg vs 400 mg	-9.71 [-18.06 ; -1.35]
	- 1200 mg vs 400 mg	-12.39 [-20.74 ; -4.04]

Diltiazem
For diltiazem group, addition of diltiazem to dronedarone, caused ~ 2 mmHg decrease in SBP, relative to administration of dronedarone alone. There appeared to be a dronedarone dose-effect for both heart rate and SBP; this effect was independent of diltiazem presence.

- HR: Relative to the 400 mg dose, the 800 mg (p-value = 0.0130) and 1200 mg (p-value = 0.0159) dronedarone doses decreased heart rate (bradycardic effect)
- SBP: relative to the 400 mg, the 800 mg and 1200 mg dronedarone doses caused systolic hypertension
- DBP: No change was observed in DBP values.

Nifedipine

- SBP: For nifedipine, co-administration of nifedipine and dronedarone only affected SBP values relative to dronedarone alone; when nifedipine was added to dronedarone, mean SBP decreased by ~ 3 mmHg (p- value= 0.0037).
- DBP and HR: No change was observed in DBP or HR values.

PD Summary
In sum, the PD measures were generally changed (statistically significant) when either diltiazem or nifedipine was added to dronedarone compared to when dronedarone was administered alone. However, these changes tended to be small and do not appear clinically relevant. Overall dose effects with respect to the dronedarone group are summarized as follows:

1. PR for diltiazem + dronedarone vs. dronedarone increased by ~14 ms
2. QT interval for diltiazem + dronedarone vs. dronedarone increased by ~2 ms

3. QT interval for nifedipine + dronedarone vs. dronedarone decreased by ~4 ms
4. QTc for diltiazem + dronedarone vs. dronedarone increased by ~ 4 ms
5. QRS for nifedipine + dronedarone vs. dronedarone increased by 2 ms
6. SBP for diltiazem + dronedarone vs. dronedarone decreased by 2 mmHg and nifedipine + dronedarone vs. dronedarone decreased by 3 mmHg

Applicant's Safety Summary
There were no serious AEs (SAEs) or deaths reported, and no discontinuations occurred due to treatment emergent AEs. First- degree atrio-ventricular blocks were reported in three subjects, during co-administration of 400 and 1200 mg dronedarone with diltiazem, and 1600 mg with nifedipine; these three AEs were judged to be likely related to dronedarone treatment. Subjects recovered without corrective treatment. Diarrhea was reported by three subjects in the 1600 mg group co- administered with nifedipine and by one subject in each of the 800, 1200, and 1600 mg groups on dronedarone alone; relationships to treatment were judged to be unknown. Potentially clinically significant abnormalities (PCSAs) were observed in hematology, biochemistry, vital signs and ECGs; PCSAs were sporadic and no particular trends in treatment groups emerged.

Recommendations/Conclusions
The following findings from study INT4084 are acceptable for labeling as appropriate.

Pharmacokinetics
Relative to administration of dronedarone alone, concomitant administration of
1) diltiazem increased dronedarone AUC and Cmax by 1.51- and 1.69-fold respectively
2) nifedipine increased dronedarone AUC and Cmax by 1.15- and 1.20- fold, respectively.

Overall, plasma concentrations of SR35021 were decreased during co-administration with diltiazem whereas, SR35021 remained the same when co-administered with nifedipine. The differential metabolite formation in the presence of diltiazem compared to nifedipine may be due to the difference in inhibitory potential of the two compounds; although diltiazem is a less potent and inhibitor than nifedipine, diltiazem metabolites contribute significantly to metabolic inhibition that may make diltiazem effectively a more potent inhibitor than nifedipine

Pharmacodynamics
Relative to administration of dronedarone alone, co-administration of dronedarone with diltiazem increases mean PR-prolongation by 14.37 ms, increases mean QT- prolongation by 5.79 ms, and increased mean QTc-prolongation by 3.80 ms, based on all dronedarone doses. Statistically relevant decreased in SBP were observed: for diltiazem, SBP was decreased by approximately 2 mmHg and for nifedipine SBP was decreased by ~ 3 mmHg. However the listed changes in PD measures do not appear clinically relevant, as they are of relatively small magnitude.

Labeling
The labeling should reflect the study findings. A dronedarone dosage adjustment does not appear warranted based on the study findings; however, precautionary language may be included indicating that there is a potential decrease in SBP when dronedarone and nifedipine or diltiazem and other calcium channel blockers are co-administered.

4.2.33 Effect of repeated oral doses of 800 mg b.i.d. dronedarone on the pharmacokinetic profile of oral contraceptive in healthy female subjects - randomized, double- blind, placebo controlled study (INT4695)

PROTOCOL #	INT4695
INVESTIGATOR	Wolfgang Tetzloff, MD
STUDY SITE	Phoenix International Iphar, Arnikastrasse 4, 3- 85635, Höhenkirchen- Siegersbrunn, Germany
STUDY PERIOD	May 2001 – January 2002

Background Information on Study Drugs [Stediril (Ethinylestradiol/ levonorgestrel) and Dronedarone]

	Ethinylestradiol/ levonorgestrel	Dronedarone
Indication/Mechanism of Action	Oral contraceptive	Anti-arrhythmic: proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter.
Metabolites	Multiple metabolites are formed from each of the Stediril components	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	CYP3A primarily	Primarily CYP3A substrate
CYP Inhibitory Potential	None reported for either component	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Dependent on product there are different combinations of the components	400 mg BID

Objectives (per applicant)

Primary

To assess the plasma concentrations of ethinylestradiol and levonorgestrel on the fifteenth day of the oral contraceptive treatment co-administered with placebo, and of the oral contraceptive treatment co-administered with dronedarone.

Secondary

- To assess the clinical and biological safety of dronedarone in healthy female subjects under oral contraceptive.
- To assess the pharmacokinetic (PK) parameters of SR33589 (dronedarone) and SR35021 on the last day of dronedarone administration.
- To measure the ratio 6ß-hydroxycortisol/cortisol as a marker of CYP3A4 enzyme induction.

Study Design

This was a randomized, double-blind, placebo-controlled, repeated-dose and 2x2 cross-over study in healthy female volunteers. The following treatments were administered:

1. Dronedarone 1600 mg/day (800 mg BID) for 10 days (Day 6 to 15)
2. Placebo administration for 10 days (Day 6 to 15)
3. Stediril once daily in the morning after meal for 21 days (Day 1 to 21)

There were two periods separated by a 5- to 7-day washout.

Subject Demographics

Subject demographics are summarized in Table 229.

Table 229: Subject demographics (Study 4695)

Parameter	Statistics/ Category	Total
Age (yrs)	N	21
	Mean	26.1
	SD	6.0
	Minimum	18
	Maximum	37
Weight (kg)	N	21
	Mean	61.80
	SD	7.12
	Minimum	50.8
	Maximum	79.9
Height (cm)	N	21
	Mean	166.8
	SD	5.8
	Minimum	158
	Maximum	180
Body mass index (kg/m^2)	N	21
	Mean	22.24
	SD	2.47
	Minimum	18.0
	Maximum	27.0
Oral temperature (celsius)	N	21
	Mean	36.54
	SD	0.38
	Minimum	35.9
	Maximum	37.3
Gender	Female	21 (100%)
Race	Caucasian	21 (100%)

Formulation

- Dronedarone: 200 mg tablets; batch number 98-01649
- Dronedarone placebo: tablets; batch number 98-01541
- Stediril 30: tablet containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel; batch number G1671B

Pharmacokinetic and urine sampling times

The following pharmacokinetic blood samples were drawn at the given times:

- Ethinylestradiol and levonorgestrel- before dosing on Day 1, and before dosing and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after Stediril 30® administration on Day 15.
- Dronedarone and SR35021: before dosing on Day 6, before dosing and 0.5, 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours after the morning dronedarone administrations on Day 15, and 12 hours after the evening administration on Day 15.

Urine samples were collected over 24 hours, from Day 5 to Day 6 and from Day 15 to Day 16 to determine cortisol and 6ß-hydroxycortisol concentrations.

Pharmacokinetics

The following PK measures were determined:

- For ethinylestradiol and levonorgestrel - Cmax, tmax, Cmin and AUC_{0-24h}
- For dronedarone and SR35021- Cmax, tmax, Cmin and AUC_{0-12h}

Pharmacodynamics
The ratio of 6ß-hydroxycortisol to cortisol urine concentrations is the only pharmacodynamic measure (endogenous compounds).

Statistical Methods
Standard pharmaco-statistical methods were used to evaluate drug-drug interactions. The reference treatment was Stediril (Ethinylestradiol/ levonorgestrel) alone and the test treatment was Stediril + dronedarone.

Standard statistical methods were used for the pharmacodynamic assessment; these methods were similar to those for the drug-drug interaction evaluation: urinary 6ß-hydroxycortisol/ cortisol ratios at Day 15 (test) were compared to those at baseline (Day 5- reference). This evaluation was conducted to estimate the effect of dronedarone on CYP3A activity.

Bioanalytical methods
Ethinylestradiol
Plasma concentrations of ethinylestradiol were determined by a validated gas chromatography-mass spectrometry method. The assay performance was acceptable as shown in Table 230.

Table 230: Performance of ethinylestradiol Assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 10 to 500 pg/mL range; $R^2 > 0.945$	Satisfactory
Between day Precision	CV was < 9 %	Satisfactory
Accuracy	QC samples were between 0 and 6 % of nominal concentration	Satisfactory
LLOQ	10 pg/mL	Satisfactory
Specificity	Chromatograms were provided that demonstrate specificity	Satisfactory

Levonorgestrel
Plasma concentrations of levonorgestrel were determined by a validated gas chromatography-mass spectrometry method. The assay performance was acceptable as shown in Table 231.

Table 231: Performance of levonorgestrel Assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 0.1 to20.0 ng/mL range; $R^2 > 0.990$	Satisfactory
Between day Precision	CV was < 12 %	Satisfactory
Accuracy	QC samples were between -0.7 and 6.7 % of nominal concentration	Satisfactory
LLOQ	0.1 ng/ml	Satisfactory
Specificity	Chromatograms were provided that demonstrate specificity	Satisfactory

Dronedarone and SR35021 Assays
Plasma concentrations of dronedarone and SR35021 were determined using a validated liquid chromatography-mass spectrometry method (DOH0239). The assay performance was acceptable as shown in Table 232.

Table 232: Performance of dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range	Satisfactory
Between day Precision	CV values were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided, however individual QC samples were within 15 % of nominal concentration	Acceptable
LLOQ	0.5 ng/ mL	Satisfactory
Specificity	Chromatograms were not provided*	Satisfactory
Parameter	Measure	Reviewer Comment
	SR35021	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range	Satisfactory
Between day Precision	CV values were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided, however individual QC samples were within 15 % of nominal concentration	Acceptable
LLOQ	0.5 ng/ mL	Satisfactory
Specificity	Chromatograms were not provided*	Satisfactory

Cortisol and 6ß- hydroxycortisol (Bioanalytical methods in urine)
Urine concentrations of cortisol and 6ß- hydroxycortisol were determined by LC/MS/MS. The assay performance was acceptable as shown in Table 233.

Table 233: Performance of Cortisol 6ß- hydroxycortisol Assays

Parameter	Measure	Reviewer Comment
	cortisol	
Linearity	The assay was linear over the 1.0 to 150 ng/mL range; $R^2 > 0.995$	Satisfactory
Between day Precision	CV was < 12 %	Satisfactory
Accuracy	QC samples were between -9.5 and 17.8 % of nominal concentration	Satisfactory
LLOQ	1 ng/mL	Satisfactory
Specificity	Chromatograms were provided	Satisfactory
	6-beta hydrocortisol	
Linearity	The assay was linear over the 5 to 750 ng/mL range; $R^2 > 0.994$	Satisfactory
Between day Precision	CV was < 12 %	Satisfactory
Accuracy	QC samples were between -26 and 14 % of nominal concentration; bias values > 15 % were typically associated with the low QC samples (number of samples 3 out of 30 QC samples)	Acceptable
LLOQ	5 ng/mL	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Results

Dronedarone and SR35021 Pharmacokinetics
The dronedarone and SR35021 plasma concentration-time curves following administration of dronedarone and Stediril are depicted in Figure 135 and Figure 136.

The dronedarone and SR35021 PK measures are presented in Table 234.

Figure 135: Dronedarone plasma concentration-time profile following administration of dronedarone and Stediril

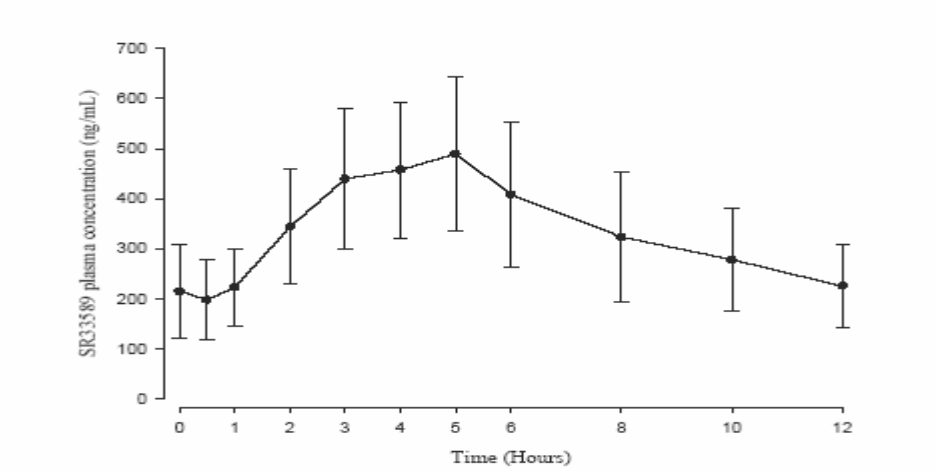


Figure 136: SR35021 plasma concentration time profile following administration of dronedarone and Stediril

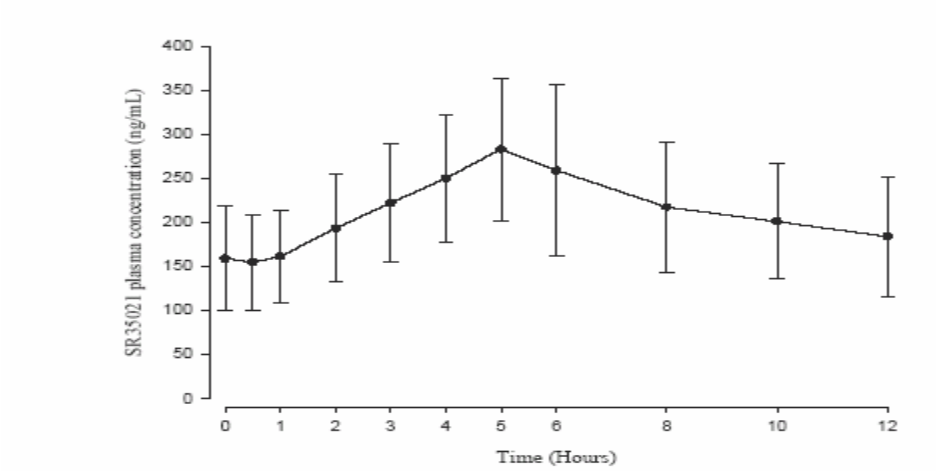


Table 234: Dronedarone PK measures following co-administration of dronedarone (800 mg BID) and Stediril

Day 15	C_{max} (ng/mL)	t_{max} (h)[a]	C_{min} (ng/mL)	AUC_{0-12h} (ng.h/mL)
Mean	515	4.5	186	4086
CV%	28	22	39	31

[a] median value

Table 235: SR35021 PK measures following co-administration of dronedarone (800 mg BID) and Stediril

Day 15	C_{max} (ng/mL)	t_{max} (h)[a]	C_{min} (ng/mL)	AUC_{0-12h} (ng.h/mL)
Mean	297	5.0	144	2588
CV%	31	26	37	30

[a]: median value

Based on a cross study comparison, Stediril does not appear to alter dronedarone PK.

Levonorgestrel and ethinylestradiol Pharmacokinetics

The ethinylestradiol and levonorgestrel plasma concentration time profiles obtained following administration of Stediril with or without dronedarone are depicted in Figure 137 and Figure 138.

Figure 137: Mean ethinylestradiol plasma concentration time profiles following administration of Stediril +/- dronedarone

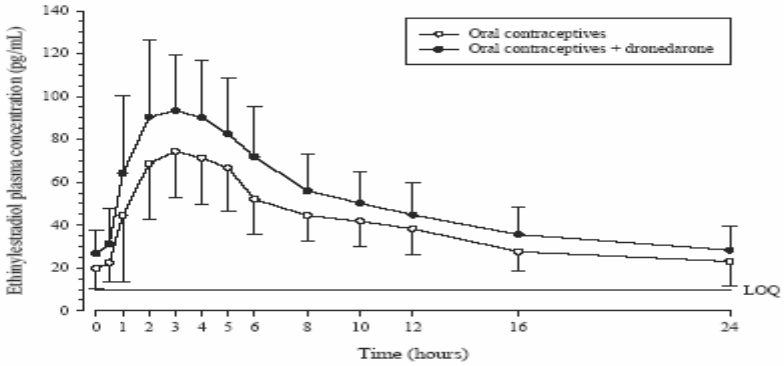
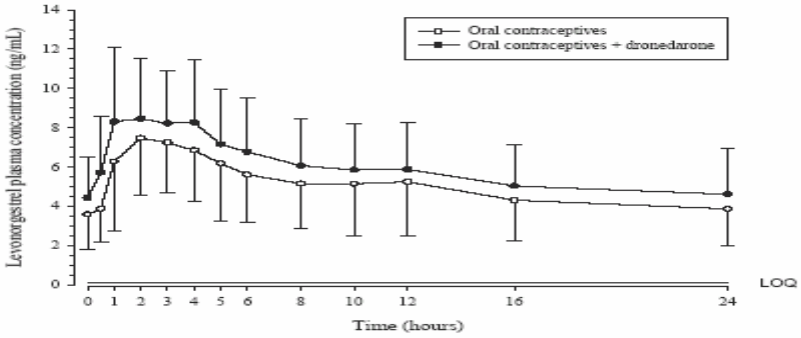


Figure 138: Mean levonorgestrel plasma concentration time profiles following administration of Stediril +/- dronedarone



The ethinylestradiol and levonorgestrel PK measures obtained following administration of Stediril with or without dronedarone are presented in Table 236.

The PK data indicate that dronedarone generally increased the exposure of the components of Stediril; the maximum mean increase was 28 %. Generally, confidence intervals were outside the no effect upper region (ranged from 1.05 to 1.38).

Reviewer comment on PK results

Typically, the concern with drug-drug interactions with respect to oral contraceptives involves a reduction in exposure of the hormones (Stediril components) that may lead to lack of effectiveness. In this case, there appears to be an increase in exposure of the Stediril components; however the mean increase is less than 30 % and unlikely to be clinically significant.

Table 236: Ethinylestradiol and levonorgestrel PK Measures following administration of Stediril +/- dronedarone (n = 18)

PK Parameter Mean (CV%)	Stediril 30® Alone	Stediril 30®+ Dronedarone	Ratio Estimates[b] and 90% CI
	ethinylestradiol		
C_{max} (pg/mL)	86.6 (28)	104.4 (26)	1.22 [1.14 – 1.30]
C_{min} (pg/mL)	18.3 (50)	24.5 (43)	1.22 [1.10 – 1.35]
t_{max} (h)[a]	3.0	2.1	-
AUC_{0-24h} (pg.h/mL)	947.9 (28)	1206.8 (30)	1.28 [1.18 – 1.38]
	levonorgestrel		
C_{max} (ng/mL)	8.8 (36)	9.8 (31)	1.13 [1.05 – 1.21]
C_{min} (ng/mL)	3.4 (50)	4.1 (49)	1.22 [1.12 – 1.32]
t_{max} (h)[a]	2.0	1.0	-
AUC_{0-24h} (ng.h/mL)	121.5 (45)	142.6 (39)	1.19 [1.11 – 1.27]

[a] : Median values, [b] : ratio Stediril 30®+dronedarone / Stediril 30®

Pharmacodynamics using 6-ß cortisol to cortisol ratio (Assessing Dronedarone CYP3A Induction Potential)

The urinary concentrations of 6-ß cortisol, cortisol and the 6-ß cortisol to cortisol ratio are summarized in Table 237.

Table 237: Pharmacodynamic Measurements (Comparisons of Cortisol ratios on Day 15 to Day 5)

Parameters	Day 15 / Day 5 Ratio Estimates and 90% CI	
	Dronedarone Treatment	Placebo Treatment
6β-hydroxycortisol	0.70 [0.53 ; 0.93]	0.74 [0.56 ; 0.98]
cortisol	0.47 [0.37 ; 0.60]	1.13 [0.89 ; 1.43]
6β-hydroxycortisol / cortisol ratio	1.48 [1.21 ; 1.80]	0.65 [0.54 ; 0.80]

Theoretically, the urinary 6ß-hydroxycortisol excretion is a measure of induction of CYP3A4 activity, as the metabolic pathway of cortisol to 6ß- hydroxycortisol is mediated by CYP3A4. Cortisol and 6ß-hydroxycortisol are endogenous compounds that can be readily measured. Generally, strong inducers such as rifampicin significantly increase (> 3-fold) the 6ß-hydroxycortisol daily excretion whereas urinary cortisol is not significantly modified. The referenced ratio was increased by ~ 1.5-fold in this study.

In the present study, the following observations were made:

1. production of 6ß-hydroxycortisol was similar during dronedarone treatment as compared to during placebo (Day 15/ Day 5 ratio of 0.70 and 0.74, respectively).
2. urinary cortisol concentration was decreased (Day 15/ Day 5 ratio of 0.47) during the dronedarone treatment, whereas it was not statistically significantly changed during the placebo treatment (Day 15/ Day 5 ratio of 1.13).
3. the 6ß- hydroxycortisol/cortisol ratio was increased by 1.48-fold during the dronedarone treatment

Although there was an increase in the ratio used to assess induction, the increase was not consistent with an induction mechanism: production of 6ß- hydroxycortisol was not increased during dronedarone treatment (remained constant), and cortisol concentration decreased, rather than remained constant. It should be noted that dronedarone did not exhibit induction properties in *in vitro* metabolism studies. The apparent induction findings were also not supported by the observations with the Stediril components. If dronedarone causes CYP3A induction, this

induction does not appear to have clinical relevance because, overall, dronedarone appeared to exhibit CYP3A inhibitory characteristics: increased the exposure of CYP3A substrates, ethinylestradiol and levonorgestrel.

Reviewer Note on Assessing Dronedarone CYP3A induction potential
A more definitive assessment of dronedarone's induction potential could be made by:
1) including a positive control (known enzyme inducer), such as rifampin
2) studying PK of a pure CYP3A substrate, such as midazolam.

Applicant's Safety Summary
No deaths or serious AEs (SAEs) were reported during this study. Adverse events were reported more frequently in the dronedarone+ Stediril 30 ® group (12/ 19 subjects) than the placebo+ Stediril 30 ® and Stediril 30 ® alone groups. Gastro-intestinal disorders were the most common treatment emergent AEs (TEAEs); these disorders included, diarrhea, abdominal pain and nausea. Other reported AEs were headache and atrioventricular (AV) block. The Investigator considered the AV block as related to study drug treatment. Frequency of Potentially clinically significant abnormalities (PCSAs) was somewhat higher in the dronedarone+ Stediril 30 ® group versus placebo, for decreases in systolic blood pressure (SBP) (9/20 versus 4/20 subjects) and diastolic blood pressure (DBP) (5/20 versus 2/20). In regards to QTc- interval PCSAs, in the dronedarone+ Stediril 30 ® group changes of between 30 and 60 ms were observed in 13/20 subjects, versus 3/20 in the placebo+ Stediril 30 ® group. No QTc over 500 ms was observed in any group. Few PCSAs in other ECG parameters were observed.

Recommendations/Conclusions
The following findings from Study INT4695 are acceptable for labeling as appropriate:

- Relative to administration of Stediril alone, dronedarone administration resulted in an approximately 25 % increase in ethinylestradiol exposure (Cmax, Cmin and AUC).
- Relative to administration of Stediril alone, dronedarone administration resulted in an approximately 18 % increase in levonorgestrel exposure (Cmax, Cmin and AUC).
- A slight apparent CYP3A induction effect was observed for dronedarone based on the 6ß-hydroxycortisol/cortisol ratio: (HC/Cr): HC/Cr increased with dronedarone administration by 1.48-fold relative to when dronedarone was absent. However the validity of this induction effect is not clear. Additionally, this effect does not appear clinically relevant: inhibition effect appears to override potential induction.

Labeling
The applicant's proposed labeling is acceptable. Based on the PK and pharmacodynamic results of this study, co-administration of dronedarone is unlikely to modify the efficacy of the oral contraceptives.

4.2.34 Study on the tolerability of SR33589B given twice daily as repeated ascending oral doses in healthy male subjects (Study TDR3549).

PROTOCOL #	TDR3549
INVESTIGATOR	Dr. W. Tetzloff
STUDY SITE	iphar, Institut für Klinische Pharmakologie GmbH, Arnikastrasse 4, D - 85635 Höhenkirchen- Siegertsbrunn, Germany
STUDY PERIOD	July 1998 to May 1999

Objectives (per applicant)

- Primary Objective

To assess the safety of repeated ascending oral doses of SR33589 (dronedarone) given twice daily for 10 days under fed conditions in healthy male subjects to determine the maximum tolerated dose (MTD).

- Secondary Objectives

To assess the effect of repeated ascending oral doses of dronedarone given twice daily on

1. electrocardiogram (ECG)
2. vital signs and exercise test parameters in order to determine the dose with the maximum pharmacodynamic effects in healthy subjects
3. to assess the PK profile of dronedarone and its N-debutyl metabolite SR35021
4. to identify the potential relationship between plasma levels and pharmacodynamics.

Reviewer Note

This review focuses on the PD information (secondary objectives) and PK information obtained at steady state that address dronedarone diurnal variation. Other PK studies provide comprehensive PK information.

Study Design

This was an ascending-dose, randomized, double- blind, placebo-controlled repeated-dose study in five successive groups. The following treatments were administered under fed conditions: dronedarone 800, 1000, 1400, 1200 and 1600 mg BID and placebo for 14 days

Subject Demographics

Subject demographics are presented in Table 238.

Formulation (2E3 Formulation)

- Dronedarone 200 mg capsules; batch number 96-00365
- Dronedarone placebo capsules; batch number 96-00344

Pharmacokinetic sampling times

Blood samples were collected at the following times:

- pretreatment and at 1, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours post-treatment for the single dose administration
- pretreatment and at 1, 2, 2.5, 3, 4, 5, 6, 8, 12, 16 and 24 hours after the 7-day repeated administration
- pretreatment and at 1, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours after the 14-day repeated administration.

Table 238: Subject Demographics (TDR3549)

Parameter	Statistics	Placebo	800 mg b.i.d.	1000 mg b.i.d.	1200 mg b.i.d.	1400 mg b.i.d.	1600 mg b.i.d.
Age (years)	N Mean (SD) Min - Max	10 34.2(5.3) 26 - 40	6 29.5(6.4) 21 - 38	6 30.8(7.1) 22 - 39	7 37.0(3.4) 32 - 40	6 28.7(7.2) 21 - 38	6 29.5(3.1) 26 - 35
Height (cm)	N Mean (SD) Min - Max	10 178.0 (6.2) 168- 187	6 180.9 (4.0) 175- 186	6 181.3 (3.5) 178- 187	7 180.2 (4.2) 175- 186	6 183.5 (4.9) 176- 189	6 178.8 (4.0) 174- 183
Weight (kg)	N Mean (SD) Min - Max	10 73.1(5.9) 61.7 - 84.0	6 77.0(5.6) 69.1 - 83.9	6 76.0(6.6) 65.8 - 86.0	7 82.1(5.1) 74.5 - 87.9	6 81.3(7.5) 69.9 - 91.3	6 74.2(3.5) 68.6 - 77.5
BMI (kg/m^2)	N Mean (SD) Min - Max	10 23.1(1.8) 20.9 - 26.4	6 23.6(2.1) 21.2 - 26.0	6 23.1(2.1) 20.7 - 26.5	7 25.3(1.6) 22.4 - 26.6	6 24.1(1.7) 21.3 - 26.0	6 23.2(1.7) 21.3 - 25.5

Bioanalytical Methods

Plasma was assayed for dronedarone and its N-debutyl metabolite, SR35021, using HPLC with UV detection. The assay performance was acceptable and had the following characteristics:

- Linear for both compounds over the 0.5 to 50 ng/mL range; $R^2 > 0.992$ for SR35021 and $R^2 > 0.992$ for dronedarone
- CV < 8 % for SR35021 and CV < 7 % for dronedarone QC samples
- Relative bias for SR35021 QC samples between -4.5 and 5.7 % of nominal concentration Relative bias for dronedarone QC samples between 0.1 and 11.8 % of nominal concentration
- Chromatograms were not provided; however, chromatograms included in the validation report demonstrate assay specificity

Pharmacokinetics

The following dronedarone and SR35021 PK measures were determined

- Day 1: $AUC_{0\text{-}12h}$, Cmax, Tmax and Rmet
- Days 2, 4, 6, 8, and 10: Ctrough
- Day 10: $AUC_{0\text{-}12h}$, Cmax, Tmax, $AUC_{0\text{-}24}$, Rmet and Rac

Pharmacodynamics (Activity)

Pharmacodynamic effects were assessed under resting conditions and during exercise test. ECG parameters (PR- QRS, QT- intervals, QTc, T-wave amplitude, and RR interval), and vital signs (diastolic blood pressure, systolic blood pressure, and heart rate) were determined. ECG parameters were measured before and during treatment at regular time points during the resting phase and at regular time points during the exercise tests. A 24-hr Holter ECG was also performed on Day 8 of the treatment to evaluate the diurnal patterns of QT, QTc and RR intervals as a function of dronedarone dose.

Statistical Methods

Pharmacokinetics

Standard pharmaco-statistical analyses were used to evaluate the following:

- Diurnal variation via ratios of means for half-day differences (night-time vs. daytime administration) for Cmax, $AUC_{0\text{-}12}$ and Ctrough, tmax, half-day

- Dose effects on the Day 10 $t_{1/2z}$ values
- Accumulation ratios of means
- Dose proportionality for AUC_{0-12} and Cmax via log transformed power model
- Steady-state assessment using log transformed Ctrough

Pharmacodynamics

ANOVA was used for most statistical evaluations. The following evaluations were made for resting and exercise test conditions.

Comparison of baseline raw data across dose groups

Comparison of changes from baseline (Day 1 and Day 10)

The ANOVA model took repeated measures into account and included terms for dose and time effects, and the dose by time interaction. Two approaches were adopted depending on if the dose by time interaction was statistically significant:

- If dose by time interaction was statistically significant (p-value ≤ 0.10), then a one-way ANOVA with a fixed term for dose was performed at each time point, separately. Pairwise dose comparisons were then performed and mean differences with 95% confidence intervals (CIs) estimated within the ANOVA framework.
- If the dose by time interaction was not statistically significant (p-value > 0.10), then the following synthetic variables were defined for each subject: hourly Area Under the Curve (AUC), maximum value of the parameter (Emax) over 12 hours post dose and the corresponding time of E max(tmax). AUC and Emax were compared between dose levels using a one-way ANOVA with a fixed term for dose, and mean differences with corresponding 95% CIs for pairwise comparisons were estimated within the ANOVA framework. Tmax was compared between dose levels using the non-parametric Kruskal-Wallis test.

ANOVA with repeated measures was applied to the hourly mean values and the 24-hour mean of HR (bpm), RR-, QT-, and QTc (Bazett) intervals (ms) measured from the 24-hour ECG recordings.

Reviewer Note on Statistical analyses

This review focuses on the following:

- Pharmacodynamics- Day 10 results compared to baseline
- Pharmacokinetics- diurnal variation

Results

Dronedarone PK

The plasma concentration time profiles for dronedarone and SR35021 following single and multiple dose oral administration are depicted in Figure 139 and Figure 140.

Figure 139: Mean dronedarone plasma concentration-time profiles following BID and QD dosing

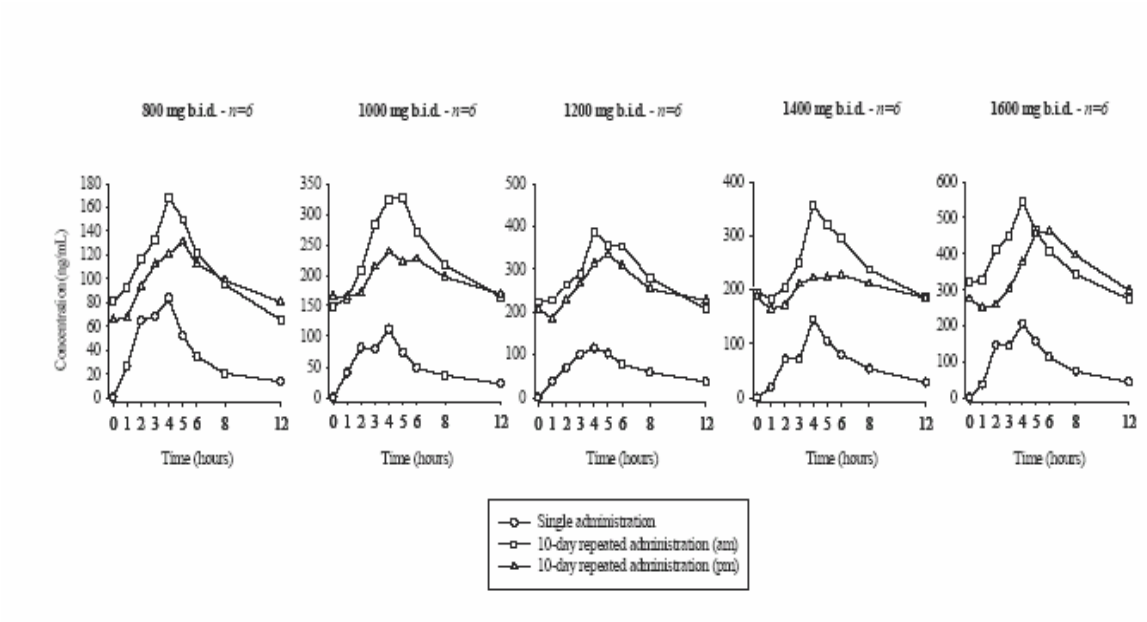
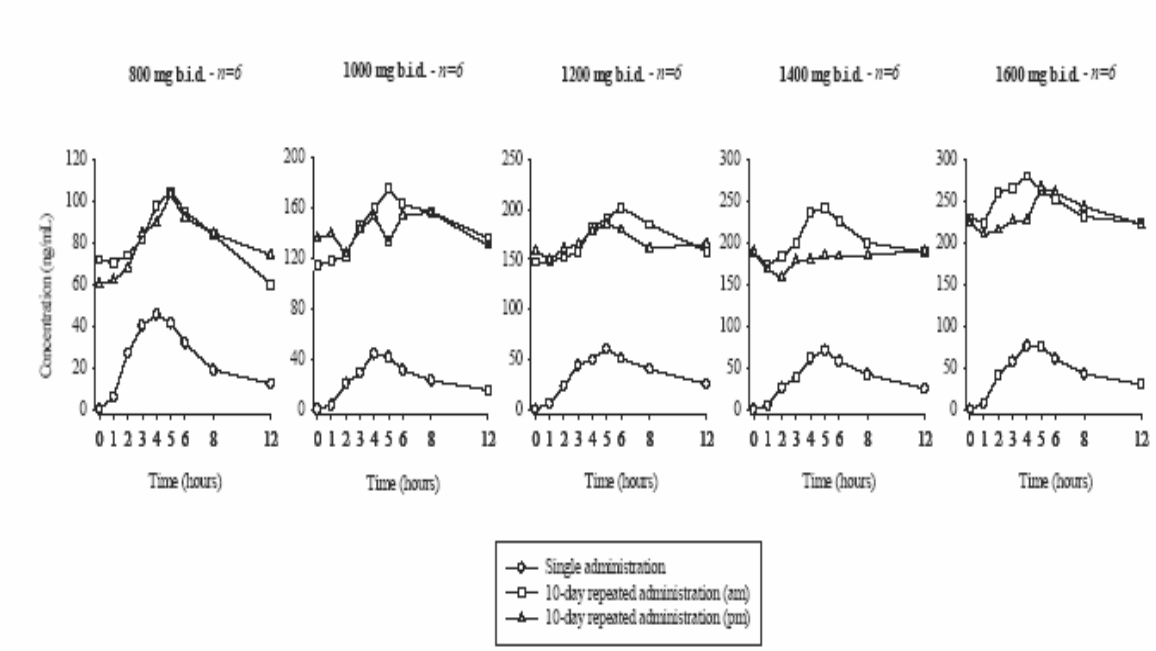


Figure 140: Mean SR35021 plasma concentration-time profiles following BID and QD dosing



The mean (SD) PK parameters of dronedarone after repeated administration of dronedarone 400, 600 or 800 mg BID and 800, 1200 or 1600 mg QD are shown in Table 239 and Table 240.

Table 239: Dronedarone PK measures following administration of dronedarone at different dose levels

C_{max} (ng/mL)	Dose administered				
	800 mg b.i.d.	1000 mg b.i.d.	1200 mg b.i.d.	1400 mg b.i.d.	1600 mg b.i.d.
C_{max} - Single administration					
Mean	86.7	132	135	147	223
SD	16.8	55.7	56.6	90.0	51.5
CV%	19	42	42	61	23
C_{max} - 10-days repeated administration (daytime)					
Mean	177	337	400	363	552
SD	57.7	92.8	131	118	139
CV%	33	28	33	33	25
C_{max} - 10-days repeated administration (night-time)					
Mean	136	264	343	242	476
SD	29.1	122	130	90.1	141
CV%	21	46	38	37	30

Table 240: Dronedarone PK measures following administration of dronedarone at different dose levels

AUC (ng.h/mL)	Dose administered				
	800 mg b.i.d.	1000 mg b.i.d.	1200 mg b.i.d.	1400 mg b.i.d.	1600 mg b.i.d.
AUC_{0-12} - Single administration					
Mean	432	609	790	742	1155
SD	81.2	203	368	499	271
CV%	19	33	47	67	24
AUC_{0-12} - 10-days repeated administration (daytime)					
Mean	1291	2758	3397	2919	4525
SD	303	819	1442	1138	953
CV%	23	30	42	39	21
AUC_{0-12} - 10-days repeated administration (night-time)					
Mean	1182	2783	3105	2416	4253
SD	200	1102	1281	907	1146
CV%	17	40	41	38	27
AUC_{0-24} - 10-days repeated administration (daytime and night-time)					
Mean	2473	5540	6501	5335	8778
SD	449	1619	2719	1996	2040
CV%	18	29	42	37	23

Highlights

- Accumulation: approximately 2- to 3- fold accumulation occurs (Day 10 vs. Day 1)
- Diurnal variation occurs: Daytime Cmax > Nighttime Cmax
- Steady state achieved within 10 days

Overall the PK findings in this study are consistent with those in previous PK studies.

SR35021 PK

PK characteristics of SR35021 are similar to dronedarone, as demonstrated in previous studies; however SR35021 results will not be presented in this review.

Table 241: Dronedarone PK measures following administration of dronedarone at different dose levels

C_{trough} (ng/mL)	Dose administered				
	800 mg b.i.d.	1000 mg b.i.d.	1200 mg b.i.d.	1400 mg b.i.d.	1600 mg b.i.d.
Day 2 (daytime)					
Mean	38.8	64.7	82.4	89.3	121
SD	11.0	29.8	57.2	40.4	45.9
CV%	28	46	69	45	38
Day 4 (daytime)					
Mean	65.2	111	147	115	215
SD	16.0	51.9	58.8	31.8	50.1
CV%	24	47	40	28	23
Day 6 (daytime)					
Mean	83	113	197	149	203
SD	19.2	46.7	116.8	64.6	49.4
CV%	23	41	59	43	24
Day 8 (daytime)					
Mean	74.9	134	233	164	280
SD	14.9	43.4	143	60.5	86.6
CV%	20	32	61	37	31
Day 10 (daytime)					
Mean	80.7	150	223	195	322
SD	14.7	31.7	117.4	80.4	70.2
CV%	18	21	53	41	22

Pharmacodynamics (Activity)

Several PD measures were determined in this study; the changes in these measures with respect to dronedarone dose are summarized in the following tables and figures. It should be noted that the results in italics (tables) are not statistically significant.

Resting Conditions (Day 10 Results)

1. PR Interval

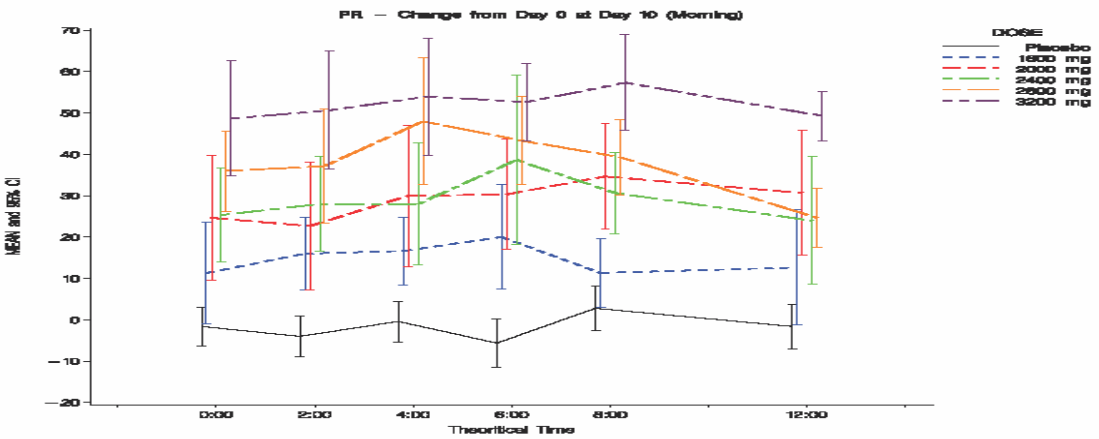
On Day 10 there was a statistically significant overall treatment effect ($p < 0.0001$) thus pairwise comparison was done between dose groups using AUC and Emax measures. As shown in Table 242, PR prolongation was statistically significantly higher in all active dose groups compared to placebo.

Table 242: Differences in the PR* AUC and Emax for various dose groups on Day 10 (resting conditions)

Analysis	Difference	Estimate [95% CI] (Day)	Estimate [95% CI] (Night)
AUC	Placebo vs 800 mg b.i.d	16.0 [4.0 ; 28.0]	19.0 [6.2 ; 31.8]
	Placebo vs 1000 mg b.i.d.	31.0 [19.0 ; 43.1]	25.4 [12.6 ; 38.2]
	Placebo vs 1200 mg b.i.d.	30.9 [18.9 ; 42.9]	22.8 [9.9 ; 35.6]
	Placebo vs 1400 mg b.i.d.	39.8 [27.8 ; 51.8]	32.9 [20.1 ; 45.7]
	Placebo vs 1600 mg b.i.d.	54.2 [42.2 ; 66.2]	46.3 [33.5 ; 59.1]
	800 mg b.i.d vs 1000 mg b.i.d.	15.0 [1.6 ; 28.4]	*6.4 [-8.0 ; 20.7]*
	800 mg b.i.d vs 1200 mg b.i.d.	14.9 [1.5 ; 28.3]	*3.7 [-10.6 ; 18.1]*
	800 mg b.i.d vs 1400 mg b.i.d.	23.7 [10.3 ; 37.2]	*13.9 [-0.5 ; 28.2]*
	800 mg b.i.d vs 1600 mg b.i.d.	38.2 [24.8 ; 51.6]	27.3 [12.9 ; 41.6]
E_{max}	Placebo vs 800 mg b.i.d	15.9 [0.1 ; 31.6]	23.3 [8.9 ; 37.8]
	Placebo vs 1000 mg b.i.d.	29.2 [13.5 ; 44.9]	26.7 [12.2 ; 41.1]
	Placebo vs 1200 mg b.i.d.	35.2 [19.5 ; 50.9]	24.3 [9.9 ; 38.8]
	Placebo vs 1400 mg b.i.d.	43.9 [28.1 ; 59.6]	38.7 [24.2 ; 53.1]
	Placebo vs 1600 mg b.i.d.	52.5 [36.8 ; 68.3]	44.7 [30.2 ; 59.1]
	800 mg b.i.d vs 1000 mg b.i.d.	19.3 [1.7 ; 36.9]	*1.0 [-15.1 ; 17.1]*
	800 mg b.i.d vs 1400 mg b.i.d.	28.0 [10.4 ; 45.6]	*15.3 [-0.8 ; 31.5]*
	800 mg b.i.d vs 1600 mg b.i.d.	36.7 [19.1 ; 54.3]	21.3 [5.2 ; 37.5]

At night-time, the range of differences in PR prolongation was smaller than in daytime. It is unclear if this diurnal variation is due to the different plasma concentrations. There was a trend towards a linear dose-response relationship as illustrated in Figure 141.

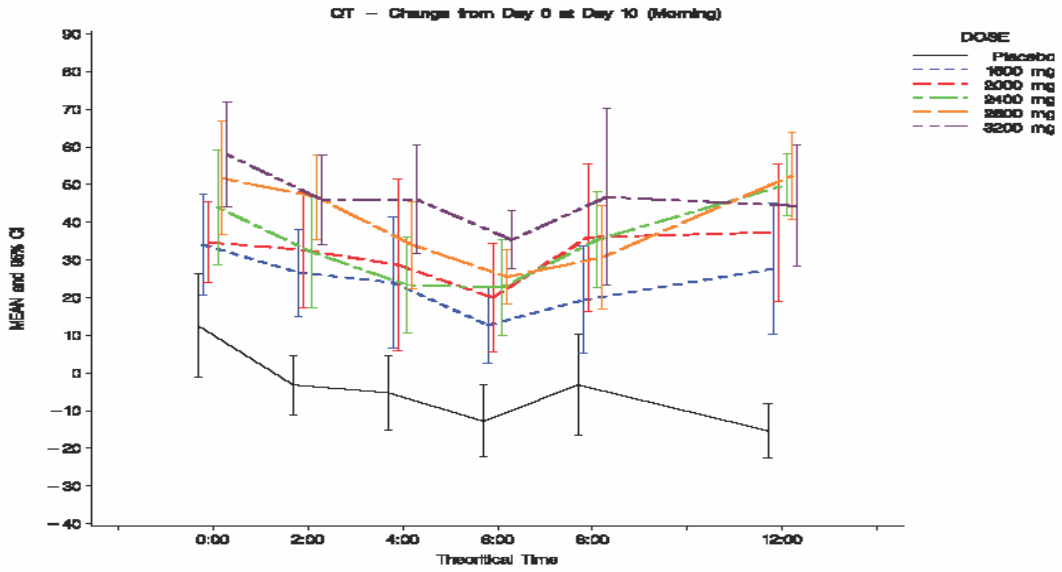
Figure 141: Relationship between change in PR and time at different dronedarone dose levels (morning)



2. QT Interval

Relative to placebo, dronedarone treatment generally increased the QT interval (Figure 142 and Table 243.

Figure 142: Relationship between change in QT and time at different dronedarone dose levels (morning)



There appeared to be diurnal variation with respect to QT prolongation: the QT prolongation before the morning dose at all dose levels seemed lower than prior to the evening dose. The reason for the diurnal variation is not clear. There was also a fairly wide range fluctuation in QT interval prolongation that appeared to be both time- and dose-dependent.

There was a trend towards increasing QT interval with increasing dose.

Table 243: Change in QT interval over time at different dronedarone dose levels

Parameter	Theoretical time	Difference	Estimate [95% CI] (Day)	(Night)
QT-interval (ms)	T0	Placebo vs 800 mg b.i.d.	21.5 [1.9 ; 41.1]	43.1 [25.2 ; 60.9]
		Placebo vs 1000 mg b.i.d.	22.2 [2.6 ; 41.8]	52.7 [34.9 ; 70.6]
		Placebo vs 1200 mg b.i.d.	31.5 [11.9 ; 51.1]	65.4 [47.5 ; 83.3]
		Placebo vs 1400 mg b.i.d.	39.2 [19.6 ; 58.8]	67.7 [49.9 ; 85.6]
		Placebo vs 1600 mg b.i.d.	45.5 [25.9 ; 65.1]	59.7 [41.9 ; 77.6]
		800 mg b.i.d. vs 1200 mg b.i.d.	*10.0 [-11.9 ; 31.9]*	22.3 [2.4 ; 42.3]
		800 mg b.i.d. vs 1400 mg b.i.d.	*17.7 [-4.3 ; 39.6]*	24.7 [4.7 ; 44.6]
		800 mg b.i.d. vs 1600 mg b.i.d.	24.0 [2.1 ; 45.9]	*16.7 [-3.3 ; 36.6]*
		1000 mg b.i.d. vs 1600 mg b.i.d.	23.3 [1.4 ; 45.3]	*7.0 [-13.0 ; 27.0]*
	T2	Placebo vs 800 mg b.i.d.	29.9 [13.6 ; 46.1]	34.3 [10.8 ; 57.7]
		Placebo vs 1000 mg b.i.d.	35.9 [19.6 ; 52.1]	34.9 [11.5 ; 58.4]
		Placebo vs 1200 mg b.i.d.	35.2 [19.0 ; 51.4]	36.3 [12.8 ; 59.7]
		Placebo vs 1400 mg b.i.d.	49.9 [33.6 ; 66.1]	40.9 [17.5 ; 64.4]
		Placebo vs 1600 mg b.i.d.	49.2 [33.0 ; 65.4]	68.3 [44.8 ; 91.7]
		800 mg b.i.d. vs 1400 mg b.i.d.	20.0 [1.8 ; 38.2]	*6.7 [-19.6 ; 32.9]*
		800 mg b.i.d. vs 1600 mg b.i.d.	19.3 [1.2 ; 37.5]	34.0 [7.8 ; 60.2]
		1000 mg b.i.d. vs 1600 mg b.i.d.	*13.3 [-4.8 ; 31.5]*	33.3 [7.1 ; 59.6]
		1200 mg b.i.d. vs 1600 mg b.i.d.	*14.0 [-4.2 ; 32.2]*	32.0 [5.8 ; 58.2]
		1400 mg b.i.d. vs 1600 mg b.i.d.	*-0.7 [-18.8 ; 17.5]*	27.3 [1.1 ; 53.6]
	T4	Placebo vs 800 mg b.i.d.	29.3 [9.0 ; 49.6]	34.4 [13.6 ; 55.2]
		Placebo vs 1000 mg b.i.d.	34.0 [13.7 ; 54.3]	23.7 [3.0 ; 44.5]
		Placebo vs 1200 mg b.i.d.	28.6 [8.3 ; 48.9]	*20.4 [-0.4 ; 41.2]*
		Placebo vs 1400 mg b.i.d.	39.3 [19.0 ; 59.6]	31.7 [11.0 ; 52.5]
		Placebo vs 1600 mg b.i.d.	51.3 [31.0 ; 71.6]	61.9 [41.1 ; 82.7]
		800 mg b.i.d. vs 1600 mg b.i.d.	*22.0 [-0.7 ; 44.7]*	27.5 [4.3 ; 50.7]
		1000 mg b.i.d. vs 1600 mg b.i.d.	*17.3 [-5.4 ; 40.0]*	38.2 [14.9 ; 61.4]
		1200 mg b.i.d. vs 1600 mg b.i.d.	*22.7 [0.0 ; 45.4]*	41.5 [18.3 ; 64.7]
		1400 mg b.i.d. vs 1600 mg b.i.d.	*12.0 [-10.7 ; 34.7]*	30.2 [6.9 ; 53.4]
	T6	Placebo vs 800 mg b.i.d.	25.5 [10.8 ; 40.2]	39.9 [20.0 ; 59.8]
		Placebo vs 1000 mg b.i.d.	32.8 [18.1 ; 47.5]	36.5 [16.6 ; 56.4]
		Placebo vs 1200 mg b.i.d.	35.5 [20.8 ; 50.2]	27.2 [7.3 ; 47.1]
		Placebo vs 1400 mg b.i.d.	38.3 [23.6 ; 53.0]	47.9 [28.0 ; 67.8]
		Placebo vs 1600 mg b.i.d.	48.1 [33.4 ; 62.8]	51.5 [31.6 ; 71.4]
		800 mg b.i.d. vs 1600 mg b.i.d.	22.7 [6.2 ; 39.1]	*11.7 [-10.6 ; 33.9]*
		1200 mg b.i.d. vs 1600 mg b.i.d.	*12.7 [-3.8 ; 29.1]*	24.3 [2.1 ; 46.6]
Parameter	**Theoretical time**	**Difference**	**Estimate [95% CI] (Day)**	**(Night)**
QT-interval (ms)	T8	Placebo vs 800 mg b.i.d.	*22.5[-0.1 ; 45.1]*	45.5[24.6 ; 66.4]
		Placebo vs 1000 mg b.i.d.	39.2[16.6 ; 61.8]	45.5[24.6 ; 66.4]
		Placebo vs 1200 mg b.i.d.	38.5[15.9 ; 61.1]	42.2[21.3 ; 63.1]
		Placebo vs 1400 mg b.i.d.	33.9[11.3 ; 56.5]	48.5[27.6 ; 69.4]
		Placebo vs 1600 mg b.i.d.	49.9[27.3 ; 72.5]	72.2[51.3 ; 93.1]
		800 mg b.i.d. vs 1600 mg b.i.d.	27.3 [2.1 ; 52.6]	26.7 [3.3 ; 50.0]
		1000 mg b.i.d. vs 1600 mg b.i.d.	*10.7 [-14.6 ; 35.9]*	26.7 [3.3 ; 50.0]
		1200 mg b.i.d. vs 1600 mg b.i.d.	*11.3 [-13.9 ; 36.6]*	30.0 [6.6 ; 53.4]
		1400 mg b.i.d. vs 1600 mg b.i.d.	*16.0 [-9.3 ; 41.3]*	23.7 [0.3 ; 47.0]
	T12	Placebo vs 800 mg b.i.d.	43.1 [25.2 ; 60.9]	45.6 [25.7 ; 65.5]
		Placebo vs 1000 mg b.i.d.	52.7 [34.9 ; 70.6]	41.3 [21.4 ; 61.1]
		Placebo vs 1200 mg b.i.d.	65.4 [47.5 ; 83.3]	56.9 [37.1 ; 76.8]
		Placebo vs 1400 mg b.i.d.	67.7 [49.9 ; 85.6]	48.3 [28.4 ; 68.1]
		Placebo vs 1600 mg b.i.d.	59.7 [41.9 ; 77.6]	70.9 [51.1 ; 90.8]
		800 mg b.i.d. vs 1200 mg b.i.d.	22.3 [2.4 ; 42.3]	*11.3 [-10.9 ; 33.5]*
		800 mg b.i.d. vs 1400 mg b.i.d.	24.7 [4.7 ; 44.6]	*2.7 [-19.5 ; 24.9]*
		800 mg b.i.d. vs 1600 mg b.i.d.	*16.7 [-3.3 ; 36.6]*	25.3 [3.1 ; 47.5]
		1000 mg b.i.d. vs 1600 mg b.i.d.	*7.0 [-13.0 ; 27.0]*	29.7 [7.5 ; 51.9]
		1400 mg b.i.d. vs 1600 mg b.i.d.	*-8.0 [-28.0 ; 12.0]*	22.7 [0.5 ; 44.9]

Reviewer Note

The applicant notes that a statistically significant (p = 0.0109) treatment by time interaction was detected for QT-interval at baseline, in daytime, possibly due to a difference in mean values between

placebo and 1000 mg BID groups at T0. However, the applicant does not consider this interaction likely to compromise treatment group comparison with respect to changes from baseline. The applicant's interpretation appears reasonable and is acceptable; however, the applicant should have determined the reason for this unexpected observation. Potentially the subject could have committed a protocol violation.

3. QTc Interval

On Day 10 there was no treatment by time interaction for QTc. As shown in Table 244, the subsequent analyses indicated:

- Relative to placebo there was a statistically significant overall treatment effect (p = <0.0001) for QTc with respect to Emax and AUC
- QTc prolongation was correlated to dose

Table 244: Change in QTc as a function of dronedarone dose

Analysis	Difference	Estimate [95% CI] (Day)	Estimate [95% CI] (Night)
AUC	Placebo vs 800 mg b.i.d	10.5 [1.9 ; 19.1]	16.7 [6.3 ; 27.0]
	Placebo vs 1000 mg b.i.d.	27.0 [18.3 ; 35.6]	23.4 [13.1 ; 33.8]
	Placebo vs 1200 mg b.i.d.	24.5 [15.8 ; 33.1]	23.4 [13.1 ; 33.8]
	Placebo vs 1400 mg b.i.d.	29.8 [21.1 ; 38.4]	30.0 [19.6 ; 40.3]
	Placebo vs 1600 mg b.i.d.	31.1 [22.4 ; 39.7]	35.4 [25.1 ; 45.8]
	800 mg b.i.d vs 1000 mg b.i.d.	16.5 [6.8 ; 26.1]	*6.8 [-4.8 ; 18.3]*
	800 mg b.i.d vs 1200 mg b.i.d.	14.0 [4.3 ; 23.6]	*6.8 [-4.8 ; 18.3]*
	800 mg b.i.d vs 1400 mg b.i.d.	19.3 [9.6 ; 28.9]	13.3 [1.7 ; 24.9]
	800 mg b.i.d vs 1600 mg b.i.d.	20.6 [10.9 ; 30.2]	18.7 [7.2 ; 30.3]
E_{max}	Placebo vs 800 mg b.i.d	12.9 [1.2 ; 24.7]	16.4 [3.3 ; 29.5]
	Placebo vs 1000 mg b.i.d.	30.3 [18.5 ; 42.0]	22.1 [9.0 ; 35.2]
	Placebo vs 1200 mg b.i.d.	23.8 [12.0 ; 35.5]	19.1 [6.0 ; 32.2]
	Placebo vs 1400 mg b.i.d.	30.6 [18.9 ; 42.3]	36.9 [23.8 ; 50.0]
	Placebo vs 1600 mg b.i.d.	34.4 [22.7 ; 46.2]	37.2 [24.1 ; 50.3]
	800 mg b.i.d vs 1000 mg b.i.d.	17.3 [4.2 ; 30.4]	*5.7 [-9.0 ; 20.3]*
	800 mg b.i.d vs 1400 mg b.i.d.	17.7 [4.6 ; 30.8]	20.5 [5.9 ; 35.1]
	800 mg b.i.d vs 1600 mg b.i.d.	21.5 [8.4 ; 34.6]	20.8 [6.2 ; 35.5]

4. T-wave amplitude

A statistically significant treatment effect was detected for AUC and Emax on both daytime and nighttime measures (Table 245).

Table 245: Change in T-wave amplitude as a function of dronedarone dose

Analysis	Difference	Estimate [95% CI] Daytime	Estimate [95% CI] Night-time
AUC	Placebo vs 800 mg b.i.d	-157 [-302 ; -12.2]	*-112 [-253 ; 29.6]*
	Placebo vs 1000 mg b.i.d.	-204 [-349 ; -58.6]	-195 [-336 ; -53.4]
	Placebo vs 1200 mg b.i.d.	-183 [-328 ; -38.0]	-170 [-311 ; -28.5]
	Placebo vs 1400 mg b.i.d.	-228 [-373 ; -83.3]	-208 [-349 ; -67.0]
	Placebo vs 1600 mg b.i.d.	-296 [-441 ; -151]	-284 [-425 ; -143]
	800 mg b.i.d vs 1600 mg b.i.d.	*-139 [-301 ; 22.9]*	-173 [-330 ; -14.7]
E_{max}	Placebo vs 800 mg b.i.d	-213 [-363 ; -63.0]	*-146 [-301 ; 8.1]*
	Placebo vs 1000 mg b.i.d.	-251 [-401 ; -101]	-237 [-391 ; -82.2]
	Placebo vs 1200 mg b.i.d.	-237 [-386 ; -86.6]	*-154 [-309 ; 0.3]*
	Placebo vs 1400 mg b.i.d.	-276 [-425 ; -126]	-254 [-409 ; -99.9]
	Placebo vs 1600 mg b.i.d.	-363 [-513 ; -213]	-301 [-455 ; -146]

Table 246 summarizes the mean differences in Emax for changes from baseline in ECG parameters on Day 10 in the 800 mg (lowest dose) and 1600 mg (highest dose) BID groups, compared to placebo. The findings for the 800 and 1600 mg groups support the existence of a dose-response relationship for the ECG measures, as the effect of 1600 mg was always numerically greater than that of 800 mg in the same direction.

Table 246: Mean differences in Emax for changes from baseline in ECG parameters on Day 10

ECG parameters on Day 10	Placebo vs 800 mg bid	Placebo vs 1600 mg bid
PR-interval (ms) (daytime)	15.9	52.5
QT-interval (ms) (daytime)	29.3 (T4h)	51.3 (T4h)
QT-interval (ms) (night-time)	34.4 (T4h)	72.2 (T8h)
QTc-interval (ms) (daytime)	12.9	34.4
QTc-interval (ms) (night-time)	16.4	37.2
T-wave (µV) (daytime)	- 213	- 363

5. Heart rate

On Day 10, a treatment difference was detected on hourly AUC and E_{max} for both daytime and night-time measures.

Table 247: Mean differences in Emax for changes from baseline in HR parameters on Day 10

Analysis	Difference	Estimate [95% CI] on Day 10	
		Daytime	Night-time
AUC	Placebo vs 800 mg b.i.d	-4.5 [-8.2 ; -0.8]	-7.7 [-11.0 ; -4.5]
	Placebo vs 1000 mg b.i.d.	*-3.4 [-7.2 ; 0.3]*	-3.9 [-7.2 ; -0.7]
	Placebo vs 1200 mg b.i.d.	*-1.7 [-5.4 ; 2.0]*	-4.1 [-7.3 ; -0.8]
	Placebo vs 1400 mg b.i.d.	-4.0 [-7.7 ; -0.3]	-4.2 [-7.5 ; -1.0]
	Placebo vs 1600 mg b.i.d.	-6.1 [-9.9 ; -2.4]	-6.5 [-9.7 ; -3.2]
	800 mg b.i.d vs 1000 mg b.i.d.	*1.1 [-3.1 ; 5.2]*	3.8 [0.1 ; 7.5]
	800 mg b.i.d vs 1200 mg b.i.d.	*2.8 [-1.4 ; 7.0]*	3.7 [0.0 ; 7.3]
E_{max}	Placebo vs 800 mg b.i.d	*-3.0 [-6.8 ; 0.7]*	-8.1 [-12.5 ; -3.6]
	Placebo vs 1000 mg b.i.d.	*-3.4 [-7.1 ; 0.4]*	-7.9 [-12.3 ; -3.5]
	Placebo vs 1200 mg b.i.d.	*-2.2 [-5.9 ; 1.5]*	-6.7 [-11.2 ; -2.3]
	Placebo vs 1400 mg b.i.d.	-5.5 [-9.3 ; -1.8]	-6.4 [-10.8 ; -2.0]
	Placebo vs 1600 mg b.i.d.	-6.5 [-10.3 ; -2.8]	-8.7 [-13.2 ; -4.3]

Only the two highest dose groups (1400 mg and 1600 mg) were able to affect the maximum change in HR relative to placebo during the daytime; conversely, during the nighttime, all dronedarone doses had higher maximum changes in HR than placebo. There was no clear dose-response (HR) relationship

6. SBP

There was no clear dose-response in SBP; however, the 800 mg and 1200 mg BID exhibited a higher decrease in SBP than placebo (Table 248).

Table 248: Mean differences in Emax for changes from baseline in ECG parameters on Day 10

Difference	Estimate [95% CI]
Placebo vs 800 mg b.i.d	-6.4 [-12.3 ; -0.5]
Placebo vs 1200 mg b.i.d.	-9.1 [-15.0 ; -3.2]

7. DBP

There was no clear dose-response in DBP; however, there were differences between placebo and some dronedarone dose groups in DBP at T8 and T12 (Table 249).

Table 249: Mean differences in Emax for changes from baseline in DBP parameters on Day 10 (nighttime)

Theoretical time	Difference	Estimate [95% CI]
T8	Placebo vs 800 mg b.i.d	-11.2 [-17.7 ; -4.7]
	Placebo vs 1200 mg b.i.d.	-10.2 [-16.7 ; -3.7]
	Placebo vs 1600 mg b.i.d.	-8.2 [-14.7 ; -1.7]
T12	Placebo vs 1200 mg b.i.d.	-12.7 [-20.4 ; -4.9]
	Placebo vs 1400 mg b.i.d.	-11.5 [-19.2 ; -3.8]
	Placebo vs 1600 mg b.i.d.	-12.5 [-20.2 ; -4.8]

The maximal differences in vital signs are summarized in Table 250.

Table 250: Mean differences in Emax for changes from baseline in DBP parameters on Day 10 (nighttime)

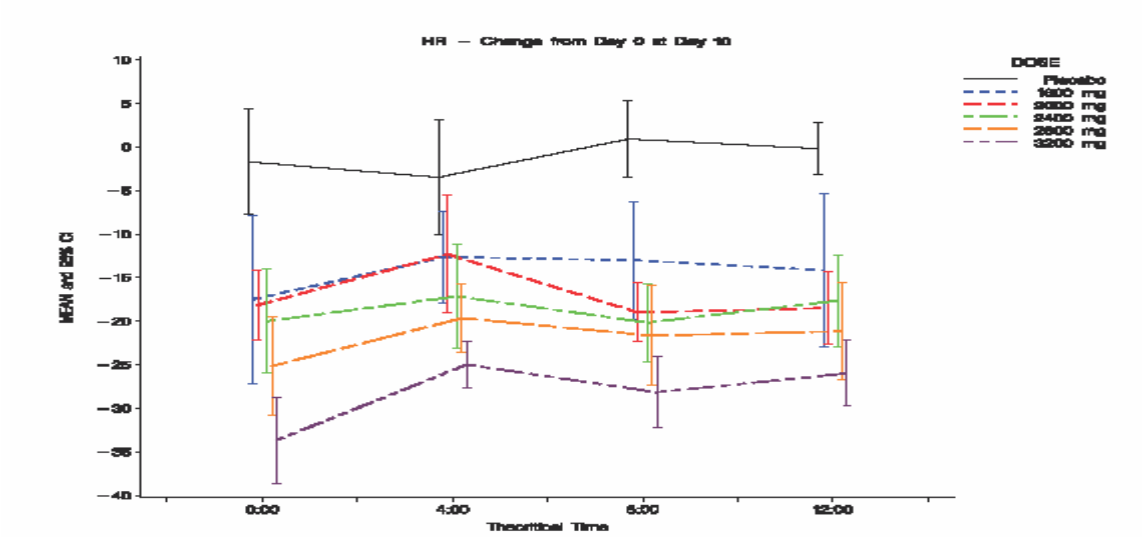
Vital signs	Placebo vs 800 mg bid	Placebo vs 1600 mg bid
HR (bpm)	- 3.0	- 6.5
SBP (mmHg)	- 13.5 (T8h)	-12.2 (T8h)
DBP (mmHg)	- 11.2 (T8h)	- 12.7 (T12h)

Exercise Tests (Day 10 Results)

1. HR

The heart rate changes from baseline as a function of dronedarone dose are shown in Figure 143.

Figure 143: Heart Rate Changes form Day 0 and Day 10 during exercise testing



The decrease in all active groups was statistically significantly greater than in the placebo group, at all time points. A statistically significant decrease in maximum HR was observed at all time points during the exercise test. For example at T0 (after exercise test), before morning administration on Day 10, the range of relative HR decrease was 15 bpm (placebo vs. 800 mg BID) to 32 bpm (placebo vs. 1600 mg BID). There was a linear trend between dose and response, but it was not clear if a plateau effect had been achieved.

Table 251: Pairwise Comparisons of Heart Rate obtained during Exercise Test for Various dronedarone doses

Theoretical time	Difference	Estimate	95% CI
T0	Placebo vs 800 mg b.i.d	-15.8	[-24.7 ; -6.9]
	Placebo vs 1000 mg b.i.d.	-16.5	[-25.4 ; -7.6]
	Placebo vs 1200 mg b.i.d.	-18.3	[-27.2 ; -9.4]
	Placebo vs 1400 mg b.i.d.	-23.5	[-32.4 ; -14.6]
	Placebo vs 1600 mg b.i.d.	-32.0	[-40.9 ; -23.1]
	800 mg b.i.d vs 1600 mg b.i.d.	-16.2	[-26.1 ; -6.2]
T4	Placebo vs 800 mg b.i.d	-9.2	[-17.3 ; -1.0]
	Placebo vs 1000 mg b.i.d.	-8.8	[-17.0 ; -0.7]
	Placebo vs 1200 mg b.i.d.	-13.7	[-21.8 ; -5.5]
	Placebo vs 1400 mg b.i.d.	-16.2	[-24.3 ; -8.0]
	Placebo vs 1600 mg b.i.d.	-21.5	[-29.6 ; -13.4]
	800 mg b.i.d. vs 1600 mg b.i.d.	-12.3	[-21.4 ; -3.2]
T8	Placebo vs 800 mg b.i.d	-13.9	[-20.8 ; -7.0]
	Placebo vs 1000 mg b.i.d.	-19.9	[-26.8 ; -13.0]
	Placebo vs 1200 mg b.i.d.	-21.1	[-27.9 ; -14.2]
	Placebo vs 1400 mg b.i.d.	-22.6	[-29.4 ; -15.7]
	Placebo vs 1600 mg b.i.d.	-29.1	[-35.9 ; -22.2]
	800 mg b.i.d vs 1400 mg b.i.d.	-8.7	[-16.3 ; -1.0]
	800 mg b.i.d vs 1600 mg b.i.d.	-15.2	[-22.8 ; -7.5]
T12	Placebo vs 800 mg b.i.d	-14.0	[-21.0 ; -6.9]
	Placebo vs 1000 mg b.i.d.	-18.3	[-25.3 ; -11.3]
	Placebo vs 1200 mg b.i.d.	-17.5	[-24.5 ; -10.4]
	Placebo vs 1400 mg b.i.d.	-21.0	[-28.0 ; -13.9]
	Placebo vs 1600 mg b.i.d.	-25.8	[-32.8 ; -18.8]
	800 mg b.i.d vs 1600 mg b.i.d.	-11.8	[-19.7 ; -4.0]

2. SBP

Relative to placebo, a statistically significant decrease in SBP occurred at T4 and T8 for some active dose groups; however the 1000 mg BID dose group did not produce an effect (Table 252).

Table 252: Pairwise Comparisons of SBP during Exercise Test for Various dronedarone doses

Theoretical time	Difference	Estimate	95% CI
T4	Placebo vs 800 mg b.i.d	-23.9	[-38.5 ; -9.3]
	Placebo vs 1400 mg b.i.d.	-21.2	[-35.8 ; -6.6]
T8	Placebo vs 800 mg b.i.d	-15.9	[-31.6 ; -0.1]
	Placebo vs 1200 mg b.i.d.	-29.4	[-45.1 ; -13.6]
	Placebo vs 1400 mg b.i.d.	-18.0	[-33.8 ; -2.3]
	Placebo vs 1600 mg b.i.d.	-17.4	[-33.1 ; -1.6]

There was no clear dose-response relationship.

3. DBP

No treatment differences could be detected on Day 10 for maximum DBP in exercise tests.

Twenty-four (24) hour Holter ECG (summary)

Highlights of the 24-hr Holter ECG data are summarized in the following section. All plots were generated by the applicant and are consistent with the provided data. Table 253 provides a summary of the p-values for the various tested hypotheses. ECG parameters are addressed in turn. It should be noted that there were no statistically significant differences in the tested variables

among different treatment groups prior to drug administration and no statistically significant differences in the placebo group between screening and Day 8.

Table 253: Summary of p-values for various tested hypotheses

Dependent Variable	H1: p-Value Dose Effect	H2: p-Value* Hour Effect	H3: p-Value* Hour-Dose Interaction	H4: p-Value Placebo vs. Drug Contrast
RR Scrn	0.5785	<0.0001	0.5019	0.9288
RR Day8	0.1508	<0.0001	0.5974	0.0407
Del RR	0.0759	<0.0001	0.2752	0.0063
QT Scrn	0.9493	<0.0001	0.9164	0.6759
QT Day8	<0.0001	<0.0001	0.2062	<0.0001
Del QT	<0.0001	<0.0001	0.3711	<0.0001
QTc Scrn	0.9304	<0.0001	0.0654	0.6435
QTc Day8	<0.0001	0.0166	0.7624	<0.0001
Del QTc	0.0014	<0.0001	0.0975	<0.0001

- QT-interval and QTc

Relative to placebo, there was a statistically significant increase induced by steady-state dronedarone treatment; conversely placebo did not induce QT changes (placebo Day 8 vs. Placebo Day 0).

- RR interval

There were no statistically significant differences among all treated groups on Day 8. However, when all drug treated groups were contrasted against placebo, both RR Day 8 (p = 0.0407) and the difference between RR on Day 8 and screening (p= 0.0063) were statistically significant.

- Dose-Response

The dose-response curves were statistically significantly linear with respect to relative prolongation of 24-hour mean QT, QTc, and RR intervals induced by 8-day treatment with dronedarone or placebo (Figure 144, Figure 145, and Figure 146).

Figure 144: QT % increase as a function of dronedarone dose

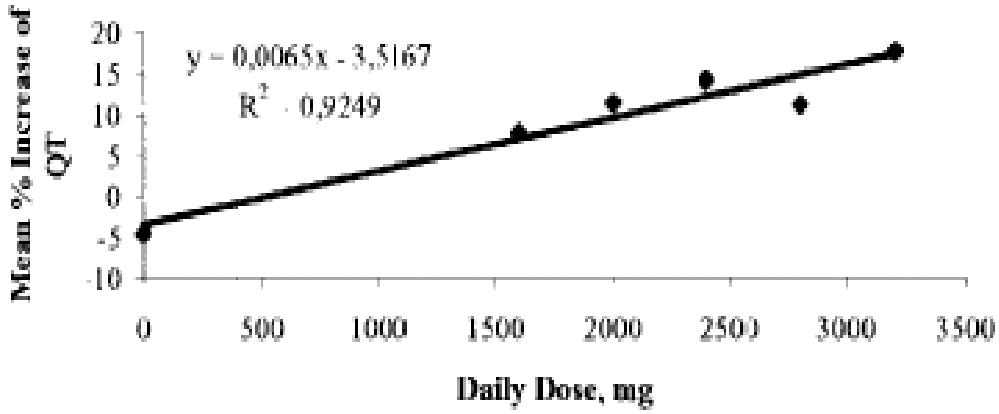


Figure 145: Mean QT % increase as a function of dronedarone dose

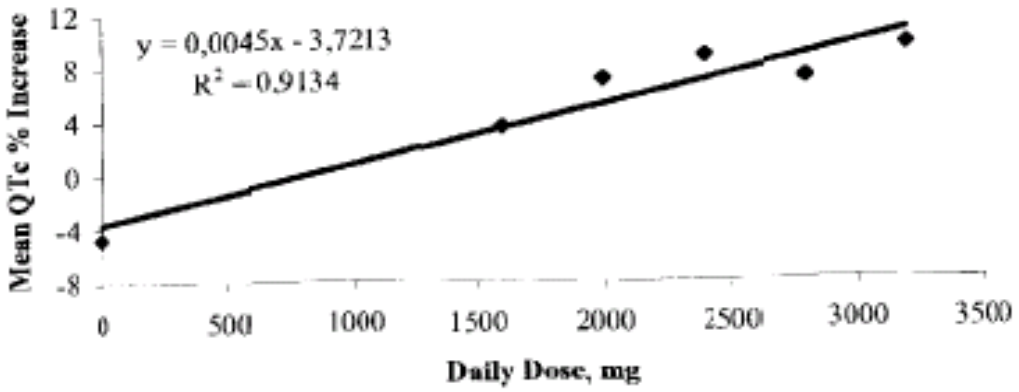
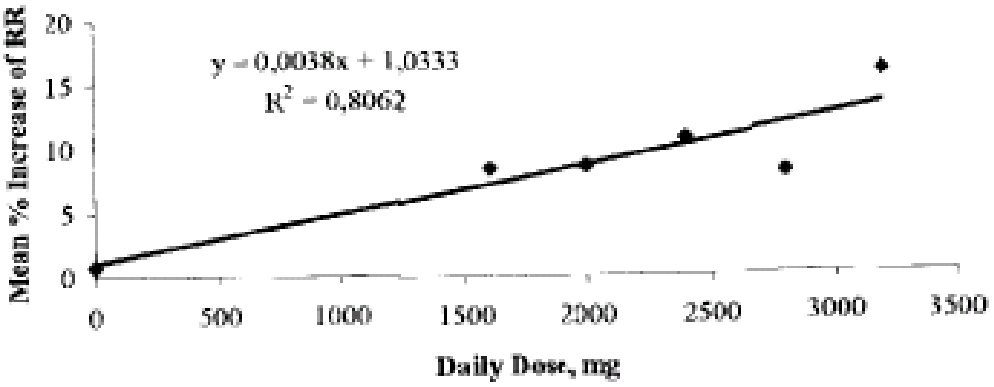


Figure 146: RR dose response



1. Circadian patterns

Statistically significant hourly fluctuations occurred in all groups at screening as well as on Day 8, but only QT and RR exhibited a clearly recognizable circadian pattern common to all treatment groups.

In the following plots on circadian variation, Placebo refers to placebo group and Dose 16, 20, 24, 28 and 32 refer to 800, 1000, 1200, 1400 and 1600 mg BID dronedarone, respectively.

Figure 147: RR circadian variation at screen (left panel) and on Day 8 (right panel)

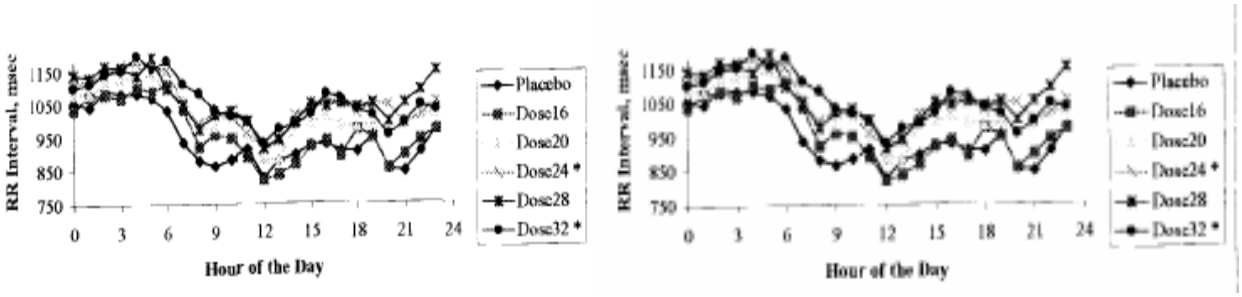


Figure 148: QT circadian variation at screen (left panel) and on Day 8 (right panel)

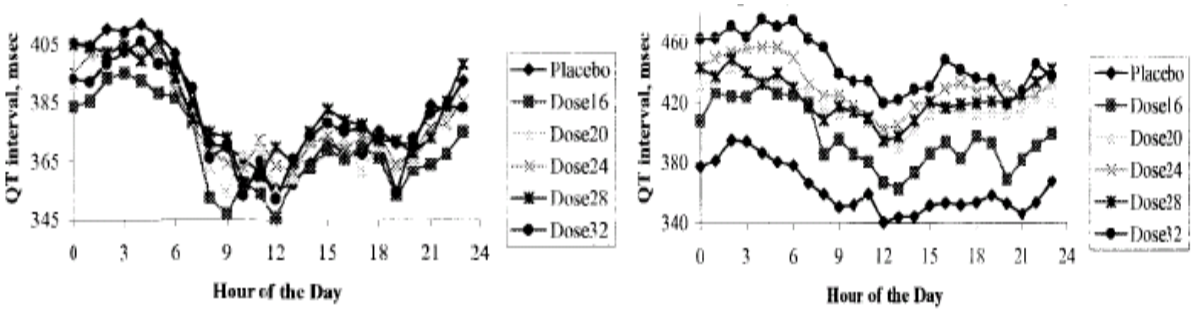
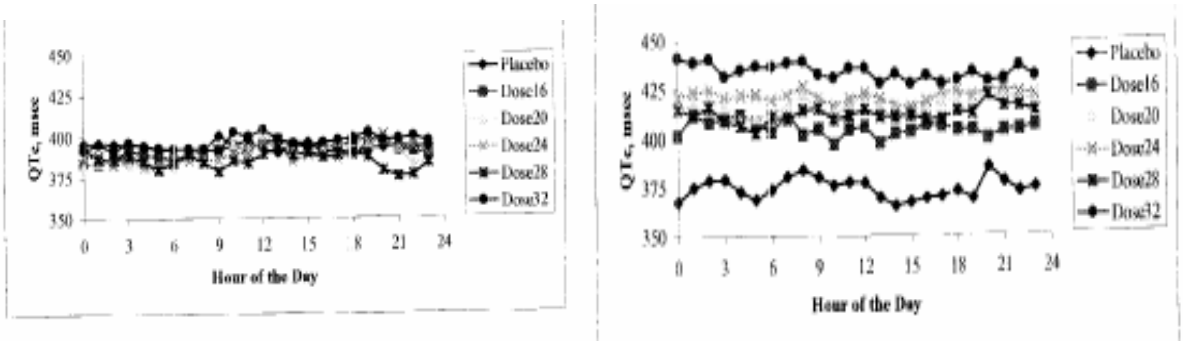


Figure 149: QTc circadian variation at screen (let panel) and on Day 8 (right panel)



Applicant's Safety Analyses

The most frequent adverse event (AE) was atrioventricular (AV) block, occurring in 16 subjects on dronedarone. All these episodes were mild and the subjects recovered. The second most frequent AE was non-sustained ventricular tachycardia (n = 9, five subjects on dronedarone and four subjects on placebo). Three subjects (one on 1400 mg BID and two on 1600 mg) had QTc prolongation (> 450 ms), declared as an AE. Gastro-intestinal disorders appeared at doses of 1000 mg BID and above.

Conclusions/Recommendations

The following findings from Study TDR3549 are acceptable, although the dosages evaluated in this study are more than two times higher than the proposed clinical dosages. These additional, high doses help potentially define the dronedarone exposure (dose)-response relationship.

Pharmacokinetics

- Overall, the dronedarone pharmacokinetic results obtained in Study TDR3549 are similar to those obtained in other dronedarone pharmacokinetic studies.
- Diurnal variation in dronedarone pharmacokinetics occurs

Pharmacodynamics

All conclusions are

- Resting Conditions: PR-, QT- and QTc intervals increased with dronedarone dose and there were trends towards a linear dose-response relationship. T-wave amplitude decreased with dose. Heart rate (HR) tended to decrease with active dronedarone doses; however there was no clear dose-response relationship. Diastolic and systolic blood

pressures (DBP and SBP) were decreased with some active dronedarone doses at some time points; however, the effect was not consistent and there was no clear dose-response relationship.

- Exercise Test: HR was decreased by all active dose groups, and a linear trend in dose-response was evident. Some active dose groups lowered SBP, but dronedarone did not appear to have a consistent DBP lowering effect.
- ECG Holter: Dronedarone significantly prolonged QT- and QTc- intervals and had a moderate effect on prolonging RR-intervals. A linear dose-response relationship was observed for dronedarone and the prolongation of the mentioned ECG parameters. Circadian patterns were evident at screening and after eight days of treatment with respect to the QT and RR intervals.

Overall, the PD results indicate that dronedarone exhibits anti-arrhythmic properties (prolongs repolarization) as well as decreases heart rate.

4.2.35 Dissolution Methodology and Specification

Background on Dronedarone Tablet Formulations*

Several dronedarone formulations were developed: the final formulation (to-be-marketed), 2E5 is identical to the 2E3 formulation used in the pivotal clinical trials. Bioequivalence was demonstrated between 2E2 formulation, used in the Phase 2 trials, and 2E3 formulation. Most of the dissolution method development was carried out with the 2E2 formulation. The use of 2E2 for dissolution development is acceptable because the 2E2 has similar physicochemical characteristics as the 2E5 formulation.

Formulations*

200 mg film- coated tablets, reference 2E2 used for Phase 2B, 400 mg film-coated tablets, reference 2E3 used for Phase 3, reference 2E4 used for primary stability batches, and reference 2E5 to be marketed

Development of the dissolution method

Aim (per applicant)

To select a method applicable to the final 400 mg formulation with ability to discriminate tablet composition and process changes, yet to ensure that 85 % of drug substance will be dissolved in 60 minutes, as recommended for BCS 2 compound.

Reviewer Note on BCS

Specific BCS information was not provided by the applicant or reviewed in detail; however the provided solubility information indicate that dronedarone is a low solubility compound. The *in vivo* data do not demonstrate high permeability: absolute bioavailability < 20 %. The applicant will be asked to provide additional permeability information to support the high permeability designation.

Selection of Dissolution Medium

According to the applicant, the dissolution method development was based on dronedarone physicochemical characteristics; the main characteristic considered was solubility. The solubility of dronedarone hydrochloride in aqueous solutions was obtained in different media and pH as summarized in Table 254 and Figure 150.

Table 254: Dronedarone dissolution in various media

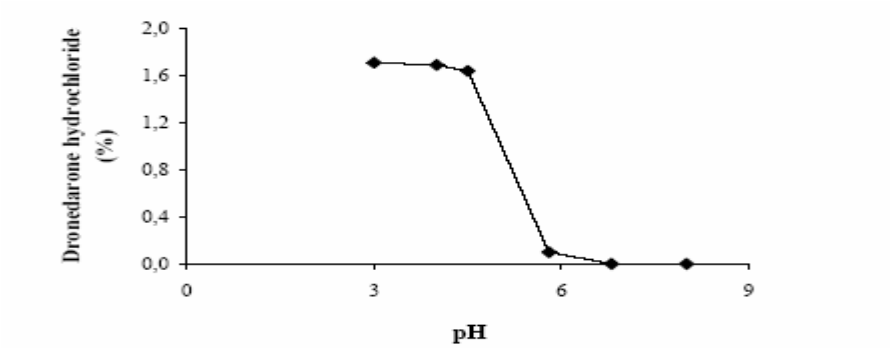
Solvents	Solubility
Water	0.64 mg/ml
Hydrochloride medium (KCl 0.05 M/HCl) pH 1.2	< 0.01 mg/ml
Phosphate medium (KH_2PO_4 0.05 M/NaOH) pH 6.8	< 0.01 mg/ml
Phosphate medium (KH_2PO_4 0.05 M/NaOH) pH 8.0	< 0.01 mg/ml
Ethanol (96 per cent)	113.6 mg/ml
Macrogol 400	13.2 mg/g
Lauroyl macrogolglycerides, type 1500	3.0 [a] mg/g

[a] Solubility determined at 60°C given the semi-solid characteristic of the ingredient at room temperature

The solubility information suggests:

- Dronedarone has low aqueous solubility in strongly acid or basic media; the highest aqueous solubility (~1.7 mg/ml) is obtained over the 3.0- 4.5 pH range in phosphate buffer
- Dronedarone is highly soluble in ethanol

Figure 150: Dronedarone solubility in aqueous solution at 25° C in phosphate buffer systems



Dissolution testing conditions for the 400 mg tablet formulation included the following:

- dissolution media from pH 1 to 6.8
- addition of surfactant
- different apparatus- paddle (varying agitation speed) and basket

Results

1. **Influence of medium pH** on Dissolution of 400 mg tablet (2E3 formulation without coating suspension)

- **Method**: paddle apparatus with rotation speeds of 75 rpm and 100 rpm in 1000 ml of media at 37 ± 0.5° C for 60 minutes.
- **Findings**: as shown in Table 255, the most feasible dissolution results occur over the pH range of 3.5- 4.6; the best buffer systems were the phosphate (pH 4.5) and acetate (pH 4.6) buffers. As expected, dissolution was faster at 100 rpm compared to 75 rpm.

Table 255: Dissolution of 400 mg dronedarone tablets in various media (pH 1 to 7)

Media	pH	Speed (r/min)	Dissolution (%) after 60 min Mean (3 individual values)
HCl 0.1N	1.0	75	7 (7 ; 7; 7)
Acetate buffer	3.5	75	82 (83 ; 94 ; 69)
	4.0		88 (82 ; 84 ; 97)
	4.6		85 (77 ; 93 ; 84)
Phosphate buffer	4.5	75	83 (89 ; 78 ; 81)
	5.7		30 (30 ; 31 ; 28)
	7.0		1 (0 ; 1 ; 1)
Tris acetate buffer	4.5	75	9 (9 ; 9 ; 9)
Acetate buffer	4.6	100	94 (96 ; 93 ; 92)
Phosphate buffer	4.5	100	96 (100 ; 97 ; 90)

Conclusion: dissolution should be carried out in pH 3 to 4.5 media

2. **Effect of Addition of surfactants** on dissolution of 400 mg tablet formulation (2E3, without coating suspension) and 200 mg (base) film-coated tablets, reference 2E2

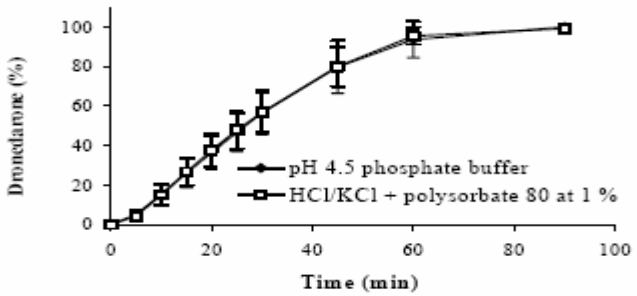
- **Method**: same as for influence of medium with the following exceptions- rotation speed of only 75 rpm used, and media (pH ~ 4.5 only) contained surfactants [(sodium dodecyl sulfate (SDS) or polysorbate 80]. The applicant noted that SDS (0.2 or 0.5 %) could not be used with pH 4.5 phosphate buffer, since a precipitate is formed; similarly a precipitate was formed by the addition of 0.2 or 0.1 % SDS.

- **Findings**: as shown in Table 24, dissolution is not significantly more rapid in media containing a surfactant than those obtained in the media without surfactant.

Table 256: Dissolution of 400 mg dronedarone tablets in pH ~ 4.5 media containing surfactant

Media	pH	Dissolution (%) after 60 min Mean (3 individual values)
Acetate buffer	4.6	85 (77 ; 93 ; 84)
Acetate buffer + SDS 0.2 %	4.6	85 (71 ; 91 ; 91)
Acetate buffer + SDS 0.5 %	4.6	81 (81 ; 73 ; 87)
Phosphate buffer	4.5	83 (89 ; 78 ; 81)
Phosphate buffer + polysorbate 80 at 0.2 %	4.4	83 (86 ; 82 ; 82)
Phosphate buffer + polysorbate 80 at 0.5 %	4.4	76 (79 ; 77 ; 74)

Figure 151: Dissolution profiles of 2E2 formulation in different media

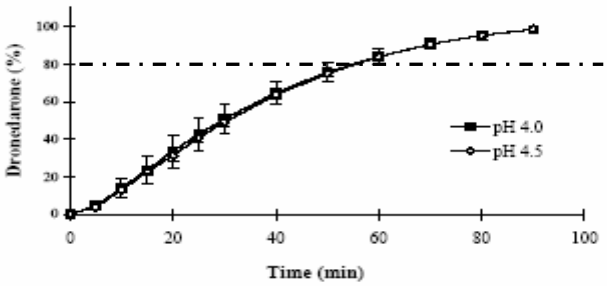


Conclusion: Addition of surfactant does not lead to further optimization of dissolution method (medium); however, addition of surfactant may decease variability in dissolution based on limited data (Dissolution was more variable in Phosphate buffer at pH 4.5 than in Phosphate buffer at pH 4.4 that included 0.2 % polysorbate 80).

3. **Selection of pH**

- **Method:** Same approach as described previously, however only pH 4.0 and 4.5
- **Findings:** As shown in Figure 152, dissolution profiles overlapped at the two studied pHs; however, sink conditions were achieved at pH 4.5.

Figure 152: Comparative dissolution profiles of 400 mg (base) film-coated tablets, reference 2E3 (batch BBU6- 180) at pH 4.0 and pH 4.5 (paddle at 75 rpm)



Conclusion: further dissolution development should be carried out at pH 4.5

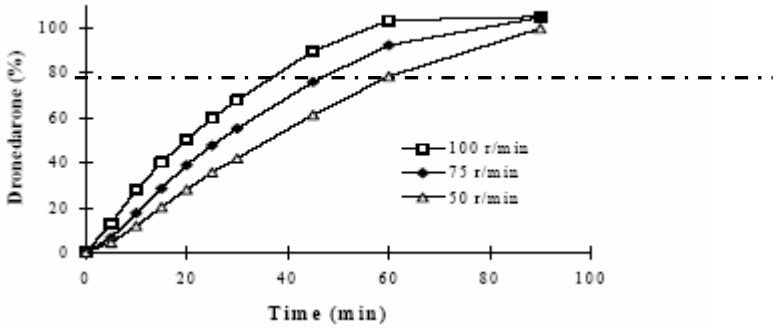
OVERALL SUMMARY ON DISSOLUTION MEDIUM

The medium should be at pH 4.5; this can be achieved using a phosphate buffer system with a surfactant to potentially minimize variability.

Selection of Paddle Speed

- **Method**: Three paddle speeds were tested- 50, 75 and 100 rpm in pH 4.5 phosphate buffer.
- **Findings:** As shown in Figure 153, dissolution increased as paddle speed increased. Dissolution with a paddle stirrer speed of 100 rpm led to about 100 % of dronedarone dissolved after 60 minutes.

Figure 153: Dissolution profile of 2E2 formulation (technical batch 3) at different rotation speeds

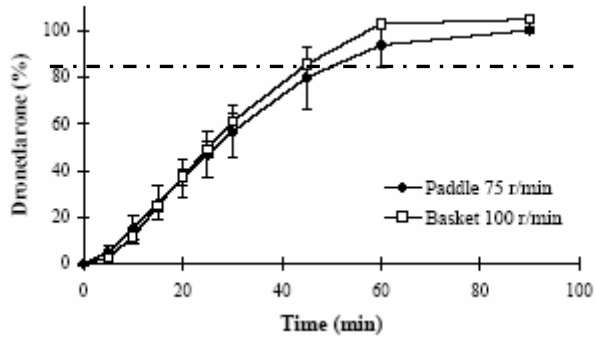


Conclusion: Rotation speed of 75 rpm should be used rather than 100 rpm, to avoid the potential loss of the discriminatory power.

Selection of Apparatus: Paddle vs. Basket

- **Method:** The basket method was compared with the paddle method using 200 mg film-coated tablets, reference 2E2 and pH 4.5 phosphate buffer. The methods were tested under the following conditions (designated as maximal speeds):100 and 75 rpm for the basket and paddle, respectively.
- **Findings:** As shown in Figure 154, dissolution profiles appear comparable

Figure 154: Dissolution profile of 2E2 formulation (batch 99- 02753) with paddle and basket methods



Conclusion: Since paddle and basket methods produced comparable dissolution, the paddle was selected.

Discriminating properties of the dissolution method

According to the applicant, the proposed dissolution method has discriminating ability specifically with respect to quantity of poloxamer and quantity of granulation water. The applicant notes that there was no in vitro/in vivo correlation (IVIVC) for dronedarone formulations (results form, GAR3585 study).

The discriminatory ability of the proposed dissolution method is supported by the following dissolution profiles.

Figure 155: Dissolution profiles of 400 mg (base) tablets (n = 6) containing different quantities of poloxamer 407 (expressed as percent)

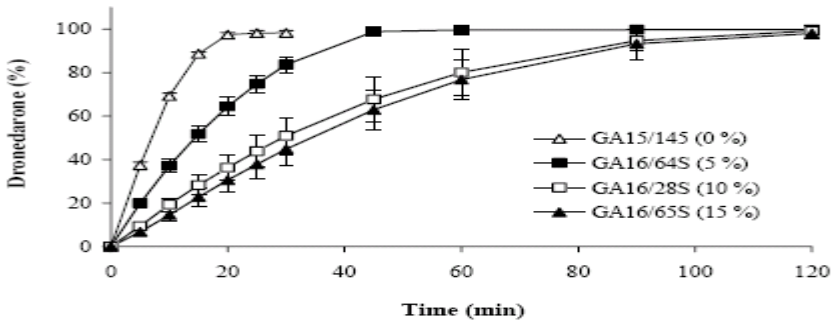
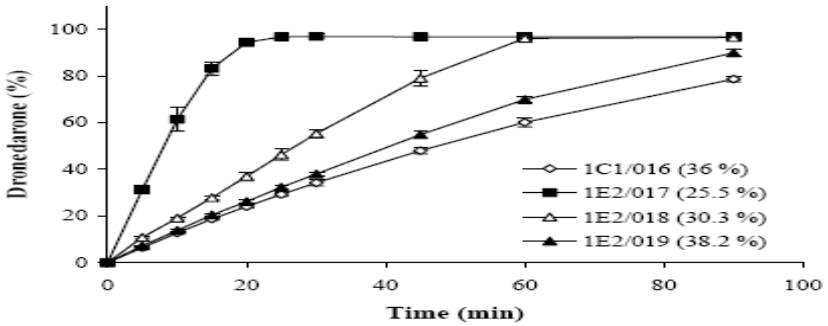


Figure 156: Dissolution profiles* of dronedarone hydrochloride 400 mg (base) tablets (n = 6) manufactured with increasing amounts of granulation water (expressed as %)



* profiles were obtained in media at pH = 4

The figures show that:

- as poloxamer content increased, the initial dissolution rate decreased
- as water content increased, generally, the initial dissolution rate decreased

Reviewer Note on Discriminatory Ability

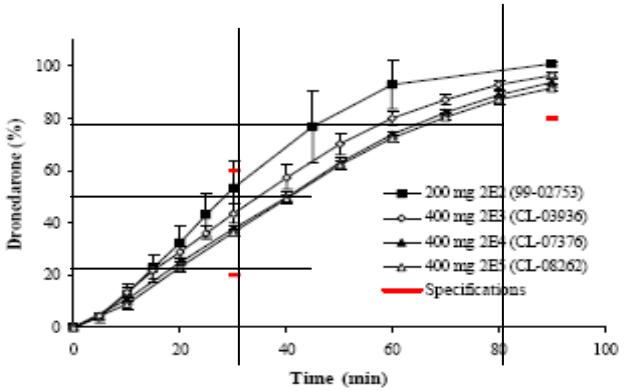
The findings on discriminatory ability are relevant as they cover the range of poloxamer concentrations and amount of granulation water for various dronedarone formulations that were evaluated during drug development. The final formulation has 10 % poloxamer and water is removed during the manufacturing process. For the water study, the pH of the media was 4 rather than the proposed pH = 4.5; however, this is acceptable as dissolution at pH 4 and 4.5 are comparable.

Conclusion: The dissolution method has discriminatory ability with respect to determining the content of poloxamer and granulation water. The main limitation of the study is the lack of assessment of different manufacturing processes, such as varying pressure and temperature. The applicant will be asked to test for these other characteristics.

Comparative dissolution profiles of film-coated tablets*

Comparative dissolution profiles of film-coated tablets are depicted in Figure 157. As shown in the dissolution profiles of all formulations appear generally comparable (formal f2 comparisons were not done). These comparisons appear to support the discriminatory ability of the dissolution method, as separation in profiles is observed between formulations with different particle size (2E2 vs. 2E3, 2E4, and 2E5).

Figure 157: Dissolution profiles of 200 mg (base) film- coated tablets, reference 2E2 and 400 mg (base) film- coated tablets, references 2E3, 2E4 and 2E5 with the pH 4.5 method



* Formulations

200 mg film-coated tablets, reference 2E2 manufactured with fine/medium particle size of drug substance for Phase 2B and

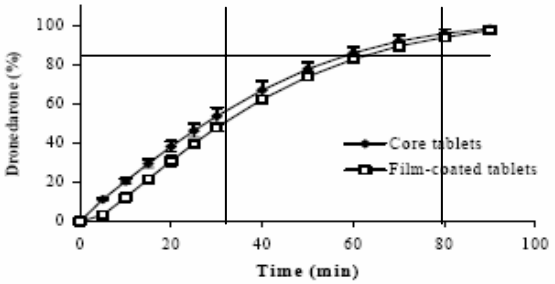
400 mg film-coated tablets, reference 2E3 manufactured with milled drug substance for Phase 3, exhibit similar bioavailability as 2E2.

400 mg film-coated formulation, reference 2E5 intended for marketing has same qualitative and quantitative compositions as the reference 2E3 used in the pivotal Phase 3 efficacy/ safety studies with only a minor punch marking modification.

2E4 formulation was used for primary stability batches,

Compared to core tablets, a slight delay in dissolution is obtained for 400 mg film-coated tablets (reference 2E3); this delay appears due to the dissolution of the coating observed at the beginning of the curve until 5 minutes.

Figure 158: Dissolution profiles of 400 mg (base) core tablets (batch RD35- 08) and film- coated tablets (batch BBU6- 180), reference 2E3 with the pH 4.5 method



Conclusion: Overall, dissolution of to-be-marketed formulation, 2E5 is comparable to that of Phase 2 and Phase 3 formulations. It should be noted that there is no IVIVC for dronedarone tablets; therefore minor dissolution differences do not necessarily result in *in vivo* differences.

PROPOSED DISSOLUTION METHODOLOGY
Apparatus: paddle at 75 rpm; Medium: 1000 ml of pH 4.5 phosphate buffer

Reviewer Comment on Methodology
Based on the information provided, the proposed methodology is acceptable; however, the method may be limited by the overall poor dissolution profile of dronedarone that is related to dronedarone solubility.

PROPOSED DISSOLUTION SPECIFICATION

- Not less than 20 % and not more than 60 % dissolved after 30 min
- Q = 75 after 90 min

Applicant's Rationale for setting Q specifications
The applicant indicates that during the development of the dissolution method they could not routinely obtain 85 % dissolution of the drug substance after 60 minutes; this was mainly due to the poor solubility of the drug substance.

Reviewer Comment on Specification
Based on the poor solubility profile of dronedarone and its putative BCS designation, the setting of a two-point dissolution specification is reasonable. However, the data do not support the applicant's specification proposal. The proposed specifications, particularly Q = 75 after 90 minutes, are not rigid enough to ensure product quality. Per the Dissolution Guidance for Industry, the following criteria should be considered for slowly dissolving or poorly water soluble drugs such as dronedarone to characterize product quality:

- Two point specification: specification at 15 minutes including a dissolution range or window and specification at later time point such as 30, 45, or 60 minutes
- Dissolution profile

Using the two point approach the data suggest (visual inspection of dissolution profiles, particularly in Figure 157 and Figure 158):

- Not less than 20 % and not more than 50 % is dissolved within 20 minutes
- Not less than 70 to 75 % is dissolved within 60 minutes

It is challenging to define the dissolution specification due to incomplete dissolution of dronedarone using the chosen method. Consequently, it is also feasible to use a complete dissolution profile in the interim while the dissolution method is optimized further.

Reviewer's Dissolution Recommendations

- Dissolution Method: applicant's proposal is acceptable
- Dissolution specification: 1) Not less than 25 % and not more than 50 % is dissolved within 30 minutes 2) Q = 80 % in 80 minutes

Additionally, the applicant should evaluate the discriminatory ability of the dissolution method when different manufacturing conditions, such as varying temperature and pressure conditions, are used.

APPENDIX

Composition of dronedarone hydrochloride 400 mg (base) film-coated tablets (reference 2E5)

Ingredients	Compendial grade	Function	Unit quantity (mg/tablet)	% (w/w)
CORE				
Drug substance				
Dronedarone hydrochloride (a)	In-house monograph	Active substance	426.00 (b)	65.54
Excipients				
Hypromellose (6 mPa)	Ph. Eur.-USP	Binder	26.00	4.00
Maize starch	Ph. Eur.-NF	Diluent-Disintegrant	45.50	7.00
Crospovidone (type A)	Ph. Eur.-NF	Disintegrant	65.00	10.00
Poloxamer 407	Ph. Eur.-NF	Solubilizing agent	40.00 (c)	6.15
Lactose monohydrate (d)	Ph. Eur.-NF	Diluent	41.65	6.41
Colloidal anhydrous silica	Ph. Eur.-NF	Flow aid	2.60	0.40
Magnesium stearate (e)	Ph. Eur.-NF	Lubricant/Anti-adherent	3.25	0.50
Purified water (f)	Ph. Eur.-USP	Granulation solvent	-	-
Core mass			***650***	***100***
COATING/POLISHING				
Hypromellose (6 mPa.s)	Ph. Eur.-USP	Film agent	7.25	72.50
Titanium dioxide	Ph. Eur.-USP	Opacifier	1.00	10.00
Macrogol 6000	Ph. Eur.-NF	Plasticizer	1.75	17.50
Purified water (f)	Ph. Eur.-USP	Coating solvent	-	-
Film-coating mass			***10***	***100***
Carnauba wax	Ph. Eur.-NF	Polishing agent	Traces	-
Film-coated tablet mass			***660***	

(a) The strength of the tablet is expressed as base (dronedarone)
(b) Corresponds to 400 mg of the base
(c) Corresponds to 10 % of the dronedarone quantity (400 mg)
(d) BSE free
(e) From vegetable origin
(f) Removed during manufacture

4.3 Consult Review (Pharmacometric)

Pharmacometrics Review

NDA:	21-913
Compound:	Dronedarone HCl (Multac)
Submission Dates:	10 June 2005
Sponsor:	Sanofi Aventis
PM Reviewer:	Christine Garnett, PharmD
PM Team Leader and Secondary Reviewer	Joga Gobburu, PhD

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1 EXECUTIVE SUMMARY

Dronedarone (SR33589B) is a new anti-arrhythmic agent belonging to the benzofurane class of anti-arrhythmic compounds that also includes amiodarone. The proposed indications are rhythm and rate control in patients with atrial fibrillation or atrial flutter and to decrease ventricular rate. The sponsor has proposed one dosage strength, 400 mg BID, for both indications and in all subpopulations of patients.

Recommendation

After reviewing the data collected in the DAFNE clinical trial, a concentration (dose)-response relationship for the primary endpoint (time to AF recurrence) could not be established. Possible reasons for the lack of a concentration (dose)-response includes concomitant use of beta blockers and higher dropout rate in the 1600 mg dose group due to adverse events.

Comments to Sponsor

Please forward the following comments to the sponsor which pertains to the population pharmacokinetic analysis of dronedarone:

- In future submissions, any concentrations and/or subjects that have been excluded from the analysis should be maintained in the datasets. For this analysis, the sponsor identified 123 concentrations (from 10 subjects) as outliers and excluded these observations from the dataset.

Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The sponsor submitted one dose-ranging trial, DAFNE (DRI13550). This was a multinational, multicenter, double-blind, placebo-controlled study. Three doses of dronedarone, 800, 1200, and 1600 mg daily (b.i.d.), were tested in the maintenance of sinus rhythm in patients undergoing cardioversion for AF. The primary endpoint was time to AF recurrence.

There was no trend for an increasing or decreasing concentration (dose)-response relationship for the primary endpoint. The longest median time was 60 days, observed in the 800 mg group, compared to 5 days in the placebo group. Covariates structural heart disease and duration of current AF episode at baseline did not have significant effects. Exploratory analyses of patient covariates showed that beta blockers increased the time to AF recurrence. This concomitant medication was unevenly distributed in the primary analysis population (PPM, see Figure (10.1)1) with approximately 40% of subjects in the placebo and 800 mg groups and approximately 20% in the 1200 and 1600 mg groups taking a beta blocker. Furthermore, there were more subjects in the 1600 mg dose group who dropped out of the study due to adverse events (gastrointestinal-related). This may have also contributed to the lack of a concentration (dose)-response.

There was a trend for lower ventricular rate at AF recurrence with higher concentrations of dronedarone. This relationship is illustrated in Figure 4. In addition, the sponsor showed a statistically significant lower heart rate at recurrence compared to placebo in each of the three treatment groups.

In the DAFNE trial the incidence and severity of treatment-emergent diarrhea was dose related, with the highest dose group (1600 mg) having the highest incidence and intensity of diarrhea. Diarrhea does not, however, appear to be related to plasma concentrations of dronedarone. There

was no difference in trough concentrations of dronedarone for subjects with and without diarrhea (see Figure 5).

Treatment with dronedarone caused an elevation of serum creatinine. In DAFNE creatinine clearance is reduced throughout the study (Days 1-150) in the treatment groups. After treatment is discontinued for 10 days, creatinine clearance returns to baseline.

A population analysis of pooled concentration-time data from three phase 3 clinical trials showed that the data followed a two-compartment model with first order elimination and absorption. Data for this analysis represented steady state concentrations from a 800 mg daily dose (400 mg bid) in 73% of the study population. It has been shown in other studies that the pharmacokinetics were nonlinear between 800 mg to 1600 mg daily doses of dronedarone.

Mean population parameter parameters for CL/F and V/F were 290 L/h for a 83 kg male and 3140 L, respectively. Between-subject variability, expressed as %CV, in CL/F and V/F were 30% and 110%. The residual variability, expressed as a standard deviation, was 14 ng/mL.

The significant covariates explaining between-subject variability in CL/F were sex, weight and age. There were no significant covariates for V/F. In this dataset, the influence of renal function, congestive heart failure degree, CYP3A4 inhibitors co-administration (mainly moderate CYP3A4 inhibitors, since strong inhibitors were contraindicated), race or study on the model parameters was not statistically significant.

The model was not used by the sponsor to justify the dose or to make labeling statements.

Christine Garnett, Pharm.D. _____
RD/FT Initialed by Joga Gobburu, Ph.D. _____

cc: NDA 21-913, HFD-120, HFD-860 (Garnett, Marroum, Kumi, Gobburu), Central Documents Room (CDR-Biopharm)

2 INTRODUCTION

The sponsor submitted a NDA for a new chemical entity, dronedarone HCl. Dronedarone (SR33589B) is a new anti-arrhythmic agent belonging to the benzofurane class of anti-arrhythmic compounds that also includes amiodarone. There are two main physical-chemical differences that distinguish dronedarone from amiodarone: 1) the absence of iodine substituents on the benzofurane ring that was expected to eliminate thyroid side effects, and 2) the adjunction of a methane-sulfonamyl group that was expected to make the drug less lipophilic and therefore less subject to tissue accumulation (a probable mechanism of amiodarone organ toxicity).

The sponsor is seeking two indications for dronedarone: rhythm and rate control in patients with atrial fibrillation or atrial flutter and to decrease ventricular rate. The sponsor has proposed one dosage strength, 400 mg BID, for both indications and in all subpopulations of patients.

Data to support these indications came from four controlled clinical trials which are summarized in the following table. The DAFNE study was the only dose-ranging trial. The sponsor also conducted an additional controlled clinical trial in patients with severe congestive heart failure, EFC4966/ANDROMEDA, which is not included in the table.

Table (2.7.3.1) 1 - Adequate and well-controlled studies providing evidence of the efficacy of dronedarone in the proposed indications

Study Identifier	Study design	Indication	
		Maintenance of Sinus Rhythm	Control of Ventricular Rate
DRI3550/DAFNE	Maintenance of normal sinus rhythm after cardioversion for atrial fibrillation – dose-ranging	supportive	supportive
EFC3153/EURIDIS	Maintenance of normal sinus rhythm after conversion of AF/AFL	confirmatory	supportive
EFC4788/ADONIS	Maintenance of normal sinus rhythm after conversion of AF/AFL	confirmatory	supportive
EFC4508/ERATO	Control of ventricular rate during AF	--	confirmatory

The focus of this review is to address the following key questions based on the submitted exposure-response data from the DAFNE clinical trial:

1. Is there a concentration-response relationship for the effectiveness endpoints 1) time to AF recurrence and 2) ventricular rate?
2. Is there a concentration-response relationship for treatment-emergent diarrhea?
3. Does elevated serum creatinine return to baseline after dronedarone treatment is discontinued?

The sponsor also submitted a population pharmacokinetic analysis of data collected in ADONIS, EURIDIS, and ANDROMEDA clinical trials. Results from this analysis are considered by the reviewer to only be supportive since the analysis was not used to support the dose nor used to in the label. A brief description of the population pharmacokinetic model is also included in this review.

3 QUESTION-BASED REVIEW

3.1 Is there a concentration-response relationship for the effectiveness endpoints 1) time to AF recurrence and 2) ventricular rate?

To assess whether there is a concentration–response relationship for the primary endpoint, mean individual trough concentration values from each dose group (Figure 1) were pooled and stratified into concentration quartiles (Figure 2). There were 15 subjects with missing trough concentrations; 4 in the 800 mg, 6 in the 1200 mg, and 5 in the 1600 mg groups.

Figure 1. Distribution of mean individual trough concentrations by dose group. The lines represent the mean ± 1 SD of trough concentrations from the combined phase 3 clinical trials (ADONIS and EURIDIS) where subject received 400 mg bid dronedarone.

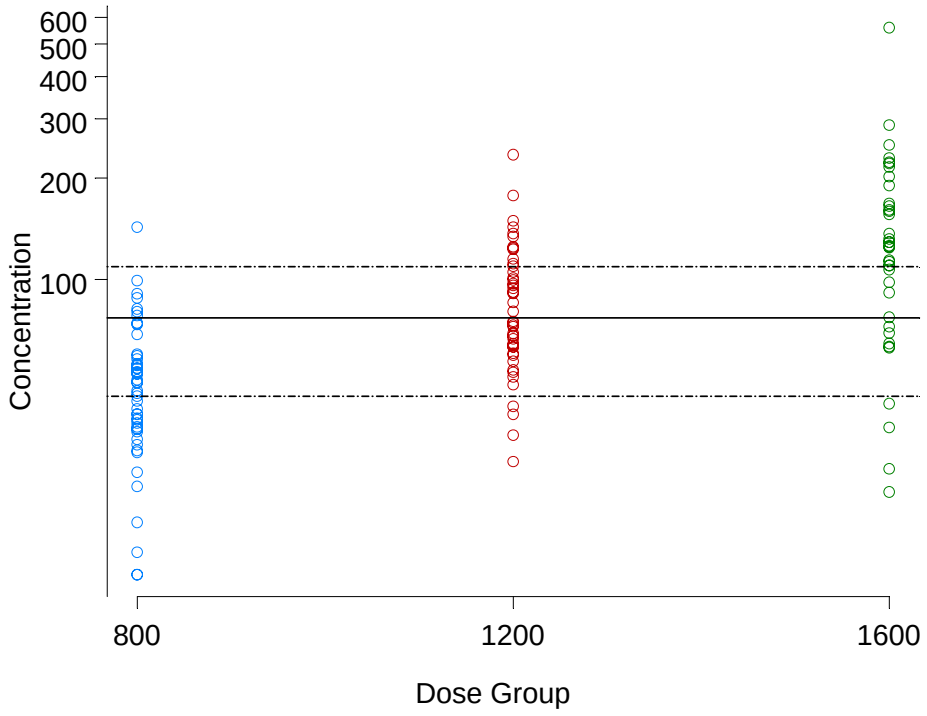
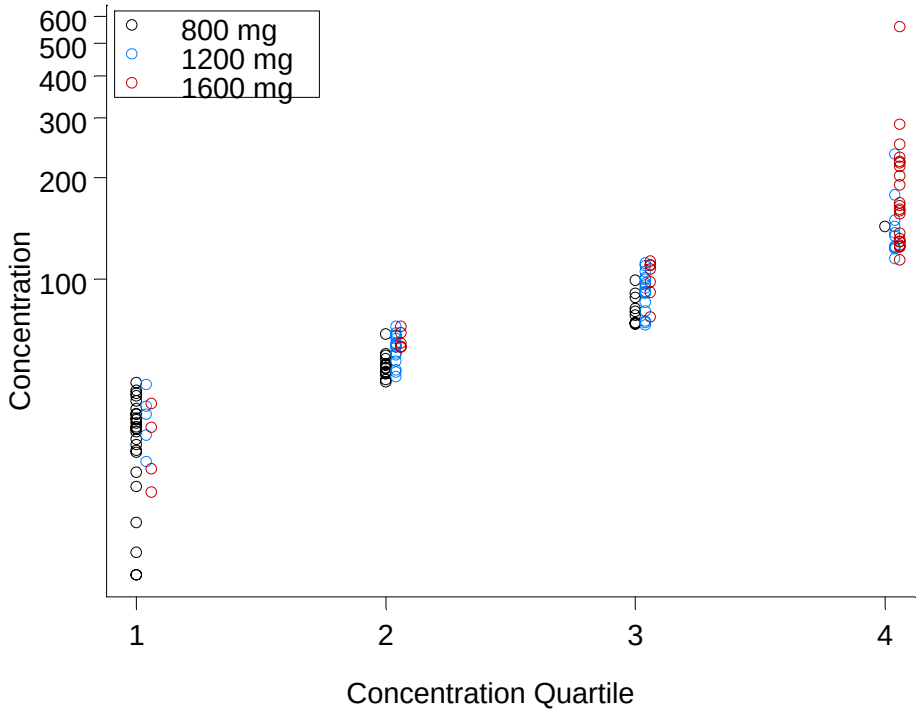


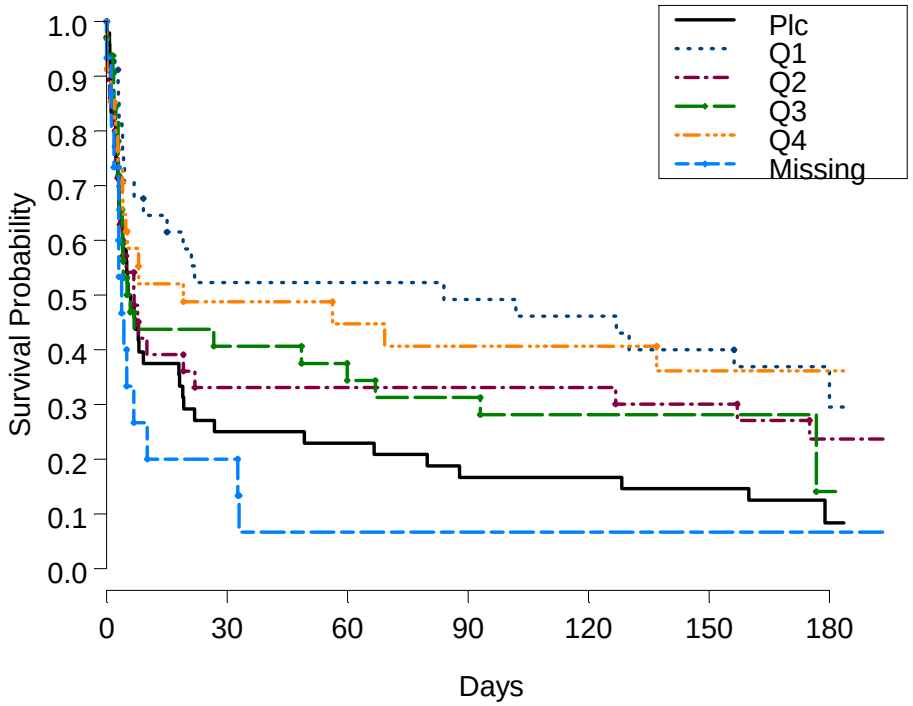
Figure 2. Distribution of mean individual trough concentrations by quartile.



Kaplan Meier survival curves for time to AF recurrence (days) by concentration quartile is shown in Figure 3. There was no trend for increasing or decreasing concentration-response relationships. The median time to recurrence was longest for the group of subjects with the lowest concentrations (Q1); median = 84 days.

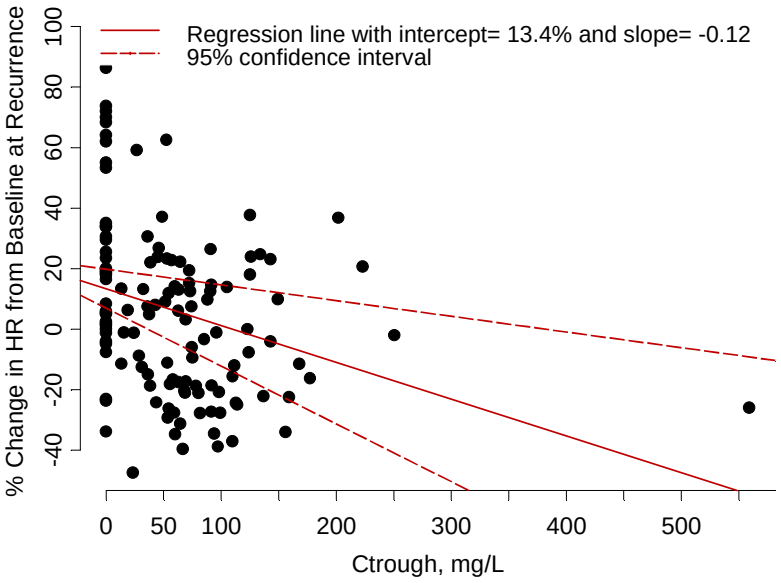
Fourteen of the 15 subjects (93.3%) with missing concentration experienced AF recurrence. The median (range) of event times for this group were 3.4 (.003 to 33) days. Therefore, the majority of subjects (12/14, 86%) in this group had an event prior to the scheduled pharmacokinetic sample on Day14.

Figure 3. Kaplan-Meier Survival Curves by Concentration Quartile (Q1 = 13.3-49.5, Q2 = >9.5-72.4, Q3 = >2.4-113.5, and Q4 = >113.5-559)



To assess the concentration-response relationship for ventricular rate control at recurrence, a scatter plot of percent change in heart rate from baseline vs. trough concentration is shown in Figure 4. For this plot, baseline was defined as the ventricular rate (measured by ECG) during the initial AF episode prior to dronedarone treatment. There was a trend for lower heart rate at AF recurrence with higher trough concentrations. Subjects with missing trough concentrations were excluded from the analysis.

Figure 4. Ventricular Rate Control vs. Trough Concentration



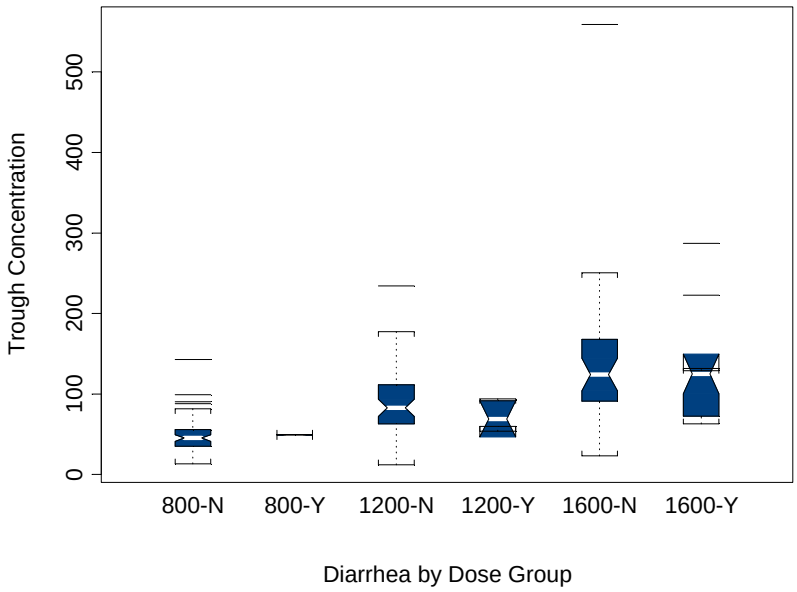
3.2 Is there a concentration-response relationship for treatment-emergent diarrhea?

In the DAFNE trial the incidence and severity of treatment-emergent diarrhea was dose related, with the highest dose group (800 mg bid) having the highest incidence and intensity of diarrhea (Table 1). Diarrhea does not, however, appear to be related to plasma concentrations of dronedarone. There was no difference in trough concentrations of dronedarone for subjects with and without diarrhea (Figure 5).

Table 1. Overview of Diarrhea TEAE

Intensity	Placebo N=66	800 mg N=76	1200 mg N=66	1600 mg N=62	Total Drug N=204
Total	2 (3.0)	2 (2.6)	5 (7.6)	17 (27.4)	24 (11.8)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.8)	3 (1.5)
Moderate	0 (0.0)	1 (1.3)	1 (1.5)	5 (8.1)	7 (3.4)
Mild	2 (3.0)	1 (1.3)	4 (6.1)	9 (14.5)	14 (6.9)
SAE	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)

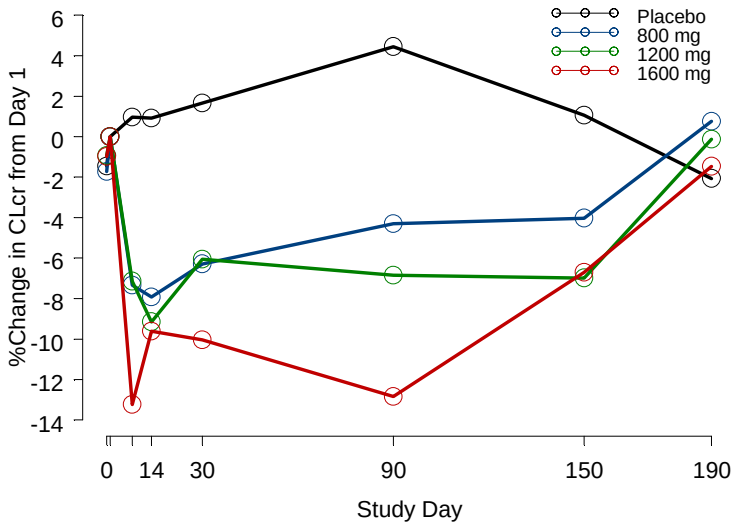
Figure 5. Boxplots of Trough Concentrations for Subjects With (Y) and Without (N) Diarrhea by Dose Group



3.3 Does elevated serum creatinine return to baseline after dronedarone treatment is discontinued?

Treatment with dronedarone caused an elevation of serum creatinine. Figure 6 shows that creatinine clearance is reduced throughout the study (Days 1-150). After treatment is discontinued for 10 days, serum creatinine returns to baseline. This is illustrated in Figure 6 by Day 190 which represents the last patient visit at 10 days after stopping study drug.

Figure 6. Mean Percent Change in CLcr by Study Visit



4 DAFNE CLINICAL TRIAL (DRI13550)

4.1 Study Design

This was a multinational, multicenter, double-blind, placebo-controlled, dose-ranging study, referred to as DAFNE (Dronedarone Atrial FibrillatioN study after Electrical cardioversion). Three doses of dronedarone, 800, 1200, and 1600 mg daily (b.i.d.), were tested in the maintenance of sinus rhythm in patients undergoing cardioversion for AF. A Safety Committee blinded to treatment allocation (the Chairman only had access to an unblinded treatment list) was formed to monitor patient safety. The overall study design and its duration are summarized in the following figure.

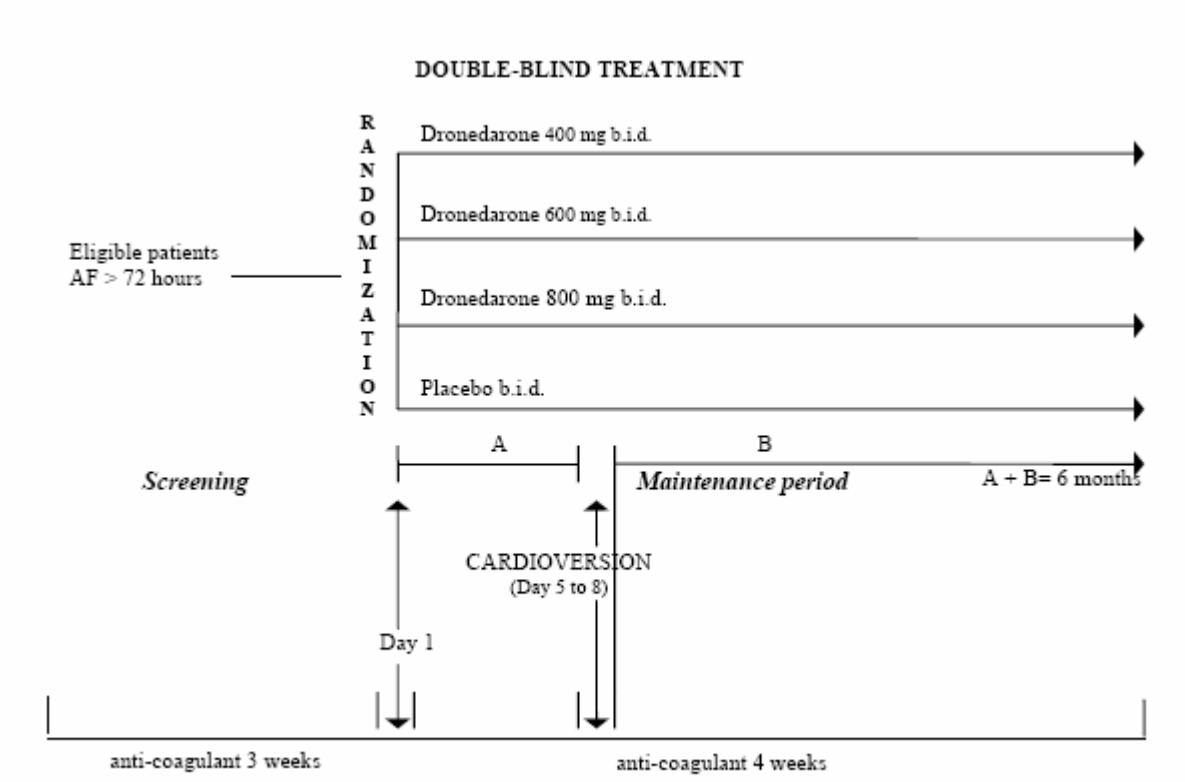


Figure (9.1) 1 - Study Design

Included in the study were adult male and female patients who currently have persistent atrial fibrillation as defined as duration of more than 72 hours but less than 12 months. The AF could be unassociated with structural heart disease (lone AF) or associated with ischemic, hypertensive, hemodynamically insignificant primary valvular heart disease or dilated cardiomyopathy (left ventricular ejection fraction had to be ≥35%). Patients were excluded if they had NYHA class III and IV congestive heart failure, left ventricular ejection fraction <35%, QT > 500 ms, and were taking concomitant treatments with strong CYP3A4 inhibitor drugs. The primary endpoint was time to first recurrence of AF (duration > 10 minutes) in patients converted to sinus rhythm, based on transtelephonic ECG monitoring and 12-lead ECG monitoring. Secondary endpoints included the ventricular rate at time of recurrence and the number of subjects converted to sinus rhythm.

4.2 Results

4.2.1 Subject Disposition

The following table shows the number of subjects who were enrolled and completed the trial. More subjects in the 1600 mg dose group withdrew from the study than from the other dose groups. Treatment emergent adverse events were the most common reason for study withdrawal. Gastro-intestinal system disorders, leading to 9 (4.4%) patient discontinuations, were the most frequently reported; this was linked to frequency in the 1600 mg group in particular, in which 7 patients discontinued.

Table (10.1.1) 1 - Number (%) of Patients by Reasons for End of Treatment during the Whole Study and Maintenance Period

Study period	Reason	Placebo n (%)	800 mg n (%)	1200 mg n (%)	1600 mg n (%)	P- value[a]
Whole study	Patients entered	66	76	66	62	
	Adverse event	0 (0.0)	3 (3.9)	5 (7.6)	15[b] (24.2)	
	Patient request	1 (1.5)	0 (0.0)	1 (1.5)	0 (0.0)	
	Protocol deviation	0 (0.0)	2 (2.6)	0 (0.0)	2 (3.2)	
	Other[c]	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	
	Total	1 (1.5)	5 (6.6)	6 (9.1)	18 (29.0)	<0.0001
	Completed[d]	65	71	60	44	
	Cardioversion failure	17	16	7	11	
	Lack of efficacy	40	32	35	23	
	Prescribed dosing	8	23	18	10	
Maintenance	Patients entered	49	56	56	44	
	Adverse event	0 (0.0)	1 (1.8)	3 (5.4)	10 (22.7)	
	Patient request	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Other[c]	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	
	Total	1 (2.0)	1 (1.8)	3 (5.4)	11 (25.0)	
	Completed[d]	48	55	53	33	
	Lack of efficacy	40	32	35	23	
	Prescribed dosing	8	23	18	10	

a: Fisher's exact test on the total number of patients who ended treatment prematurely.
b: Including 1 non-treatment emergent AE (Patient No. 2202007)
c: Other = in spite of recurrence, patient felt better under treatment and continued for a period of time; he was eventually withdrawn in respect of protocol.
d: Patients withdrawn for conversion failure/lack of efficacy and those completing prescribed dosing were considered completed.

4.2.2 Analysis Populations

The sponsor identified four efficacy analysis populations: ITT, PP, ITTM, and PPM. The following diagram describes each of the analysis populations. This review will focus on the 199 subjects in the PPM population.

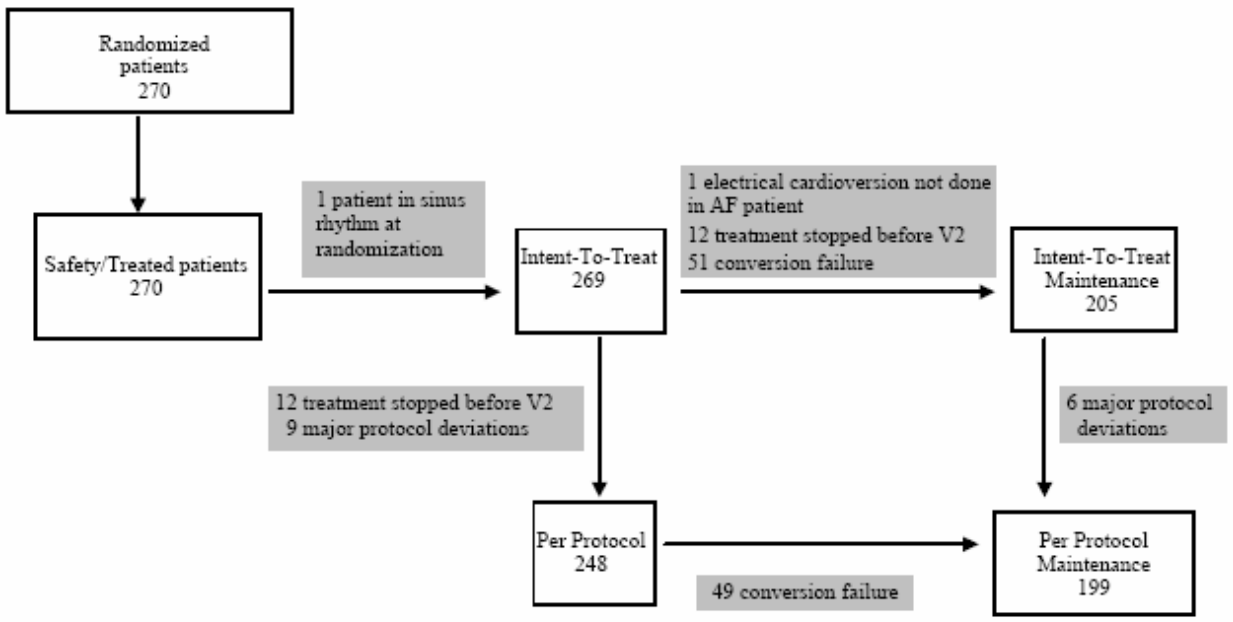


Figure (10.1) 1 - Analysis Population Flow Chart

4.2.3 Subject Demographics and Other Baseline Characteristics

A summary of patient demographics, cardiovascular history, duration of baseline AF episodes, and left ventricular ejection fraction for the PPM population are shown in Tables (10.4.1)3, (10.4.2)2, (10.4.3)2, and (10.4.4)2, respectively. A statistically significant difference in the duration of AF episodes (p=0.0133) was detected among group. All other baseline characteristics were similar across treatment groups.

With respect to concomitant medications, more subjects in the placebo and 800 mg dose group were taking beta blockers (Table (2.7.3.3.1.2)6). There were similar percentages of patients taking anticoagulant therapy, digoxin, and calcium channel blockers.

Table (10.4.1) 3 - Demographic Characteristics in Primary Efficacy Analysis Population: Per Protocol Maintenance

Demographic Characteristics	Placebo	800 mg	1200 mg	1600 mg	Total	p-value[a]
Age (yr)						
N	48	54	54	43	199	0.7047
Mean (SD)	65.6 (8.4)	64.0 (13.0)	63.7 (8.7)	62.3 (11.7)	63.9 (10.6)	
Range	46 to 80	24 to 81	39 to 78	29 to 79	24 to 81	
Age by class-n (%)						
18-40yr		4 (7.4)	1 (1.9)	3 (7.0)	8 (4.0)	
40-65yr	19 (39.6)	20 (37.0)	29 (53.7)	19 (44.2)	87 (43.7)	
65-75yr	20 (41.7)	18 (33.3)	14 (25.9)	17 (39.5)	69 (34.7)	
≥75yr	9 (18.8)	12 (22.2)	10 (18.5)	4 (9.3)	35 (17.6)	
Weight (kg)						
N	48	54	54	43	199	0.5905
Mean (SD)	80.82 (12.99)	81.80 (13.78)	83.38 (16.65)	84.35 (14.41)	82.54 (14.52)	
Range	54.5 to 120.0	54.0 to 119.9	54.0 to 136.0	62.0 to 135.0	54.0 to 136.0	
Height (cm)						
N	47	52	54	43	196	0.9629
Mean (SD)	172.87 (8.77)	170.37 (9.51)	171.11 (8.83)	171.51 (9.70)	171.42 (9.17)	
Range	146.0 to 190.0	150.0 to 200.0	141.0 to 187.0	156.0 to 209.0	141.0 to 209.0	
Missing	1	2	0	0	3	
Race – n (%)						
Caucasian	48 (100.0)	54 (100.0)	54 (100.0)	43 (100.0)	199 (100.0)	
Gender – n (%)						
Male	38 (79.2)	31 (57.4)	38 (70.4)	29 (67.4)	136 (68.3)	0.1297
Female	10 (20.8)	23 (42.6)	16 (29.6)	14 (32.6)	63 (31.7)	

a: ANOVA on age, height and weight, Fisher's exact test on gender

Table (10.4.2) 2 - Number (%) of Patients by Presence of Structural Heart Disease and Cardiovascular History in Primary Efficacy Analysis Population: Per Protocol Maintenance

Variable	Placebo N=48 n (%)	800 mg N=54 n (%)	1200 mg N=54 n (%)	1600 mg N=43 n (%)	Total N=199 n (%)	p-value[b]
Structural heart disease[a]	32 (66.7)	28 (51.9)	30 (55.6)	25 (58.1)	115 (57.8)	0.4864
Ischemic heart disease	13 (27.1)	11 (20.4)	10 (18.5)	9 (20.9)	43 (21.6)	
Congestive heart failure	11 (22.9)	8 (14.8)	13 (24.1)	5 (11.6)	37 (18.6)	
Valvular dysfunction	24 (50)	19 (35.2)	17 (31.5)	16 (37.2)	76 (38.2)	
Cardiac arrhythmias	3 (6.3)	8 (14.8)	6 (11.1)	5 (11.6)	22 (11.1)	
Arterial hypertension	27 (56.3)	28 (51.9)	27 (50)	19 (44.2)	101 (50.8)	

a: Includes congestive heart failure and/or ischemic heart disease and/or valvular dysfunction
b: Fisher's exact test

Table (10.4.3) 2 - Duration of Current Atrial Fibrillation Episode in Days in Primary Efficacy Analysis Population: Per Protocol Maintenance

Statistics	Placebo	800 mg	1200 mg	1600 mg	Total	p-value[a]
N	48	54	54	43	199	0.0177
Mean	76.1	116.8	90.4	111.3	98.7	
SD	60.3	70.3	71.2	93.8	75.3	
Median	57.5	105.0	72.5	72.0	76.0	
Minimum	9	18	4	7	4	
Maximum	311	283	343	328	343	

a: Kruskal Wallis test

Table (10.4.4) 2 - Left Atrium Measure and Left Ventricular Ejection Fraction in Primary Efficacy Analysis Population: Per Protocol Maintenance

	Placebo	Dronedarone 800 mg	Dronedarone 1200 mg	Dronedarone 1600 mg
	(N=48)	(N=54)	(N=54)	(N=43)
Left atrium diameter				
n	47	50	50	40
Mean	46.0	44.3	45.1	45.1
SD	9.5	6.3	6.0	6.3
Median	45.0	44.5	45.5	45.5
Minimum	25	26	30	33
Maximum	75	60	63	62
Missing	1	4	4	3
Left ventricular ejection fraction				
n	48	53	53	42
Mean	56.8	55.0	53.8	54.7
SD	10.1	8.8	12.2	10.7
Median	59.5	55.0	55.0	55.5
Minimum	36	35	35	35
Maximum	73	73	88	77
Missing	0	1	1	1

PGM= SR33589/DRI3550/NDAMHR/fr52583/PGM RPT/i8DaphLeftAtrium.sas OUT= OUTPUT/I4DAPHPPM Left.html (03JAN2005 - 15:50)

Table (2.7.3.3.1.2) 6 - Number (%) of patients according to baseline intake of specific medications - Per Protocol Maintenance population (DRI3550/DAFNE)

	Placebo (N=48)	Dronedarone 400 mg BID (N=54)	Dronedarone 600 mg BID (N=54)	Dronedarone 800 mg BID (N=43)
Oral anticoagulant	46 (95.8%)	50 (92.6%)	50 (92.6%)	40 (93.0%)
ACE inhibitors or A II receptor antagonists	21 (43.8%)	21 (38.9%)	22 (40.7%)	12 (27.9%)
ACE inhibitors	19 (39.6%)	16 (29.6%)	17 (31.5%)	10 (23.3%)
A II receptors antagonist	2 (4.2%)	5 (9.3%)	5 (9.3%)	2 (4.7%)
Digitalis	15 (31.3%)	20 (37.0%)	19 (35.2%)	18 (41.9%)
Digoxin	15 (31.3%)	19 (35.2%)	19 (35.2%)	18 (41.9%)
Digitalin	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Beta blocking agents	21 (43.8%)	24 (44.4%)	13 (24.1%)	9 (20.9%)
Beta blocking agents (except Sotalol)	21 (43.8%)	22 (40.7%)	13 (24.1%)	8 (18.6%)
Diuretics	9 (18.8%)	14 (25.9%)	17 (31.5%)	12 (27.9%)
Diuretics (other than spironolactone)	9 (18.8%)	13 (24.1%)	17 (31.5%)	12 (27.9%)
Spironolactone	1 (2.1%)	2 (3.7%)	1 (1.9%)	0 (0.0%)
Statins	6 (12.5%)	13 (24.1%)	7 (13.0%)	6 (14.0%)
Metabolized by CYP3A4	5 (10.4%)	11 (20.4%)	7 (13.0%)	5 (11.6%)
Not metabolized by CYP3A4	1 (2.1%)	2 (3.7%)	0 (0.0%)	1 (2.3%)
Chronic antiplatelet therapy	3 (6.3%)	1 (1.9%)	2 (3.7%)	2 (4.7%)
NSAID	2 (4.2%)	0 (0.0%)	3 (5.6%)	1 (2.3%)
Moderate inhibitors of CYP3A4	1 (2.1%)	0 (0.0%)	1 (1.9%)	0 (0.0%)
Calcium antagonists with heart rate lowering effects (a)	1 (2.1%)	0 (0.0%)	1 (1.9%)	0 (0.0%)

PGM= SR33589/OVERALL/ISEMHR/BS/PGM RPT/i4DAFbasemed.sas OUT= OUTPUT/I4DAF basemedPPM.html (23MAR2005 - 16:19)

(a) Restricted to diltiazem, verapamil and bepridil.

NSAID=nonsteroidal anti-inflammatory drug.

4.2.4 Efficacy

4.2.4.1 Primary Endpoint

The primary endpoint was time to first recurrence of AF from conversion. Kaplan-Meier curve is shown in Figure (11.1.1)1 and Table (11.1.1)1. No dose effect was observed in the primary analysis. Median values for the time to AF were 5.32, 59.92, 4.31, and 5.18 days for the placebo, 800, 1200 and 1600 mg dose groups. Covariate analysis on the presence of structural heart disease and duration of current AF episodes at baseline did not reveal significant effects. Time to AF recurrence in the 800 mg group represented a risk reduction of 55%.

Figure (11.1.1)1. Kaplan-Meier Plot for Time to First Recurrence of AF from Conversion [reviewer's figure from independent analysis of data]

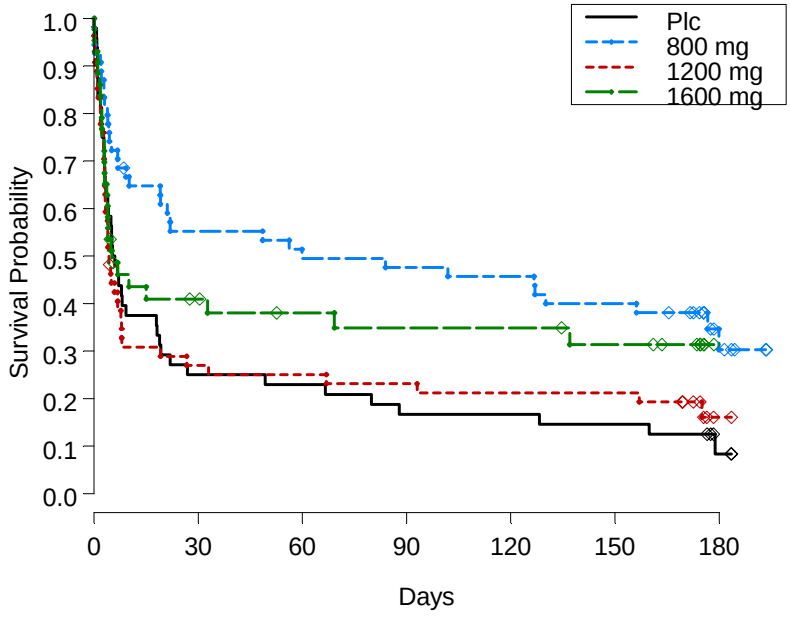


Table (11.1.1) 1 - Time to Atrial Fibrillation Recurrence (Days) - Primary Analysis on the Per Protocol Maintenance Population

Parameters	Statistics	Placebo N=48	800 mg N=54	1200 mg N=54	1600 mg N=43	Cox's model results
Time to AF recurrence						
Duration in sinus rhythm (days)	Median	5.32	59.92	4.31	5.18	Dose effect p=0.7188
	Minimum	0.028	0.059	0.002	0.089	Covariate SHD p=0.0737
	Maximum	183.5	193.6	183.5	178.5	Covariate AFD p=0.2943
Risk versus placebo	Risk ratio		0.45	0.95	0.68	
	95% CI		0.28 / 0.72	0.62 / 1.45	0.42 / 1.11	

SHD = presence of structural heart disease, AFD = duration of the current AF episode
pgm=DRI3550//biom/clinic/SR33589/DRI3550/CSR/biere/program/r_ped04.sas/10OCT2001 8:04

The sponsor performed an exploratory analysis using a stepwise Cox model to further evaluate the lack of a dose response relationship. The covariates used in this analysis were AF duration at randomization, previous ECV, previously treated, first AF episode, age, sex, CHR antecedent, ischemic heart disease antecedent, valvular dysfunction antecedent, left atrium size, shortening fraction, ejection fraction, digoxin, beta blocker, left CHF baseline, weight, and NYHA class. The only significant covariates were beta blockers and ejection fraction. Beta blockers increased the time to recurrence and, unexpectedly, ejection fraction decreased the time to recurrence.

When adjusted to these covariates, the dose effect was still not significant, and the comparison between placebo and 800 mg remained highly significant.

Table (11.1.1) 3 - Risk Ratio and Associated p-value - Exploratory Analysis of Covariates on Time to Atrial Fibrillation Recurrence in the Per Protocol Maintenance Population

Factors	800 mg vs placebo	1200 mg vs placebo	1600 mg vs placebo	Comparison between 4 doses
Treatment	0.407, p = 0.0003	0.895, p = 0.635	0.636, p = 0.089	0.954, p = 0.578
Beta blockers	0.518, p = 0.011	0.824, p = 0.436	0.421, p = 0.004	0.690, p = 0.050
Age	0.944, p = 0.625	0.798, p = 0.091	0.878, p = 0.300	0.922, p = 0.292
Ejection fraction	1.273, p = 0.055	1.114, p = 0.290	1.239, p = 0.082	1.179, p = 0.058
Structural heart disease	1.008, p = 0.976	0.860, p = 0.512	0.932, p = 0.796	0.747, p = 0.096

4.2.4.2 Secondary Endpoints

Ventricular Rate at Time of Recurrence

Table (11.1.3) 2 summarizes the ventricular rate in case of AF recurrence for the PPM population. There was a statistically significant difference between groups for ventricular rate in case of recurrence (p=0.0001). The 800, 1200, and 1600 mg dronedarone groups had statistically lower ventricular rates compared to placebo.

Table (11.1.3) 2 - Ventricular Rate (bpm) in Case of Recurrence: Analysis on Per Protocol Maintenance Population

Ventricular rate (bpm)	Statistics	Placebo	800 mg	1200 mg	1600 mg	p-value [a]
Observed value	N	43	35	44	28	0.0001
	Mean	102.9	89.7	83.6	85.1	
	SD	21.9	20.5	17.3	21.1	
	Median	99.0	90.0	82.5	79.0	
	Minimum	71	52	52	52	
	Maximum	151	141	122	143	
Adjusted difference versus placebo	Mean		-13.2	-19.2	-17.8	
	95% CI		-22.2 / -4.1	-27.8 / -10.7	-27.5 / -8.1	

a: ANOVA
<ref>pgm=DRI3550//biom/clinic/SR33589/DRI3550/CSR/armagnac/program/r_hrrec4.sas (13DEC2000 10:25)

Number of Subjects Converted to Sinus Rhythm

As shown in Table (11.1.3)1, there was a significant dose effect (p=0.0261) in the incidence of conversion without electrical cardioversion; in the 1600 mg group the incidence of conversion was different from placebo (14.81% versus 3.13%, respectively).

Table (11.1.3) 1 - Number (%) of Patients Converted to Sinus Rhythm without Electrical Cardioversion: Per Protocol Population

Variable	Statistics	Placebo N=64	800 mg N=69	1200 mg N=61	1600 mg N=54	p-value[a]
Incidence of conversion	n % 95% CI	2 3.13 0.38 to 10.84	4 5.80 1.60 to 14.18	5 8.20 2.72 to 18.10	8 14.81 6.62 to 27.12	0.0261
Incidence versus placebo	Change 95% CI		2.67 -4.30 to 9.64	5.07 -3.03 to 13.17	11.69 1.30 to 22.08	

a: Cochran-Armitage trend test
pgm=DRI3550//biom/clinic/SR33589/DRI3550/CSR/armagnac/program/r_cvsp3.sas (10OCT2001 13:53)

In the dronedarone dose groups in the PP population the incidences of successful electrical cardioversion were: 77.3% (800 mg), 87.9% (1200 mg), and 76.6% (1600 mg) of patients compared to 73.0% of placebo patients. There was no statistically significant dose effect among treatment groups.

ECG Parameters

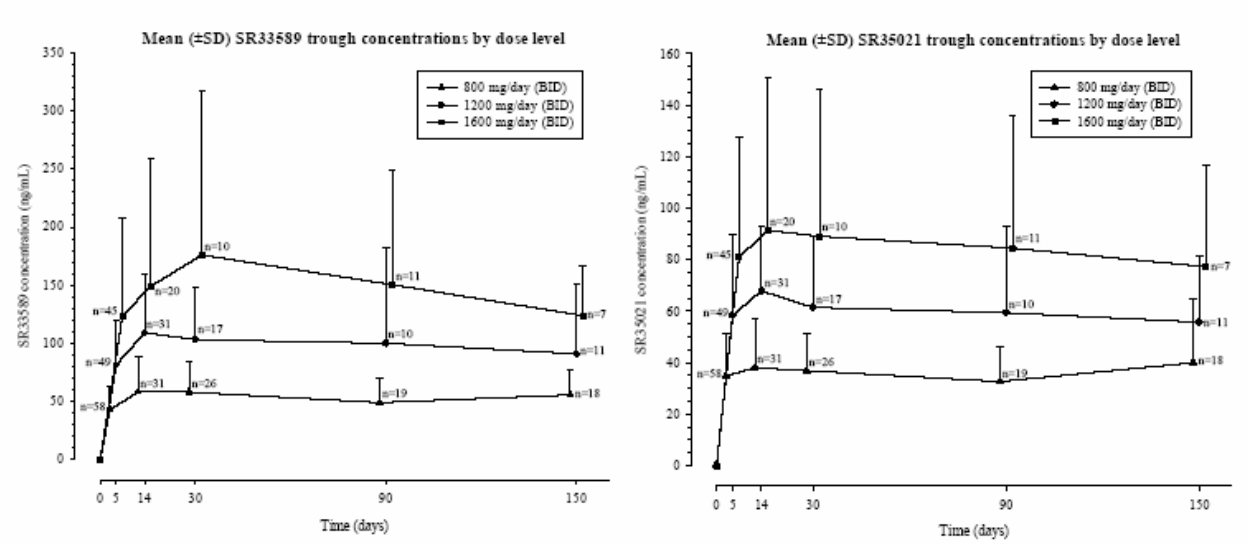
The ECG changes were consistent with the known electrophysiological properties of the drug and were well tolerated.

- The PR-interval was longer by 13.4, 16.6, and 28.4 ms in the 800, 1200 and 1600 mg groups respectively (p=0.0031, ANOVA).
- There was no clear effect on QRS-interval compared to placebo.
- The mean QTc-interval values were quite variable and a difference was found at later visits, mainly due to longer QTc-intervals in the 1600 mg group (p=0.0024 ANOVA).

4.2.5 Pharmacokinetic-Pharmacodynamic Relationship

Plasma samples for the analysis of dronedarone (SR33589) and its active metabolite (SR35021) were collected in 222 subjects. The sponsor define samples collect between 2-8 h after dosing as “CMAX” and between 0 to <2 h and 8-18 h as “CTROUGH.” Samples collected outside these intervals were undefined and not used for analysis. The following figure shows the mean CTROUGH at each study visit.

Figure: Mean (SD) SR33589 (left) and SR35021 (right) Ctrough vs. Visit Day

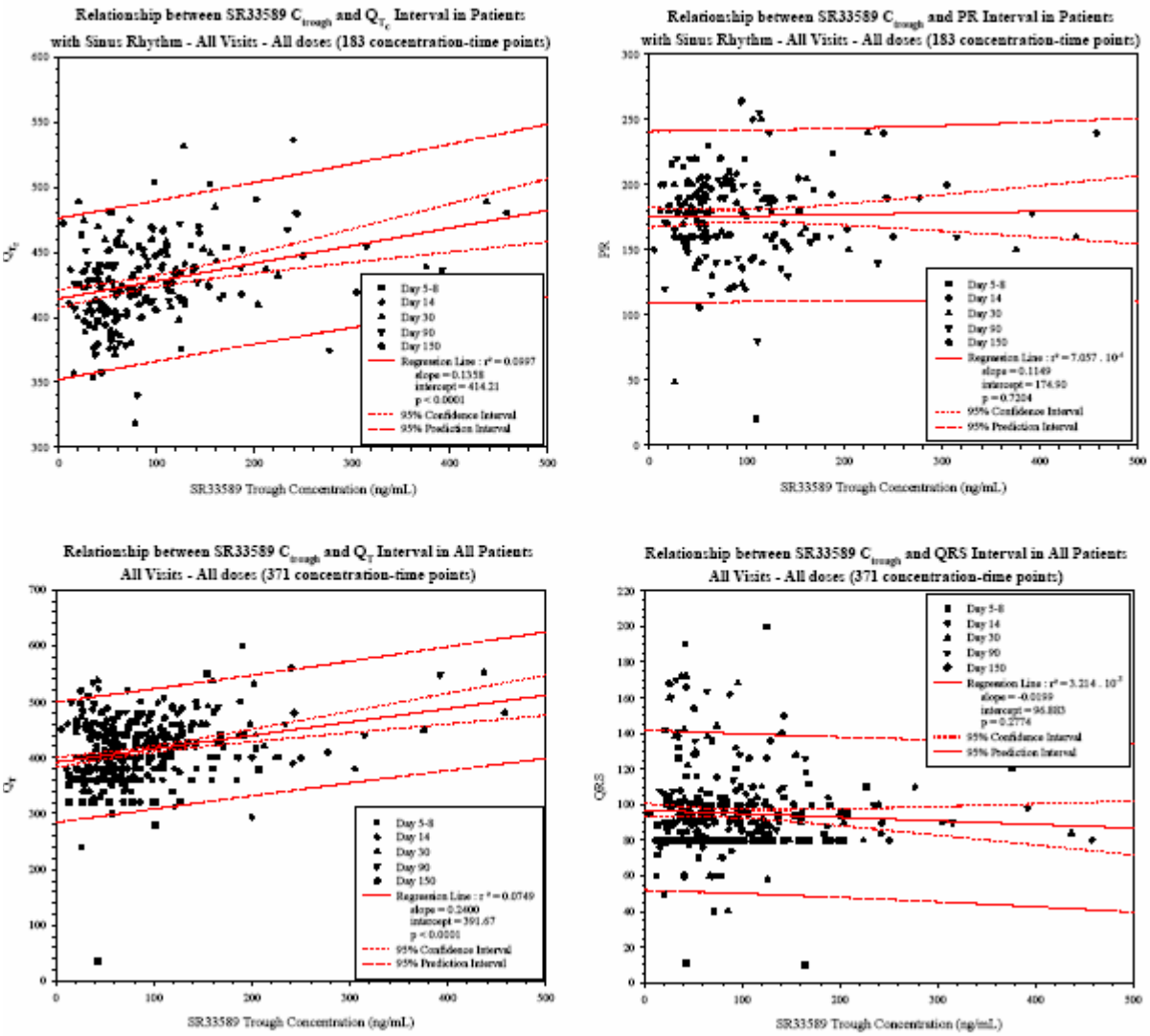


The sponsor performed ANOVA analyses on CTROUGH values to assess the impact of age, sex, day, weight, and CYP3A inhibitors.

The sponsor assessed the relationship between SR33589 CTROUGH and the time to first AF recurrence. No dose concentration effect was observed and the longest median time to recurrence occurred in the lower CTROUGH group Similar results were obtained using SR33589 +SR35021 CTROUGH.

The relationship between SR33589 and SR35021 CTROUGH and main ECG parameters (QTc, PR, QT, and QRS intervals, and Heart Rate) was studied by regression analysis. Figure (15.3.2)5 shows no clear relationship was observed between CTROUGH and ECG values. However, significant results were observed between SR33589 CTROUGH and the QTc and QT intervals ($p<0.0001$ for both).

Figure (15.3.2)5: Individual SR33589 CTROUGH Levels (ng/mL) as a Function of Electrocardiogram Parameters



4.2.6 Safety

4.2.6.1 Adverse Events

An overview of TEAEs, by type and treatment group, is provided in Table (12.2.1)1. A statistically significant dose effect was observed when AF recurrences were excluded from the evaluation of TEAEs: 47%, 53.9%, 65.2%, and 72.6% of patients receiving placebo, 800 mg, 1200 mg, and 1600 mg, respectively, reported TEAEs (p=0.00006,Cochran-Armitage test).

Table (12.2.1) 1 - Overview of Patients with at Least One Treatment Emergent Adverse Event Including or Excluding the Atrial Fibrillation Recurrences: All Treated Patients

	Placebo N=66 n (%)	800 mg N=76 n (%)	1200 mg N=66 n (%)	1600 mg N=62 n (%)	Dronedarone N=204 n (%)
Including AF recurrences					
Patients with any AEs[a]	56 (84.8)	61 (80.3)	57 (86.4)	53 (85.5)	171 (83.8)
Patient with any drug related AEs[b]	38 (57.6)	36 (47.4)	45 (68.2)	40 (64.5)	121 (59.3)
Patient with any AEs of severe intensity	5 (7.6)	2 (2.6)	3 (4.5)	7 (11.3)	12 (5.9)
Patients with SAEs[c]	3 (4.5)	2 (2.6)	5 (7.6)	7 (11.3)	14 (6.9)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Patient permanently discontinued study drug for any AE[d]	40 (60.6)	36 (47.4)	40 (60.6)	38 (61.3)	114 (55.9)
Patient permanently discontinued study drug for AEs not considered in analysis[e]	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Excluding AF recurrences					
Patients with any AEs[a]	31 (47.0)	41 (53.9)	43 (65.2)	45 (72.6)	129 (63.2)
Patient with any drug related AEs[b]	18 (27.3)	26 (34.2)	31 (47.0)	37 (59.7)	94 (46.1)
Patient with any AEs of severe intensity	2 (3.0)	2 (2.6)	3 (4.5)	7 (11.3)	12 (5.9)
Patients with SAEs[c]	3 (4.5)	1 (1.3)	5 (7.6)	7 (11.3)	13 (6.4)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Patients permanently discontinued study drug for any AE[d]	0 (0.0)	3 (3.9)	5 (7.6)	15 (24.2)	23 (11.3)
Patient permanently discontinued study drug for AEs not considered in analysis[e]	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)

N = number of patients exposed, n = number of patients with at least one AE,% = percentage of patients
Treatment-emergent = Onset date or worsening from first intake to last intake + 10 days
a: include non serious and serious adverse events
b: exclude relationship to study drug assessed by the investigator ='no'
c: include SAEs leading to death
d: Including 1 non emergent AE
e: Non emergent AE: One patient was discontinued for an AE that was reported prior to treatment initiation.
pgm=/biom/clinic/SR33589/DRI3550/CSR/clin/program/r_aesum.sas out=output/r_aesum (16AUG2001 15:56)

Gastrointestinal AEs

Diarrhea was the most frequent TEAE and was reported in a total of 24 dronedarone patients (11.8%); the dose effect was statistically significant (p<0.00001, Cochran-Armitage trend test). The following table summarizes the diarrhea TEAE. The incidence of diarrhea was the same in male and female populations (11.8% each) and was slightly higher in patients ≥65 years (12.9%) than in patients <65 years (10.7%).

No difference was observed between the mean CTROUGH of patients with and without diarrhea. Analysis of the time to diarrhea showed that most of the episodes occurred within the first 48 hours after dosing.

Table: Overview of Diarrhea TEAEs

Intensity	Placebo N=66	800 mg N=76	1200 mg N=66	1600 mg N=62	Total Drug N=204
Total	2 (3.0)	2 (2.6)	5 (7.6)	17 (27.4)	24 (11.8)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.8)	3 (1.5)
Moderate	0 (0.0)	1 (1.3)	1 (1.5)	5 (8.1)	7 (3.4)
Mild	2 (3.0)	1 (1.3)	4 (6.1)	9 (14.5)	14 (6.9)
SAE	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)

Figure. Mean CTROUGH for Subjects with and without Diarrhea

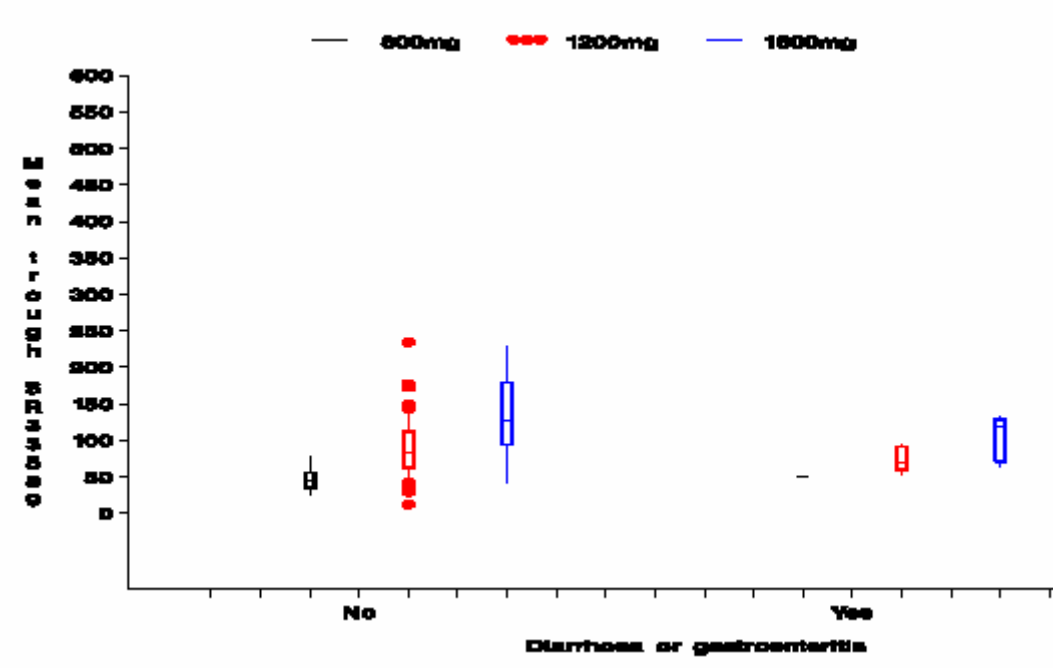
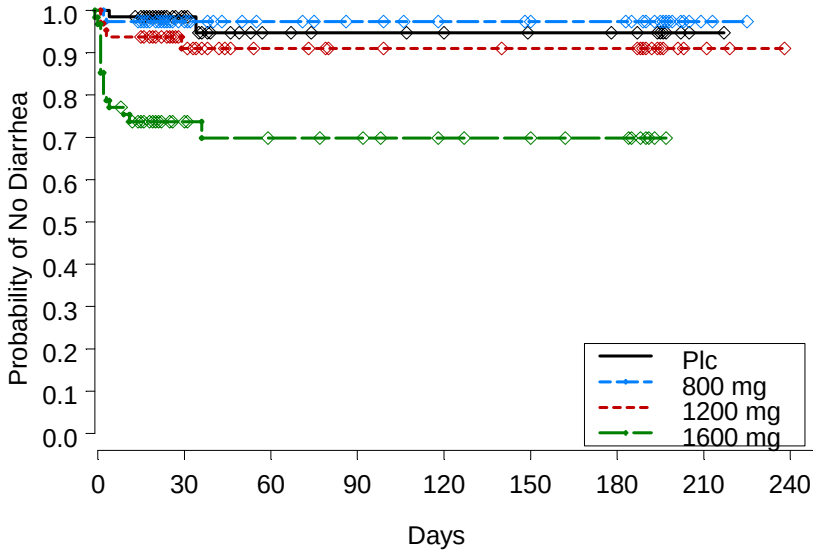


Figure. Kaplan-Meier Plot of Time to Diarrhea by Treatment Group



Heart rate and rhythm disorders and other cardiovascular disorders

The overall incidence of the heart rate and rhythm disorders did not increase with dose, nor did the incidence by preferred term categories. In the placebo group, 5 patients (7.6%) experienced supraventricular tachycardia, versus 20 patients (9.8%) on dronedarone. There were no torsades de pointes reported during the study.

4.2.6.2 Deaths and other SAEs

There was one death during this study. Patient 22050008 (1600 mg) suffered trauma due to an accidental injury on Day 162, at which time study drug was permanently discontinued. The patient's condition worsened and he died 4 weeks later. The accidental injury was judged by the investigator to have no relationship to study drug.

A total of 13 patients (6.4%) taking dronedarone and 3 patients (4.5%) on placebo reported SAEs. The overall frequency of SAEs reported increased with the dose of dronedarone: 1 patient (1.3%), 5 patients (7.6%), and 7 patients (11.3%) in the 800 mg, 1200 mg, and 1600 mg groups., respectively, reported SAEs, a total of 13 patients (6.4%).

4.2.6.3 Other Safety Measures

There was no evidence of variations in values for laboratory parameters, or unexpected variations in vital signs, in dronedarone groups. There was no evidence of thyroid, ocular nor pulmonary side effects.

5 POPULATION PK ANALYSIS

The following diagram summarizes the overview of the sponsor's modeling process.

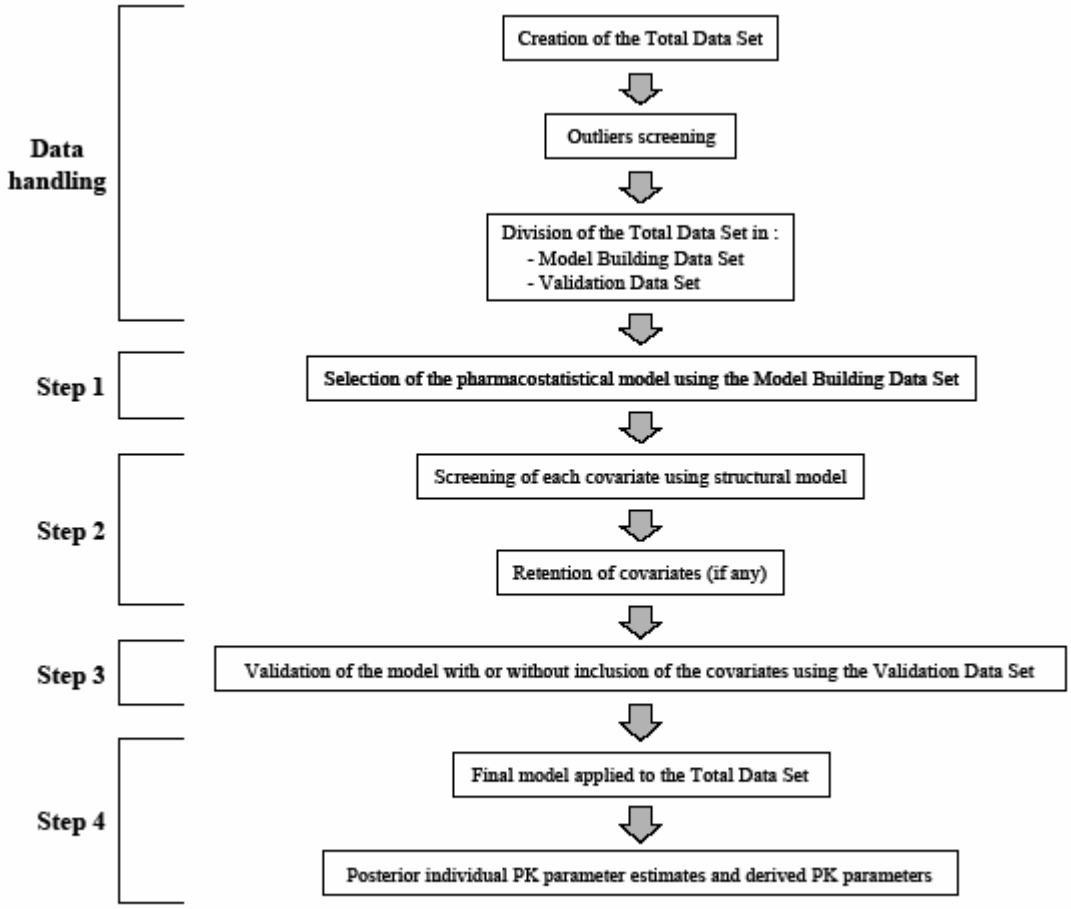


Figure (2.6.1) 1 - Population analysis scheme

5.1 Data

The population pharmacokinetic model was based on combined data from three phase III multiple dose studies, EURIDIS, EDONIS, and ANDROMENDA. The sponsor identified 126 concentrations for 10 subjects as outliers. These concentrations were deleted from the analysis datasets. The total number of subjects available for analysis was 839 which contributed 2786 plasma concentrations.

Table of Studies Included in Population Pharmacokinetic Analysis

Study	Design	Sampling	No Samples	No. Subjects Median (range) samples per subject
EURIDIS	Multicenter, multinational, double-blind, parallel-group, placebo-controlled, phase III studies of dronedarone 800 mg daily (400 mg bid) in patients with history of AF	Trough concentrations: Day 7 ± 2, Day 21 ± 3, Month 4 ± 5 days, Month 9 ± 5 days, and Month 12 ± 5 days.	1301	328 4 (1–8)
EDONIS			1032	290 4 (1–7)
ANDROMENDA	Multicenter, multinational, double-blind, parallel-group, placebo controlled study of dronedarone 800 mg daily (400 mg bid) in patients with symptomatic CHF.	Month 1 at pre-dose, 2h, 4h, 6h, 8h, 10h and 12h post-dose.	453	221 2 (1–8)
Total			2786 + 126 deleted as outliers = 2912	839 + 10 deleted as outliers =849

The sponsor divided the total dataset into two subsets that were used for model building and model validation. The model building dataset was composed of 589 patients (1984 samples) and the validation dataset was composed of 250 patients (802 samples). A summary of patient characteristics in each of the datasets are shown in Table (3.4)1.

Table (3.4) 1 - Mean and standard deviation of the patients demographic characteristics in the Model Building, the Validation and the Total Data Sets

Covariate or characteristic	Model Building Data Set	Validation Data Set	Total Data Set
Mean values (SD)			
Age (years) [a]	65.1 (10.5)	64.6 (11.6)	65.0 (10.8)
Body Weight (Kg)	84.0 (16.9)	83.9 (17.2)	84.0 (17.0)
Height (cm)	173 (10.0)	173 (9.38)	173 (9.83)
Number of patients (%)			
ADONIS + EURIDIS (%) [a]	434 (73.7 %)	184 (73.6 %)	618 (73.7 %)
ANDROMEDA (%) [a]	155 (26.3 %)	66 (26.4 %)	221 (26.3%)
$CL_{CR} < 80$ mL/min	370 (62.8 %)	148 (59.2 %)	518 (61.7 %)
$CL_{CR} \geq 80$ mL/min	219 (37.2 %)	102 (40.8 %)	321 (38.3 %)
Sex (Males) [a]	424 (72.0 %)	180 (72.0 %)	604 (72.0 %)
Sex (Females) [a]	165 (28.0 %)	70 (28.0 %)	235 (28.0 %)
Caucasians (%)	577 (98.0 %)	241 (96.4 %)	818 (97.5 %)
Blacks (%)	3 (0.5 %)	2 (0.8 %)	5 (0.6 %)
Asians (%)	3 (0.5 %)	2 (0.8 %)	5 (0.6 %)
Others (%)	6 (1.0%)	5 (2.0%)	11 (1.3 %)
No Congestive Heart Failure (CHF)	346 (58.7 %)	159 (63.6 %)	505 (60.2 %)
CHF – NYHA Score 1	24 (4.1 %)	13 (5.2 %)	37 (4.4 %)
CHF – NYHA Score 2	132 (22.4 %)	39 (15.6 %)	171 (20.4 %)
CHF – NYHA Score 3	84 (14.3 %)	38 (15.2 %)	122 (14.5 %)
CHF – NYHA Score 4	3 (0.5 %)	1 (0.4 %)	24 (0.5 %)
No CYP3A4 inhibitor co-admin. [b]	541 (91.8 %)	224 (89.6 %)	765 (91.2 %)
Moderate CYP3A4 inhibitor co-admin. [b]	46 (7.8 %)	25 (10.0 %)	71 (8.5 %)
Strong CYP3A4 inhibitor co-admin. [b]	1 (0.2 %)	0	1 (0.1 %)
Both moderate & strong CYP3A4 inhibitor co-admin. [b]	1 (0.2 %)	1 (0.4 %)	2 (0.2 %)
Total	589	250	839

[a]: covariates used in the drawing lot procedure

[b]: CYP3A4 inhibitor co-administration was considered if its duration represented at least 80% of the dronedarone treatment duration.

5.2 Pharmacokinetic Models

5.2.1 Structural and Random Variance Models

The sponsor explored one- and two- compartmental models with first order absorption and elimination for analyzing the concentration-time data. Models were parameterized in terms of CL/F and V/F. A lag time was also tested. Inter-individual variability in PK parameters was modeled using proportional and additive models. Residual error was modeled using proportional, additive, power, and combined proportional plus additive models. In total, 994 NONMEM runs were performed and the selection of the best structural model was based the objective function value, the sponsor's pre-specified acceptance criteria, and diagnostic plots.

The sponsor selected a two-compartment model with first order absorption (measured by ka) and elimination (evaluated by CL/F) from the central compartment (V2/F) as the best model to describe the data. CL/F and V2/F were log-normally distributed. Residual error was described by a additive model. Interindividual variability for Q/F could not be estimated (no minimization or 95%CIs on ηQ/F or θQ/F included zero) and ka was fixed to the value obtained in the preliminary PopPK analysis performed on the pool of TDR2395 and DRI3550 data.

The sponsor assessed the impact of the fixed value of ka on the model by performing 17 runs with different ka values. The different fixed ka values tested ranged from 0.15 h-1 to 1 h-1 with a step-size of 0.05 h–1. Figure (3.5.1.1.1) 1 shows that ka = 0.291 was the best parameter value.

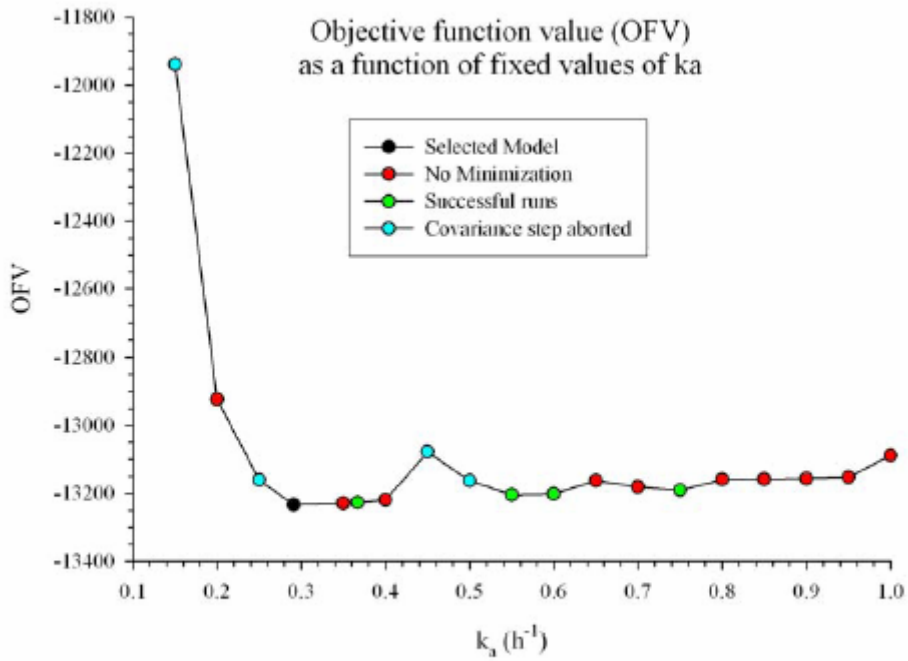


Figure (3.5.1.1.1) 1 - Impact of the fixed value of k_a on OFV

The following table shows the parameter estimates for the structural model.

	FINAL ESTIMATE	%RSE	95% CONFIDENCE INTERVAL LBOUND	UBOUND	DESCRIPTOR/ VARIABILITY
THETA					
1	353	2.27%	337	369	CL
2	3.32e+003	8.43%	2.77e+003	3.87e+003	V2
3	333	13.7%	244	422	Q
4	6.12e+003	14.9%	4.33e+003	7.91e+003	V3
5	0.291	...	...	...	KA
OMEGA					INTERINDIVIDUAL VARIABILITY
1,1	0.122	8.69%	0.101	0.143	CV = 34.9%
2,2	1.31	13.4%	0.965	1.65	CV = 114%
3,3	0.651	39.0%	0.153	1.15	CV = 80.7%
SIGMA					RESIDUAL VARIABILITY
1,1	0.000192	7.08%	0.000165	0.000219	SD = 0.0139

*Indicates 95% confidence interval that includes zero
%RSE is percent relative standard error (100% x SE/EST)

5.2.2 Covariate Models

The sponsor evaluated the influence of body weight, age, height, sex, race, study, renal function (normal vs. impaired), CHF status (no CHF vs. CHF), and CYP3A4 inhibitor indicator (yes vs. no). The sponsor evaluated linear, exponential, and power functional forms of the parameter-continuous covariate relationship. Dichotomous and categorical variables were evaluated as proportional or additive shifts.

After screening all covariates using EXPOSE software, the sponsor identified WGT, HGT, AGE, SEX and CAUC together with NYHO, ICCL, INHI and study as potential covariates for CL/F, V2/F and V3/F. A univariate stepwise forward addition method in NONMEM was used to test the significance of each covariate in explaining the interindividual variability in population PK parameters. A change in objective function of 10.83 (corresponding to a $p<0.001$ for a chi-squared distribution with 1 degree of freedom) was used as the inclusion criteria. Once all significant covariates were included in the model, the sponsor performed a univariate stepwise backward elimination of covariates. For a covariate to be retained in the model the objective function had to increase by 10.83 ($p<0.001$ for chi-square distribution with 1 degree of freedom) when it was removed from the model.

A total of 103 NONMEM runs were performed and Table (3.5.2.2)2 summarizes the results of the stepwise addition of covariates. None of the covariates tested should explain the interindividual variability in V2/F and V3/F, based on the statistical criteria of change in objective function of 10.83.

Table (3.5.2.2) 2 - Covariates retained in the PopPK model

Analysis step	Selected model	ΔOFV [a]	ΔIIV [b]
PSM [c]	No covariate	NA	NA
Step 1	$TVCL1 = \theta_{(1)} * (WGT / 83) ** \theta_{(6)}$	-77.8	- 18 %
Step 2	$TVCL2 = TVCL1 * SEX + TVCL1 * \theta_{(7)} * (1-SEX)$	-24.3	- 3.8 %
Step 3	$TVCL3 = TVCL2 * AGE / (\theta_{(8)} + AGE)$	-11.9	- 3.0 %

[a]: Difference in OFV before and after covariate inclusion. A difference of at least 10.83 is needed for statistical significance ($p<0.001$).
[b]: Difference in interindividual variability, as expressed by the percentage of decrease of variance, before and after covariate inclusion.
[c]: PSM = Pharmacostatistical model. NA: Not Applicable.
In the equations of Step 1, 83 Kg is the median values of WGT.

Table (3.5.5) 1 - Effects of sequential covariate deletion on NONMEM OFV

Purpose / Covariate	ΔOFV	Observations
Final model, all subsequent runs compared to this run	NA	Terms for WGT, SEX and Age on CL/F
Delete WGT on CL/F	49.0	Kept
Delete SEX on CL/F	24.6	Kept
Delete AGE on CL/F	11.9	Kept

NA: Not applicable.

The following table shows the parameter estimates and precision of estimates for the covariate model. Diagnostic plots of the covariate model are also shown.

	FINAL ESTIMATE	%RSE	95% CONFIDENCE INTERVAL LBOUND	UBOUND	DESCRIPTOR/ VARIABILITY
THETA					
1	301	5.12%	271	331	CL
2	3.47e+003	7.98%	2.93e+003	4.01e+003	V2
3	349	6.07%	307	391	Q
4	6.15e+003	9.67%	4.98e+003	7.32e+003	V3
5	0.291	...	...	...	KA
6	0.500	17.0%	0.333	0.667	WGT_on_CL
7	0.827	4.01%	0.762	0.892	Sex on CL
8	-12.1	18.9%	-16.6	-7.61	AGE_on_CL
OMEGA					INTERINDIVIDUAL VARIABILITY
1,1	0.0933	8.46%	0.0778	0.109	CV = 30.5%
2,2	1.29	12.5%	0.974	1.61	CV = 114%
3,3	0.662	13.7%	0.485	0.839	CV = 81.4%
SIGMA					RESIDUAL VARIABILITY
1,1	0.000193	2.45%	0.000184	0.000202	SD = 0.0139

*Indicates 95% confidence interval that includes zero
%RSE is percent relative standard error (100% x SE/EST)

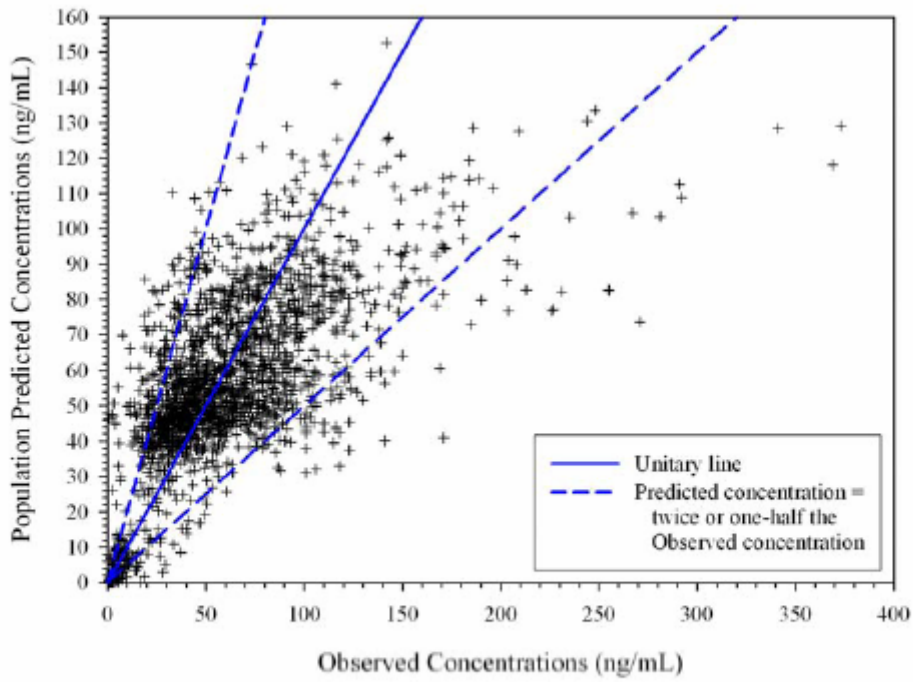


Figure (3.5.4) 1 - Relationship between population predicted and observed dronedarone plasma concentrations in the Model Building Data Set (n=589 patients)

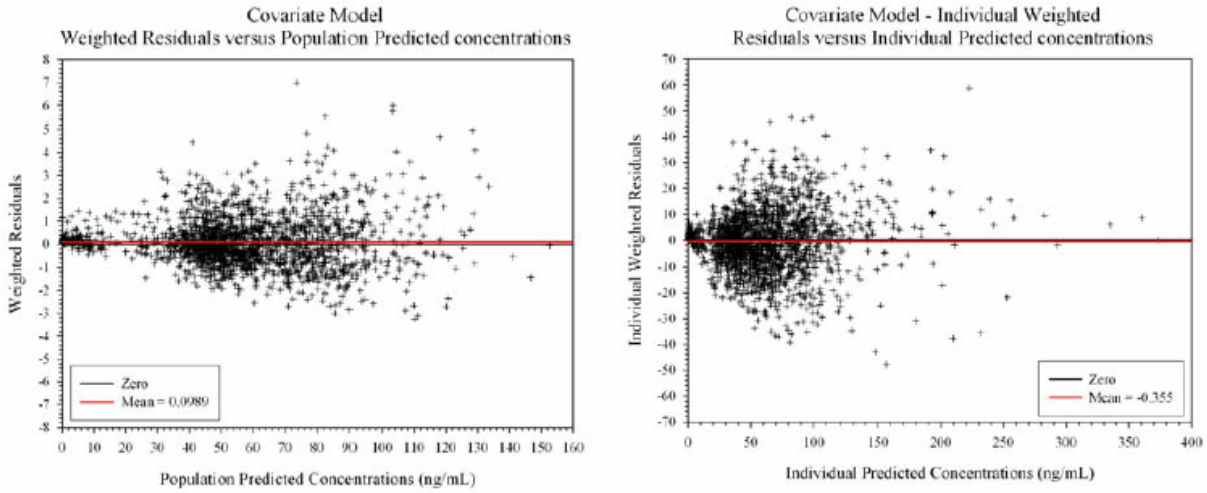


Figure (3.5.4) 3 - Relationship between population weighted residuals and population predicted concentrations (*left*) and individual weighted residuals and individual predicted concentrations (*right*)

5.2.3 Model Qualification

The final model obtained in the Model Building Data Set was validated using its parameters as prior estimates for the assessment of the individual parameters and concentrations of the patients from the Validation Data Set. The estimation step was omitted using MAXEVAL=0 option to obtain the individual estimates based on the final population estimates of θ, ω and σ. Table

(3.5.6.1)1 and Table (3.5.6.2)1 shows the performance of the population-predicted and individual-predicted concentrations, as expressed by bias, precision and AFE.

Table (3.5.6.1) 1 - Performance of the population concentrations prediction, assessed on the Model Validation Data Set (values in parenthesis were expressed in % of mean C_{Obs} values)

Concentrations (ng/mL)	n= 250 ; 802 concentration-time points	
	Mean	**SD**
Observed (reference)	60.5	45.9
Population Predicted	54.3	26.3
Student paired t test	p-value < 0.0001	
WRES (Mean, 95%CI)	0.136 [0.0594 – 0.212]	
Regression characteristics		
Slope	0.403	
Intercept	29.9	
Correlation coefficient r	0.706	
Criteria in ng/mL (%)	**Value**	**95% CI**
Bias (%)	6.21 (10 %)	[3.92 – 8.50]
Precision (%)	33.7 (56%)	[30.1 – 36.9]
AFE	1.68	

Table (3.5.6.2) 1 - Performance of the individual concentrations prediction, assessed on the Validation Data Set (values in parenthesis were expressed in % of mean C_{Obs} values)

Concentrations (ng/mL)	n=250 ; 802 time points	
	Mean	**SD**
Observed (reference)	60.5	45.9
Individual Predicted	60.8	43.1
Student paired t test	P value = 0.535	
IWRE (Mean, 95%CI)	-0.260 [-1.08 – 0.562]	
Regression characteristics		
Slope	0.907	
Intercept	5.87	
Correlation coefficient r	0.967	
Criteria in ng/mL (%)	**Value**	**95%CI**
Bias (%)	-0.260 (-0.43 %)	[-1.08 – 0.560]
Precision (%)	11.8 (20 %)	[10.8 – 12.8]
AFE	1.34	

5.2.4 Final Model

To obtain parameter estimates for the final population model, the model building and validation datasets were combined and analyzed, using the final parameter estimates of the covariate model as the initial estimates of the final model. The following table shows the final parameter estimates. PK parameters were nearly identical between the final model from the model building and total dataset analyses.

	FINAL ESTIMATE	%RSE	95% CONFIDENCE INTERVAL LBOUND	UBOUND	DESCRIPTOR/ VARIABILITY
THETA					
1	290	3.93%	268	312	CL
2	3.14e+003	6.43%	2.74e+003	3.54e+003	V2
3	316	4.75%	287	345	Q
4	6.34e+003	7.82%	5.37e+003	7.31e+003	V3
5	0.291	...	...	...	KA
6	0.528	14.0%	0.383	0.673	WGT_on_CL
7	0.843	3.32%	0.788	0.898	Sex on CL
8	-12.9	12.9%	-16.2	-9.65	AGE_on_CL
OMEGA					INTERINDIVIDUAL VARIABILITY
1,1	0.0913	7.15%	0.0785	0.104	CV = 30.2%
2,2	1.20	11.8%	0.924	1.48	CV = 110%
3,3	0.495	11.2%	0.386	0.604	CV = 70.4%
SIGMA					RESIDUAL VARIABILITY
1,1	0.000201	2.00%	0.000193	0.000209	SD = 0.0142

*Indicates 95% confidence interval that includes zero
%RSE is percent relative standard error (100% x SE/EST)

The robustness of the final model and the accuracy of parameter estimate (SE computation) was assessed using a nonparameteric bootstrap methodology. Table (3.5.7.2)1 shows a comparison between the uncertainty in parameter estimates obtained from NONMEM and from 500 bootstrap datasets.

Table (3.5.7.2) 1 - Comparison of final model parameters and bootstrap results (results from the 500 successful runs)

Parameter	NONMEM Estimate	Bootstrap Estimate (SD)	Difference %	NONMEM % RSE	Bootstrap % RSE	NONMEM 95%CI	Bootstrap 5th - 95th percentiles
$\theta_{(1)}$ in [CL/F = $\theta_{(1)}$ * WGT/ 83], L/h	290	296 (14.2)	-2.03 %	3.93 %	4.37 %	[268 – 312]	[269 – 316]
$\theta_{(6)}$ in [CL/F = $\theta_{(1)}$ * (WGT / 83) ** $\theta_{(6)}$]	0.528	0.554 (0.0762)	-4.69 %	14.0 %	12.7 %	[0.383 – 0.673]	[0.430 – 0.688]
$\theta_{(7)}$ Gender effect on CL/F for female	0.843	0.856 (0.0250)	-1.52 %	3.32 %	3.15 %	[0.788 – 0.898]	[0.820- 0.901]
$\theta_{(8)}$ in [CL/F = TVCL*AGE / ($\theta_{(8)}$ + AGE)]]	-12.9	-11.2 (1.92)	15.2 %	12.9 %	18.8 %	[-16.2 – -9.65]	[-14.5 - -8.54]
Central volume V2/F [$\theta_{(2)}$], L	3140	2959 (418)	6.12 %	6.43 %	5.81 %	[2740 – 3540]	[2179 – 3530]
Inter-compartmental clearance Q/F [$\theta_{(3)}$], L/h	316	350 (75.4)	-9.71 %	4.75 %	5.24 %	[287 – 345]	[266 – 513]
Peripheral volume V3/F [$\theta_{(4)}$], L	6340	6919 (1055)	-8.37 %	7.82 %	7.73 %	[5370 – 7310]	[5430 – 8886]
Absorption rate constant k_a [$\theta_{(5)}$], h^{-1}	0.291 FIXED						
Interindividual variability (CV%)							
CL/F	30.2 %	30.1 % (1.11)	< 1 %	7.15 %	7.76 %	[28.0 % – 32.2 %]	[28.3 – 31.9]
V2/F	110 %	114 % (9.91)	-3.51 %	11.8 %	12.1 %	[96.1 % – 122 %]	[100 – 133]
V3/F	70.4 %	49.4 % (30.8)	42.5 %	11.2 %	>10^{12}	[62.1 % – 77.7 %]	[0 – 84.4]
Residual variability - Y = C_{ipred} + ε							
σ (SE[ε] in ng/mL)	0.0142	0.0143 (0.000462)	< 1 %	2.00 %	2.14 %	[0.0139 – 0.0145]	[0.0136 – 0.0150]

Clinical Application of PK Model

Neither dosing regimen decisions nor labeling statements were based on the results of the model. As a result, the reviewer considers the model to be only supportive.

5.4 Reviewer's Comments

- In future submissions, any concentrations and/or subjects that have been excluded from the analysis should be maintained in the datasets. For this analysis, the sponsor identified 123 concentrations (from 10 subjects) as outliers and excluded these observations from the dataset.

6 APPENDICES

6.1 NM-TRAN CODE FOR BASE STRUCTURAL MODEL

```
Jan 5 2005 13:50
Compiler Version: DIGITAL Visual Fortran Optimizing Compiler Version 6.0 (Update A)
Fortran Options: /optimize:1 /fpe:0
;Model Desc: base model
;Project Name: model refinement
;Project ID: DRONEDARONE - ANDROMEDA, EURIDIS & ADONIS STUDIES
; Premier run BICOMP - $PK proportionnel, 3 ETAs (Ka FIXED & Q sans ETA), $ERROR Additif
$PROB RUN# 209 (Dronedarone - ANDROMEDA, EURIDIS & ADONIS Studies)
$INPUT C ID TIME AMT DV ADDL II MDV EVID SEX AGE CAUC WGT HGT ICCL NYH0
INHI STUD IDEN
$DATA CONSTRUC.CSV IGNORE=C
;Data file name must use the .csv extension (e.g. 12a.csv)
$SUBROUTINES ADVAN4 TRANS4
$PK
TVCL = THETA(1)
CL = TVCL * EXP(ETA(1))
ETCL = ETA(1)
TVV2 = THETA(2)
V2 = TVV2 * EXP(ETA(2))
ETV2 = ETA(2)
TVQ = THETA(3)
Q = TVQ
TVV3 = THETA(4)
V3 = TVV3 * EXP(ETA(3))
ETV3 = ETA(3)
TVKA = THETA(5)
KA = TVKA
S2 = V2
$ERROR
W = 1
IPRED = F
IRES = DV - IPRED
IWRES = IRES
Y = F + ERR(1)
$THETA
(0, 460) ;[CL]
(0, 1860) ;[V2]
(0, 212) ;[Q]
(0, 4240) ;[V3]
(0.291 FIXED) ;[KA]
;*************************************************************
;A "descriptor" for the THETA parameter may be added in [] after a semicolon
; eg. ;[KA] or [CL, L/hr]
;Start initial estimates for OMEGA and SIGMA on the line below the $OMEGA or $SIGMA
;After the initial estimate, there must be a ';' followed by
; 'A', 'F', 'P' or 'N' enclosed in brackets '[]'.
;The enclosed letter is not case sensitive.
;No spaces are allowed in the brackets.
; A=additive error, F=off-diagonal covariance, P=proportional error, N=not defined
;*************************************************************
$OMEGA
0.2 ;[P] INTERIND VAR IN CL
0.2 ;[P] INTERIND VAR IN V2
```

```
0.2 ;[P] INTERIND VAR IN V3
$SIGMA
0.005 ;[A] ADDITIVE COMPONENT
$EST PRINT = 5 MAXEVAL = 9000 NOABORT POSTHOC METHOD = 1 INTERACTION
$COVARIANCE
$TABLE FILE=209.TAB ID TIME DV IPRED IRES IWRES TVCL CL ETCL TVV2 V2 ETV2
TVQ Q TVV3 V3 ETV3 TVKA KA SEX AGE CAUC WGT HGT ICCL NYH0 INHI STUD
IDEN NOPRINT ONEHEADER
$TABLE FILE=patab209 ID TVCL CL ETCL TVV2 V2 ETV2 TVQ Q TVV3 V3 ETV3 TVKA
KA NOPRINT ONEHEADER
$TABLE FILE=cotab209 ID WGT HGT AGE NOPRINT ONEHEADER
$TABLE FILE=catab209 ID SEX CAUC ICCL NYH0 INHI STUD NOPRINT ONEHEADER
$TABLE FILE=sdtab209 ID TIME IPRED IRES IWRES NOPRINT ONEHEADER
```

6.2 NM-TRAN CODE FOR COVARIATE MODEL

```
Jan 17 2005 11:24
Compiler Version: Compaq Visual Fortran Optimizing Compiler Version 6.1
Fortran Options: /optimize:1 /fpe:0
;Model Desc: base model
;Project Name: step3c
;Project ID: DRONEDARONE - ANDROMEDA, EURIS & ADONIS STUDIES
; Premier run BICOMP - $PK proportionnel, 3 ETAs (Ka FIXED & Q sans ETA), $ERROR Additif
$PROB RUN# Step3_004 (Dronedarone - ANDROMEDA, EURIDIS & ADONIS Studies)
$INPUT C ID TIME AMT DV ADDL II MDV EVID SEX AGE CAUC WGT HGT ICCL NYH0
INHI STUD IDEN
$DATA CONSTRUC.CSV IGNORE=C
;Data file name must use the .csv extension (e.g. 12a.csv)
$SUBROUTINES ADVAN4 TRANS4
$PK
Cov1 = THETA(1) * ( WGT / 83 ) ** THETA(6)
TVCL = (Cov1 * SEX + Cov1 * THETA(7) * (1-SEX)) * AGE / (THETA(8) + AGE)
CL = TVCL * EXP(ETA(1))
ETCL = ETA(1)
TVV2 = THETA(2)
V2 = TVV2 * EXP(ETA(2))
ETV2 = ETA(2)
TVQ = THETA(3)
Q = TVQ
TVV3 = THETA(4)
V3 = TVV3 * EXP(ETA(3))
ETV3 = ETA(3)
TVKA = THETA(5)
KA = TVKA
S2 = V2
$ERROR
W = 1
IPRED = F
IRES = DV - IPRED
IWRES = IRES
Y = F + ERR(1)
$THETA
(0, 353) ;[CL]
(0, 3320) ;[V2]
(0, 333) ;[Q]
(0, 6120) ;[V3]
(0.291 FIXED) ;[KA]
(1) ;[WGT_on_CL]
(1) ;[Sex on CL]
(0.001) ;[AGE_on_CL]
;*************************************************************
;A "descriptor" for the THETA parameter may be added in [] after a semicolon
; eg. ;[KA] or [CL, L/hr]
;Start initial estimates for OMEGA and SIGMA on the line below the $OMEGA or $SIGMA
;After the initial estimate, there must be a ';' followed by
; 'A', 'F', 'P' or 'N' enclosed in brackets '[]'.
;The enclosed letter is not case sensitive.
;No spaces are allowed in the brackets.
; A=additive error, F=off-diagonal covariance, P=proportional error, N=not defined
;*************************************************************
```

```
$OMEGA
0.2 ;[P] INTERIND VAR IN CL
0.2 ;[P] INTERIND VAR IN V2
0.2 ;[P] INTERIND VAR IN V3
$SIGMA
0.005 ;[A] ADDITIVE COMPONENT
$EST PRINT = 5 MAXEVAL = 9000 NOABORT POSTHOC METHOD = 1 INTERACTION
$COVARIANCE MATRIX=S
$TABLE FILE=Step3_004.TAB ID TIME DV IPRED IRES IWRES TVCL CL ETCL TVV2 V2 ETV2
TVQ Q TVV3 V3 ETV3 TVKA KA SEX AGE CAUC WGT HGT ICCL NYH0 INHI STUD
IDEN NOPRINT ONEHEADER
$TABLE FILE=patabStep3_004 ID TVCL CL ETCL TVV2 V2 ETV2 TVQ Q TVV3 V3 ETV3 TVKA
KA NOPRINT ONEHEADER
$TABLE FILE=cotabStep3_004 ID WGT HGT AGE NOPRINT ONEHEADER
$TABLE FILE=catabStep3_004 ID SEX CAUC ICCL NYH0 INHI STUD NOPRINT ONEHEADER
$TABLE FILE=sdtabStep3_004 ID TIME IPRED IRES IWRES NOPRINT ONEHEADER
```

6.3 NM-TRAN CODE FOR FINAL MODEL

```
Jan 18 2005 09:00
Compiler Version: Compaq Visual Fortran Optimizing Compiler Version 6.1
Fortran Options: /optimize:1 /fpe:0
;Model Desc: base model
;Project Name: total data set
;Project ID: DRONEDARONE - ANDROMEDA, EURIDIS & ADONIS STUDIES
; Premier run BICOMP - $PK proportionnel, 3 ETAs (Ka FIXED & Q sans ETA), $ERROR Additif
$PROB RUN# final4 (Dronedarone - ANDROMEDA, EURIDIS & ADONIS Studies)
$INPUT C ID TIME AMT DV ADDL II MDV EVID SEX AGE CAUC WGT HGT ICCL NYH0
INHI STUD IDEN
$DATA Total.CSV IGNORE=C
;Data file name must use the .csv extension (e.g. 12a.csv)
$SUBROUTINES ADVAN4 TRANS4
$PK
Cov1 = THETA(1) * ( WGT / 83 ) ** THETA(6)
TVCL = (Cov1 * SEX + Cov1 * THETA(7) * (1-SEX)) * AGE / (THETA(8) + AGE)
CL = TVCL * EXP(ETA(1))
ETCL = ETA(1)
TVV2 = THETA(2)
V2 = TVV2 * EXP(ETA(2))
ETV2 = ETA(2)
TVQ = THETA(3)
Q = TVQ
TVV3 = THETA(4)
V3 = TVV3 * EXP(ETA(3))
ETV3 = ETA(3)
TVKA = THETA(5)
KA = TVKA
S2 = V2
$ERROR
W = 1
IPRED = F
IRES = DV - IPRED
IWRES = IRES
Y = F + ERR(1)
$THETA
(0, 301) ;[CL]
(0, 3470) ;[V2]
(0, 349) ;[Q]
(0, 6150) ;[V3]
(0.291 FIXED) ;[KA]
(0.5) ;[WGT_on_CL]
(0.827) ;[Sex on CL]
(-12.1) ;[AGE_on_CL]
;*************************************************************
;A "descriptor" for the THETA parameter may be added in [] after a semicolon
; eg. ;[KA] or [CL, L/hr]
;Start initial estimates for OMEGA and SIGMA on the line below the $OMEGA or $SIGMA
;After the initial estimate, there must be a ';' followed by
; 'A', 'F', 'P' or 'N' enclosed in brackets '[]'.
;The enclosed letter is not case sensitive.
;No spaces are allowed in the brackets.
; A=additive error, F=off-diagonal covariance, P=proportional error, N=not defined
;*************************************************************
```

```
$OMEGA
0.0933 ;[P] INTERIND VAR IN CL
1.29 ;[P] INTERIND VAR IN V2
0.662 ;[P] INTERIND VAR IN V3
$SIGMA
0.000193 ;[A] ADDITIVE COMPONENT
$EST PRINT = 5 MAXEVAL = 9000 NOABORT POSTHOC METHOD = 1 INTERACTION
$COVARIANCE MATRIX=S
$TABLE FILE=final4.TAB ID TIME DV IPRED IRES IWRES TVCL CL ETCL TVV2 V2 ETV2
TVQ Q TVV3 V3 ETV3 TVKA KA SEX AGE CAUC WGT HGT ICCL NYH0 INHI STUD
IDEN NOPRINT ONEHEADER
$TABLE FILE=patabfinal4 ID TVCL CL ETCL TVV2 V2 ETV2 TVQ Q TVV3 V3 ETV3 TVKA
KA NOPRINT ONEHEADER
$TABLE FILE=cotabfinal4 ID WGT HGT AGE NOPRINT ONEHEADER
$TABLE FILE=catabfinal4 ID SEX CAUC ICCL NYH0 INHI STUD NOPRINT ONEHEADER
$TABLE FILE=sdtabfinal4 ID TIME IPRED IRES IWRES NOPRINT ONEHEADER
```

4.4 Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-913	Brand Name (proposed)	Multac
OCPB Division (I, II, III)	I	Generic Name	Dronedarone HCl
Medical Division	CARDIORENAL	Drug Class	Antiarrhythmic
OCPB Reviewer	Robert O. Kumi	Indication(Proposed)	Rhythm and rate control in patients with atrial fibrillation or atrial flutter, to maintain normal sinus rhythm or to decrease ventricular rate
OCPB Team Leader	Patrick Marroum	Dosage Form	Tablets, 400 mg
		Dosing Regimen	400 mg twice daily
Date of Submission	June 10, 2005	Route of Administration	Oral
Estimated Due Date of OCPB Review	, 2006	Applicant	Pharmaceuticals
PDUFA Due Date	April 10, 2006	Priority Classification	To be determined
Division Due Date	TBD		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	16		
I. Clinical Pharmacology				
Mass balance:	x	1		
Isozyme characterization:	x	7		Studies included assessment of inhibition, induction and interactions with potential coadministered drugs
In vitro characterization of Transporters	x	1		PGP transporter
Blood/plasma ratio:				
Plasma protein binding:	X	2		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	4, 1b		b- Study TDR2395 (same study)
multiple dose:	x	1, 1b		
Patients-				
single dose:				
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:	X	1a		a- Study LIN2890 (same study)
fasting / non-fasting multiple dose:	x	1a		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	18		Most studies evaluate PK effect of study drug/ coadministered drug; some studies evaluate PD
In-vivo effects of primary drug:	X			
In-vitro:				
Subpopulation studies -				
age	X	1		
ethnicity:	X	1		Japanese (cross study)
gender:				
pediatrics:				
geriatrics:				
renal impairment:				Not conducted

hepatic impairment:	X	1		Additional ongoing study. Both submitted and ongoing study compare moderate/healthy
PD:				
Phase 2:	X	5		Four studies evaluated safety, hemodynamic and/or electro-physiological characteristics in patients. One study evaluated effect of study drug on renal function in healthy volunteers
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	1		Dose-ranging study
Phase 3 clinical trial:	X	2d		Pooled data from 3 trials
Population Analyses -				
Data rich:				
Data sparse:	x	1c,d		Pooled data from 3 trials
II. Biopharmaceutics				
Absolute bioavailability:	x	2		
Relative bioavailability -	X	4		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	3		
Dissolution:	X	1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x			
Electrophysiololgy Study	X			Conducted as part of Phase I studies
Pharmacodynamic studies				
Total Number of Studies Reviewed			35	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X			
Comments sent to firm ?	No			
QBR questions (key issues to be considered)	Has exposure-response been adequately characterized? Are proposed dissolution methodology and specification acceptable?			
Other comments or information not included above				
Primary reviewer Signature and Date	Robert Kumi			
Secondary reviewer Signature and Date	Patrick Marroum			

CC: NDA 21-913, HFD-850(Lee), HFD-860 (Marroum, Mehta, KumiR), Biopharm (CDER)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Kumi
3/28/2006 04:18:41 PM
BIOPHARMACEUTICS
Dear All, Please review and pass on ASAP. Thanks. Robert

Christine Garnett
3/30/2006 02:36:50 PM
PHARMACOLOGIST

Jogarao Gobburu
3/30/2006 02:40:32 PM
BIOPHARMACEUTICS

Patrick Marroum
3/30/2006 02:48:27 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-**913**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	June 10, 2005
PRODUCT:	dronedarone
INTENDED CLINICAL POPULATION:	**patients with atrial fibrillation or atrial flutter**
SPONSOR:	Sanofi
DOCUMENTS REVIEWED:	**Electronic submission.**
REVIEW DIVISION:	**Division of Cardio-Renal Drug Products**
PHARM/TOX REVIEWER:	**Elizabeth Hausner, D.V.M.**
PHARM/TOX SUPERVISOR:	**Al DeFelice, Ph.D.**
DIVISION DIRECTOR:	**Norman Stockbridge, M.D., Ph.D.**
PROJECT MANAGER:	**Russell Fortney**

Date of review submission to Division File System (DFS):

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2.6.6.2 Single-dose toxicity NDA PartII
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Appendix C Minutes of the Executive Carcinogenicity Committee Consideration of Dronedarone Study Results NDA Part IV

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approvable pending resolution of several issues

B. Recommendation for nonclinical studies: 1) qualification of impurity SR194090 1)Studies to elucidate the effect upon female cyclicity 2) receptor binding studies for the parent drug and main metabolites 3)generation of data to show the relevance or lack of relevance of the carcinogenic effects for humans

C. Recommendations on labeling

"Mechanism of Action" – "The drug has been shown non-clinically to have properties of the 4 Vaughan-Williams Classes. "Whether this statement stays in the labeling depends upon the clinical demonstration of these properties.

"Pharmacodynamic Properties"- The statement
"In animal models, dronedarone reduces the heart rate. It prolongs Wenckebach cycle length and AH-, PQ-, QT- intervals; with no marked effect on QTc-, HV- and QRS-intervals" should be removed as there is human data for these parameters.

"Dronedarone slightly decreases arterial blood pressure and myocardial contractility (dP/dt max) with no change in left ventricular ejection fraction and reduces myocardial oxygen consumption " should also be removed unless this is information derived from human studies.

The statement "Dronedarone has vasodilatory properties, more pronounced in coronary arteries (related to the activation of nitric oxide pathway) than in peripheral arteries " should be removed. This information is based on studies 1)in isolated organ culture 2) studies where dronedarone was intravenously infused into anesthetized dogs and 3)an intravenous infusion study using conscious instrumented dogs. The effects were transient and inconsistent at best.

"Carcinogenicity, Mutagenicity, Impairment of Fertility"
The statement "In animals, there was no increased incidence of tumors considered relevant for humans" should be removed. The statement should be replaced with "Dronedarone caused histiocytic sarcomas in male mice (300 mg/kg/day or 4.8X MRHD based on AUC comparisons) mammary adenocarcinomas in female mice (300 mg/kg/day or 8.2X MRHD based on AUC comparisons) and hemangiomas in male rats (70 mg/kg/day or 4.6X MRHD based on AUC comparisons). "

The statement "Dronedarone was not shown to alter fertility in animal studies up to 100 mg/kg/day" should be removed and replaced with " In studies conducted with female rats, Dronedarone caused an increase in irregular cycles (≥30mg/m^2 equivalent to 0.06X

the MRHD of 493 mg/m^2)) and also caused cycling to stop (≥30mg/m^2 equivalent to 0.06X the MRHD of 493 mg/m^2)

"Pregnancy"
The paragraph that reads

> MULTAC can cause fetal harm when administered to pregnant women. Dronedarone caused marked effects on embryo-fetal development in rats at 100 mg/kg/day such as increased post-implantation losses, reduced fetal and placental weights, various external, visceral and skeletal malformations in most fetuses. At lower dosages, up to 50 mg/kg/day (corresponding to 4.5 times the recommended human therapeutic dose), dronedarone had no effects on the litters (with the exception of a transient minor effect on the bodyweight gain of the pups from D1 to D4 post-partum). Dronedarone had no effects on the mothers up to 30 mg/kg/day. On the contrary, in rabbits, the high dose level (200 mg/kg/day) did not induce any effects to fetuses.

Should be modified to read:

> Dronedarone was teratogenic in rats given oral doses ≥80 mg/kg (480 mg/m2 or approximately 1X the MRHD of 480 mg/m2) with fetuses showing external, visceral and skeletal malformations (cranioschisis, cleft palate, incomplete evagination of pineal body, brachygnathia, partially fused carotid arteries, truncus arteriosus, abnormal lobation of the liver, partially duplicated inferior vena cava, brachydactyly, ectrodactylia, syndactylia, anterior and/or posterior club feet).

It should also be noted in the label that phototoxicity manifested as erythematous reactions was reported in Guinea Pigs given 100 mg/kg/day (800 mg/m^2 or approximately 2X the MRHD)

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: Proposed for atrial arrhythmia, dronedarone is an amiodarone analogue lacking the iodine substituents. In in vitro systems, isolated organ culture and whole animal studies have been used to compare this agent to amiodarone. There are many similarities between the effects of the two agents on the ion channels of the heart and the behavior in various non-clinical models of cardiac function that are intended to show anti-arrhythmic potential.

   The drug has relatively low oral bioavailability of in the dog 14 % and rat 22%. The volume of distribution is large, from 12 to 66 l/kg with a moderately high systemic

clearance of 2-4 l/h/kg. In all species studied, including human, dronedarone was highly protein bound (>99%). Dronedarone is also highly metabolized with one known active metabolite (SR35021).

In addition to the usual toxicological characterization, dronedarone has also been assessed for immunotoxicologic potential (no significant issues apparent at this time), effect upon thyroid function (incompletely described) and dyslipidosis (occurs to a lesser extent than seen with amiodarone). Mild respiratory effects (decreased respiratory rate and tidal volume) were seen in the single dose respiratory safety pharmacology study. Phototoxicity (mild to moderate at the equivalent of 2X MRHD) has been demonstrated in albino animals. Dronedarone has been demonstrated to bind to melanin. How this will affect phototoxicity is unknown. The sponsor has provided no characterization of the mechanism of the carcinogenic findings or the endocrine effects.

Some aspects of the non-clinical toxicology are puzzling. There are a number of instances where effects do not seem to follow a dose-response. It also appears that there is a lessening or abrogation of effects with extended dosing. That is, effects apparent after 1 month or 3 months of dosing are not evident after 6 months. Yet, plasma levels are no less at 6 months than they were at 3 months.

The sponsor is to be commended on the thoroughness of some aspects of the non-clinical characterization. That is, because of the similarity to amiodarone, immunotoxicity and phototoxicity studies were conducted and comparator compounds (positive controls) appear frequently. An outside review panel was assembled to provide a second opinion on the carcinogenicity studies. Yet the reporting does not do justice to these efforts. For example:

1) There were inconsistencies between the CTD non-clinical summary and the actual study reports.
2) There were inconsistencies within reports where textual numbers were not precisely the same numbers from the summary tables or single animal data
3) There were instances where findings were mentioned within the text of a report for which I could not find tables of numerical summaries.
4) The quality of the Carcinogenicity report by the outside review panel was disappointing at best.

None of these inconsistencies was large or nor do they change the interpretation of the studies in which they were found. The impression that I get is one of haste and a certain degree of carelessness.

B. Pharmacologic activity: Dronedarone has been shown to have properties of beta adrenergic blockade, and cardiac Na, K and Ca channel modulation. However, there is inadequate characterization of the receptor binding properties of both dronedarone and the two major metabolites SR35021 and SR90154. In particular, the possibility of

interaction with the thyroid receptor, hormonal receptors and steroidal receptors should be investigated.

C. Nonclinical safety issues relevant to clinical use : Dronedarone has been shown to be teratogenic, genotoxic, carcinogenic and to disrupt female cyclicity. The target organs of toxicity appear to be the kidney, liver, and gastrointestinal tract. Renal changes were usually without histological correlates and manifested primarily as changes in serum creatinine and serum electrolytes, excreted creatinine and electrolytes. Mild to moderate phototoxicity has been shown non-clinically in rats at a dose of 200 mg/kg (1200 mg/m2 or 2.5x MRHD based on a surface area comparison). Dronedarone does affect thyroid metabolism but this is incompletely defined. Hepatic effects range from elevations in ALT and AST to necrotic foci, possibly too small to cause perceptible changes in liver status tests. Safety pharmacology showed that dronedarone caused decreases in respiratory rate and tidal volume. Dyslipidosis manifested as foamy macrophages occurs but apparently to a lesser extent than seen with amiodarone.

A radiolabel distribution/excretion study showed that the mean concentration of total radioactivity in the heart, liver and lungs was approximately 13, 5 and 20 times higher respectively at 4 hours post-dose on day 14 compared to 24 hours post dose on day 1. This is indicative of tissue accumulation. Comparing 4-hours post-dose at the earliest steady state vs. 4-hour post-dose several weeks later would more clearly address this potential issue.

Cardiac effects are also noted in rats, dogs and macaques. These include such things as decreased heart rate, increased PR interval and increased QT interval. QTc was inconsistently increased, possibly due to the fact that Bazett's formula was uniformly used no matter what the heart rate of the animals. First degree block was reported in rats, dogs and monkeys. Second degree block was also reported in macaques. Increased T wave amplitude was also noted in some studies. Many of the changes can be viewed as extensions of the expected pharmacology. Both dronedarone and the active metabolite SR35021 inhibit the hERG channel with almost the same potency as cisapride, the positive control for the studies (see page 16 of this review, NDA part I).

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

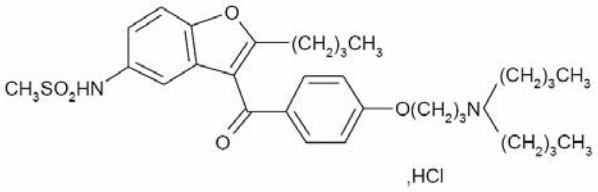
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21913
Review number: 1
Sequence number/date/type of submission:
Information to sponsor: Yes ( ) No ( )
Sponsor and/or agent: Sanofi-Synthelabo
Manufacturer for drug substance:

Reviewer name: Elizabeth Hausner, DVM
Division name: Division of Cardio-Renal Drug Products
HFD #: 110
Review completion date:

Drug:

Trade name: Multac®
Generic name: dronedarone
Code name:
Chemical name:N-{2- butyl- 3-[4-(3- dibutylaminopropoxy) benzoyl] benzofuran- 5-yl}methanesulfonamide, hydrochloride.
CAS registry number:
Molecular formula/molecular weight: $C_{31}H_{44}N_2O_5S,HCl$/ 593.2



Structure:

Relevant INDs/NDAs/DMFs: IND49484

Drug class: antiarrhythmic

Intended clinical population: patients with atrial flutter or atrial fibrillation

Clinical formulation: 400 mg of dronedarone base with inactive ingredients of hypromellose, starch, crospovidone, poloxamer 407, lactose monohydrate, colloidal silicon dioxide, magnesium stearate

Route of administration: oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

Studies Reviewed (Many of the pharmacology studies were reviewed in the IND process)

Pharmacology/Safety Pharmacology

In vitro effect of SR35021A on various receptor sites **RS0008950706/01: 685-4-052**
In vitro effects of SR90154 on various receptor sites **RS0008960726/01: 685-4-067**
Effect of SR33589B on the central and autonomic nervous systems in male mice after intravenous administration. **SNX0058**
SNX0054 Effect of SR33589B on the central and autonomic nervous systems in male mice after oral administration
Effects of dronedarone on human cardiac sodium current. Comparison to amiodarone. **CTT103.**
Effects on the hERG channel stably expressed in a mammalian cell line. **PAT0076**
Effects on the hERG channel stably expressed in a mammalian cell line. **PAT0077**
Interaction between SR33589B and Beta-adrenoceptor sites in rat cardiac membranes: in vitro study.**CTT0168** June 1994
Effect of chronic oral SR33589B administration on cardiac beta-adrenoceptor and adenylate cyclase activity in rat. **685-4-043** June 1994.
SR35021A: Effects on the hERG channel stably expressed in a mammalian cell line **PAT0082**
Effects of SR35021A on the action of potential[sic] characteristics of rabbit purkinje fibers. **685-4-054**
Effect of SR33589 in comparison with amiodarone and other class III antiarrhythmic agents on action potential duration in anesthetized rats **685-4-021** November 1991
SR33589B and amiodarone: Electrophysiological actions in anesthetized dogs **CTV0201**
Hemodynamic study after oral administration of SR33589B in the conscious dog. Comparison with amiodarone. **685-4-038** January, 1994
Evaluation of the effects of an acute oral administration of SR33589B on respiratory parameters in unrestrained conscious guinea pigs using whole body plethysmography
Effect of SR33589B on the cardiovascular and respiratory functions in anesthetized dogs after intravenous administration. **CVR0119**
Effect of SR33589B on the cardiovascular and respiratory functions in anesthetized dogs after intraduodenal administration. **CVR0125**
Effect of SR33589B on the hydroelectric balance in rats after intravenous administration **RS0040931005/ION0293**
Effect of SR33589B on the hydroelectric balance in rats after oral administration **ION0217**
Effects of dronedarone on renal function in conscious normotensive rats following repeated oral administration **PGD0133** January 2005
Effect of SR33589B on intestinal transit in mice after oral administration **GIT0029**
Effect of SR33589B on gastric emptying in rats after oral administration. **GIT0030**
Effect of SR3389B on gastric acid secretion in rats after oral administration **GIT0031**
Effects of chronic oral SR33589B administration on plasma thyroid hormone levels in rat. Comparison with amiodarone. **685-4-013**
Phospholipid content of lung and liver in rats treated orally for 14 days with SR3389B and amiodarone **685-4-040**

Pharmacokinetics/Toxicokinetics

Determination of SR33589 and its N-debutyl metabolite (SR35021) in mouse plasma by HPLC-UV following liquid/liquid extraction. **DOS0320**
HPLC-UV assay of SR33589 and its N-debutyl metabolite SR35021 in rat plasma samples **DOS0150**

Validation of an electrospray LC-MS/MS detection method for the quantitative analysis of SR33589 and its metabolite SR35021 in mouse plasma following a Disk SPE (96 well plate) extraction. **DOS0465**
Validation of an LC/MS-MS detection method for the quantitative analysis of SR33589 and its metabolite SR35021 in rat plasma following a Disk SPE (96 well plate) extraction **DOS0444.**
Long term stability of SR33589 and SR35021 in frozen rat plasma. **SPP0010**
Long term stability of SR33589 and SR35021 in frozen dog plasma **SPP0011**
Radioachemical stability and binding to glass and plastic of 14C labeled 33589B in vehicles used for animal studies. **SFA0002**

Pharmacokinetics and absolute bioavailability of SR33589B following single 10 mg/kg intravenous and 30 mg/kg oral administration of (carbonyl-14C)-SR33589B to male and female Sprague-Dawley rats. **Abs0102**
Pharmacokinetic profiles of SR33589B and SR35021 following a single (30 mg/kg) oral or (5 mg/kg) intravenous infusion administration of SR33589B or SR35021A to Beagles. **Abs0209**
The pharmacokinetics of SR33589 following a single 1 mg/kg intravenous administration of (carbonyl-14C)-SR 33589B to male Macaca [sic] monkeys. **ABS0103**
Quantitative tissue distribution and excretion balance of (carbonyl-14C)SR33589B following single oral administration (30 mg/kg) to the male Sprague-Dawley rat. **DIS0045**
Tissue distribution after a single (30 mg/kg) oral administration of (^{14}C-carbonyl) SR335589B to the female Sprague-Dawley rat **DIS0198**
Tissue distribution of radioactivity following a single (30 mg/kg) oral administration of (Carbonyl-^{14}C) SR33589B to the pregnant Sprague-Dawley rat **DIS0231**
Investigation of possible affinity of total radioactivity in melanin containing tissue following a single oral (30 mg/kg) administration of [^{14}C-carbonyl]-SR33589B to pigmented rats. **DIS0407**
Tissue distribution after a single (3 mg/kg) intravenous administration of (^{14}C-carbonyl) SR33589B to the male Sprague-Dawley rat. **DIS0140**

In Vitro Binding of [^{14}-carbonyl]- SR33589B to the Plasma Proteins of Rat, Mouse and Rabbit. **LPR0873**
In vitro binding of SR33589B to rat, dog, monkey maccaca and human plasma proteins. **LPR0508**
In Vitro Binding of [^{14}C- Carbonyl]- SR35021A to the Plasma Proteins of Rat, Dog, Mouse, Rabbit and Human **LPR0876**
Blood distribution and pharmacokinetics of radioactivity following single oral (30 mg/kg) or intravenous (10 mg/kg) administrations of 14C-labelled SR33589B to male and female Sprague Dawley rats Study **LPR0046**
Blood distribution and pharmacokinetics of radioactivity following single oral (25 mg/kg) or single intravenous (2.5 mg/kg) administration of 14C-labeled SR33589B to male Beagle dogs. **LPR0048**
Blood distribution and pharmacokinetics of radioactivity following single intravenous (1mg/kg) administration of 14C-labelled SR33589B to male Macaca monkeys. L**PR0047**
Fetal tissue distribution of radioactivity following a single (100mg/kg) oral administration of (Carbonyl-14C) SR33589B to the pregnant Sprague-Dawley rat. **DPK0054**
Placental transfer of radioactivity after a single oral (60 mg/kg expressed as unsalified compound) administration of [^{14}C-Carbonyl]-SR33589B to the pregnant New Zealand rabbit (Quantitative Whole Body Autoradioagraphy) **PLT0037**
Toxicokinetic study, complementary to the study for effects on embryo-fetal development in the rabbit. **DIV0914**
Interspecies variability in SR33589B metabolism by hepatic microsomal fractions **MIV0143**
Profile and identification of plasma, urine and fecal metabolites following a single and repeated oral administration (75 mg/kg/day) of [14C]-SR33589B to male Swiss CD1 mice. **MET 0462**
Plasma, urinary, tissue and fecal metabolites following single and repeated oral administrations (10 mg/kg/day) of [^{14}C]SR33589B to male Sprague-Dawley rats. **RME0003**
Profile and identification of plasma metabolites following single oral (30 mg/kg) or single intravenous (10 mg/kg) administration of ^{14}C-labeled SR33589B to male and female Sprague-Dawley rats **Met0138**
Profile and identification of urinary metabolites following a single oral (30 mg/kg) or intravenous (10 mg/kg) administration of ^{14}C-labelled SR33589B to male and female Sprague-Dawley rats. **Met0139**
Profile and identification of biliary metabolites following single oral (30 mg/kg) or intravenous (10 mg/kg) administration of 14C labeled SR33589B to male and female Sprague-Dawley rats. **MET0140**

Profile and identification of plasma, urine and fecal metabolites following a single oral administration (60 mg/kg) of [14C]-SR33589B to the female New Zealand white rabbit. **MET0533**
Profile and identification of plasma, urinary and fecal metabolites following single and repeated oral administrations (15 mg/kg/day) of [14C-carbonyl]-SR33589B to male dogs. **RME0009**
Profile and identification of plasma metabolites following a single oral (25 mg/kg) or a single intravenous (2.5 mg/kg) administration of (14C)-SR 33589B to male dogs. **MET0237**
Profile and identification of urinary metabolites following single oral (25 mg/kg) and intravenous (2.5 mg/kg) administrations of (14C)-SR33589B to male dogs. **MET0238**

Profile and identification of plasma metabolites following single intravenous (1 or 8 mg/kg) administration of 14C-labelled SR33589B to male macaca monkeys **MET0141**
Profile and identification of urinary metabolites following single intravenous (2.5 or 8 mg/kg) administration of 14C-labelled SR33589B to male macaca monkeys. **MET0142**

Effects of SR33589B repeated oral administration (375,450 mg/kg/day) during 14 days on various liver monooxygenase activities in CD-1(ICR)BR mouse. **TIN0089**
Effects of a 2-week repeated oral administration of SR33589B (30, 70 and 160 mg/kg/d) on various liver enzyme activities in Sprague-Dawley rats. **TIN0045**
Effect of a 2-week repeated oral administration of SR33589B (25, 60 and 140 mg/kg/d) on various liver enzyme activities in Beagle dogs. **TIN0046**
Pharmacokinetics and excretion balance after single and repeated oral (10 mg/kg/day) administration of [14C-carbonyl]-SR33589B to male Sprague-Dawley rats. **RDS0008**
Excretion balance following a single oral (30 mg/kg) or a single intravenous (10 mg/kg) administration of 14C-labelled SR33589B to male and female Sprague-Dawley rats. **EBA0056**
Enterohepatic recirculation of radioactivity following a single intravenous (10 mg/kg) administration of [^{14}C]-SR33589B to male Sprague-Dawley rats. **MET0464**
Pharmacokinetics and excretion balance after single and repeated oral (15 mg/kg/day) administration of[14C-Carbonyl]SR33589B to male dogs. **RDS0009**
Excretion balance following single oral (25 mg/kg) or single intravenous (2.5 mg/kg) administration of 14C-labelled SR33589B to male Beagle dogs.**EBA0092**
Excretion balance following a single intravenous (2.5 mg/kg) administration of 14C-labelled SR33589B to male macaca monkeys. **EBA0057**
The secretion of total radioactivity in milk of lactating albino rats following a single oral (30 mg/kg) administration of [^{14}C-carbonyl]-SR33589B. **MIL0003**

Toxicology
TXA0224 Single dose oral toxicity study in mice and rats of both sexes(3/31/93 initiated).
TXA0232 Single dose oral toxicity study in mice and rats of both sexes
TXA0231 Single dose intravenous toxicity study in mice and rats of both sexes
TXA0290 Single-dose intravenous toxicity study in mice and rats of both sexes
TXA879 Two-week oral toxicity study in the rat
TXC088 Three -month oral toxicity study in the rat
TXC0986 Six-month oral toxicity study in the rat
DDO0499 4-day intravenous dose-range finding study in the rat
DDO548 Preliminary toxicity study by intravenous infusion to CD rats for seven days
TSA0963 Toxicity study by intravenous infusion to CD rats for four weeks
4-Week intravenous infusion toxicity study in the rat: toxicokinetic data. Complement to the report RS0006950316/01. **TSA0963**
TSA0883 Two-week oral toxicity study in the dog
TXC0886 3-month oral toxicity study in the dog
TXC0970 One-year oral toxicity study in the dog
TSA0885 Two-week intravenous toxicity study in the dog
DDO0549 Preliminary toxicity study by intravenous infusion to beagle dogs
TSA0962 Toxicity study by intravenous infusion to Beagle dogs for four weeks
TSA0962 4-week intravenous infusion toxicity study in the dog: toxicokinetic data

DDO0503 Four-day intravenous dose-ranging study in the macaque
TSA0884 2-week intravenous toxicity study in the macaque

Genetic Toxicology
CEL0593 Ames test-reverse mutation assay on Salmonella typhimurium
Cel0709 Ames Test-Reverse mutation assay on Salmonella typhimurium
FSRFU-LYM0125-EN-E01 In vitro gene mutation assay at the locus TK +/- in mouse lymphoma L5178Y cells
685-3-008 In vitro gene mutation assay at the locus HPRT in Chinese Hamster V79 fibroblasts.
DNA001 In vitro DNA repair assay on rat hepatocytes in primary culture
CEL0536 In vitro DNA repair assay on rat hepatocytes in primary culture
MAF0018 Lymphocyte cytogenetic study
Mut0046 Micronucleus test in vivo genotoxicity study by the oral route in the mouse.

Reproductive and Developmental Toxicology

FER250 Preliminary Segment I study in the rat

Previously Reviewed:

Study of effects on fertility and early embryonic development in CD rat by oral gavage administration **FER0297**
TER0242 Preliminary teratology study in the rat
TER0244 Teratology study in the rat
DD0518 13-day oral dose range-finding study in female rabbits
TER0241 Preliminary teratology study in the rabbit
TER0243 Study of effects on embryo-fetal development in the rabbit.
DPN0295 Study of the effects of SR33589B on pre- and post-natal development (including maternal function) in the rat by oral gavage

Special Toxicology Studies
A four week oral immunotoxicity study in the rat.
Evaluation of phototoxicity and/or photoallergy in the guinea pig. **PHO121-137-141**

Study of the hemolytic potential in vitro. **HEM0009**
Hemolytic potential in vitro **HEM013**
Study of the hemolytic potential in vitro. **HEM0015**
Study of hemolytic potential in vitro. **HEM0026**

Carcinogenicity Studies
CAR0032 An assessment of oncogenic potential in mice following oral administration
CAR0036 A study to assess oncogneic potential in rats following oral administration
EXP0007 Mouse (CAR0032) and rat (CAR0036) carcinogenicity studies. Dronedarone (SR33589B). Scientific advisory panel report.

Studies not reviewed within this submission:

Validation of an electrospray LC-MS/MS detection method for the quantitative analysis of SR33589B and its metabolite SR35021 in guinea pig plasma following a Disk SPE (96 well plate) extraction**DOS0753**
Validation of an electrospray LC-MS/MS detection method for the quantitative analysis of SR33589B and its metabolite SR35021 in rabbit plasma following a Disk SPE (96 well plate) extraction**DOS0613**
Validation of an LC-Ms/MS method for the quantitative analysis of SR33589 and its metabolite SR35021 in dog plasma following a solid phase extraction. **DOS0534**
Determination of SR33589 and its N-monodebutyl metabolite SR35021 in dog plasma by HPLC-UV following liquid-liquid extraction **DOS0255**
HPLC-UV assay of SR33589 and its N-debutyl metabolite, SR35021 in macaca plasma samples. **DOS0149**
Long term stability of SR33589 and its metabolite (SR35021) in frozen spiked mouse plasma samples **SPP0172**

Investigation of long-term stability of SR33589 and its metabolite SR35021 in rat plasma **SPP0195**
Preliminary pharmacokinetic profile of SR33589 and SR35021 after single 2.5 mg/kg intravenous and 100 mg/kg oral administrations of SR33589B to beagle dogs. **APS0032**
Quantitative tissue distribution of total radioactivity in the male albino rat following daily repeated oral (10 mg/kg/day) administrations of [14C-carbonyl]SR33589B(quantitative whole body autoradiography) **RDI0003**
Blood distribution of SR33589B in rat, dog and macaca – in vitro study **LPR0108**

Note: For NDA reviews, all section headings should be included.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary The pharmacology of dronedarone has been explored using cell membrane preparations, various other in vitro methodologies, isolated organ systems and a number of whole animal systems including rats, guinea pigs, rabbits, dogs and pigs. The drug has been demonstrated to possess a number of pharmacologic actions primarily focused on the cardiovascular receptors and cardiac ion channels. The sponsor has also made use of concurrent comparator compounds in many of the pharmacology studies.

Dronedarone has been shown to bind to and inhibit the rapid sodium channel. The decrease in dV/dt_{max} caused by the drug was frequency dependent with rapid onset kinetics. This is characteristic of Class I anti-arrhythmic agents.

In vitro and ex vivo studies showed that dronedarone decreased stimulation of adenylate cyclase activity by both isoprenaline and glucagon but did not effect stimulation resulting from direct acting agents such as sodium fluoride or Forskolin. The drug was thus characterized as a non-competitive β-adrenergic antagonist (Class II anti-arrhythmic).

While dronedarone interacted with a number of the different K+ channels, the effects were not uniform. Concentration –dependent effects were reported for I_{kr}, I_{ks}, $I_{k(Ach)}$ and $I_{kv1.5}$. The sponsor cites these effects as suggestive of a role for dronedarone in cases where increased vagal tone is important, e.g. atrial fibrillation. $I_{kv1.5}$ is considered important in repolarization of human and canine atria. Affinity for this channel is suggested as underlying the increase in atrial effective refractory period seen in anesthetized dogs. It may be noted that dronedarone gave 94.4±1.8% inhibition of the hERG channel expressed in CHO cells at a concentration of 10 μM. Cisparide in the same experiment produced 100% inhibition of the hERG channel at the same concentration. QT interval was consistently prolonged in those studies where ECG data was gathered. The QTc values were generated by Bazette's formula, inappropriate given the heart rate of the animals used. Thus the QTc values were inconsistently elevated. Interaction with K+ channels is characteristic of Class III anti-arrhythmics.

Dronedarone also showed binding to and use-dependent inhibition of L-type calcium channels, a characteristic of Class IV anti-arrhythmic drugs. In vitro this corresponded to decreased shortening of isolated ventricular cells. In some of the whole animal studies were ECG data was gathered, changes were manifested in the PR interval and the T-wave amplitude.

Dronedarone decreased sinus rhythm by a variety of mechanisms including decreased rate of diastolic depolarization and lengthening of the APD (I_{Ca-L} and I_k). Decreased heart rate was seen when dronedarone was given to rats and dogs. Other cardiac data provided showed increases in the Wenckeback cycle length, AH and PQ interval, suggestive of changes in AV nodal conductance.

There were several safety pharmacology studies that reported decreases in peripheral resistance. The calcium channel effects may have contributed to this. In vitro studies indicated mild interaction of the drug with α1, β1 and β2 adrenergic receptors. How much this contributed to the peripheral resistance decreases in vivo is uncertain.

The circulating metabolite SR35021A was examined in isolation for its hemodynamic effects when given intravenously to anesthetized mixed-breed dogs (CVT0209). Observation after 1 mg/kg lasted 1 hour, observation after 3 mg/kg lasted 2 hours as did the observation after 10 mg/kg.

SR35021A given intravenously (sponsor's numbers)

	Baseline values mean±sem	1 mg/kg	3 mg/kg	10 mg/kg	Vehicle range
HR bpm	122±6	-8%	6%	38% (>120)**	+6 to +12%
TPR 10^2 .dynes.s/cm^5	31±1	7%	12%	-46%(15)**	-3 to +19%
SBP mm Hg	176±6	-5%	3%	-12%(60)*	-6 to +7%
DBP mm Hg	124±4	3%	6%	-15%(10)*	+3 to +6%
MBP mm Hg	146±4	3%	4%	-13%(15)*	-3 to +7%
PADP mm Hg	10±1	10%	19%(>40)	25%(20)	22 to 30%
LVEDP mm Hg	5±1	40%(5)	+29%(70) -23%(10)	90%(110)	-20 to +11%
CO (l/min)	3.8±0.2	-5%	-9%	61%(10)**	-11 to +3%
Carotid BF (ml/min)	195±23	-24% (>60)*	-27%(120)*	45%(10)	-17 to +23%
LVW	8.1±0.7	-9%	-9%	39% (10)*	6 to 9%
SV	32±2	3%	-9%	14%(5) -24%(120)*	-16 to -8%
RVEF %	42±3	-3%	-21%	-25% (110)**	NC

( ) total duration of effects *p<0.05, **p<0.01

The low dose had minimal effect on the hemodynamic parameters. The MD of 3 mg/kg produced a 21% decrease in RVEF and a 27% decrease in carotid blood flow for approximately 2 hours. The HD of 10 mg/kg produced a negative inotropic effect (-12%) and a 25% decrease in RVEF for ~110 minutes accompanied by a corresponding decrease in stroke volume. The increased HR (38%) and 46% decrease in total peripheral resistance caused a brief (10 minute) increase in cardiac output.

Detrimental ECG changes were also reported with administration of SR35021: extrasystoles (PVCs?) were seen in 1/5 (LD), 5/5 (MD) and 3/5 (HD). Most of the animals showed multiple PVCs. The vehicle used (PEG 400) did not cause the reported changes.

Most of the ECG changes are expected as extensions of the primary pharmacology.
From the data available I am not sure if both the parent drug and SR35021A or if only SR35021A are responsible for the undesirable ECG changes (AV block, extrasystoles, Torsade de Pointe). As coronary blood flow was not measured in the hemodynamic assessment of the metabolite, the same can also be said for the effect measured in previous intravenous administration studies.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: The mechanism of action appears to be due to the combination of the various ion channel effects. It cannot be determined from the available information if one mechanism predominates. Another consideration is that some single mechanism as yet undescribed is responsible for the pharmacologic action.

In vitro receptor binding for the parent drug and SR35021 and SR90154, the two main metabolites, is poorly characterized. No data was presented beyond cardiac ion channels and cardiovascular receptors.

IC50 (µmol/l) of dronedarone on different ion channels in guinea pig heart

	I_{kr}	I_{Ks}	I_{Kl}	I_f	I_{KACh}	I_{Ca-L}	I_{Ca-T}
dronedarone	≤3	~10	≥30	≥30	~0.01	0.18	>30

IC50(µmol/l) of dronedarone on human hERG channel

	hERG(expressed in CHO cells)	hERG (expressed in HEK cells)	$K_{v1\ 5}$
dronedarone	0.53	0.059	2.7

IC50 values for other targets

Target	dronedarone	Amiodarone
Calmodulin-dependent cyclic nucleotide phosphodiesterase	0.89 µmol/l	0.12µmol/l
Ca_L	546±13nmol/l	173±5 nmol/l
Na+ channel (batrachotoxin) Heart brain	 2060±104nmol/l 413±46nmol/l	 1654±227nmol/l 645±105 nmol/l

Drug activity related to proposed indication: Various in vitro, ex vivo and in vivo studies have shown that dronedarone can alter the characteristics of the ECG, action potentials, Wenckebach cycle and cardiac function parameters. The results are supposed to be indicative of anti-arrhythmic potential in the human. The various ion channels and receptors that the sponsor states to be affected by dronedarone are the mechanisms usually associated with anti-arrhythmic effects.

In the atrium, dronedarone decreased the spontaneous sinus rhythm, action potential amplitude and lengthened the action potential duration in the guinea pig sinoatrial node. In the ventricles, dronedarone decreased dV/dt max of the AP. Cardiac contraction was reduced. Dronedarone was also demonstrated to prolong the Wenckeback cycle length (reviewed in the IND) and slightly prolong the effective refractory period.

In the sponsor's proposed labeling, they also mention that dronedarone has vasodilatory properties and increased coronary blood flow (CBF). A study using isolated rat hearts in Langendorf preparations showed an increase in coronary blood flow of 20-30% compared to baseline (report 685-4-019). Anesthetized dogs given intravenous infusions of dronedarone of 1 and 5 mg/kg, 30 minutes apart showed a decrease in coronary resistance. At rest, 1 mg/kg caused a non-significant increase in (CBF). The 5 mg/kg dose caused a transient fall in MVO_2 (-69% at 35 minutes and -7% at 60 minutes post infusion) and a transient rise in CBF of +54% (32 minutes post-infusion and +46% at 45 minutes post-infusion (report 685-4-006). Decreased MVO2 may be associated with the decreased HR seen.

2.6.2.3 Secondary pharmacodynamics

In vitro effect of SR35021A on various receptor sites RS0008950706/01: 685-4-052 Using material from guinea pigs and Sprague-Dawley rats, the metabolite was used in competition experiments to examine binding of radioligands in a limited panel of receptors. Weak activity was reported for β1 and β2 adrenergic (≤10% inhibition at 3 μM), α1 and α2 adrenergic, purinergic A1 and cholinergic muscarinic receptor sites.

In vitro effects of SR90154 on various receptor sites RS0008960726/01: 685-4-067
SR90154 was examined in competition studies on specific binding to a limited array of receptors in brain, heart and lung membranes. This metabolite showed mild receptor activity for the α1-adrenergic receptor (14±1% inhibition at 30 μM), cholinergic muscarinic (19±3% at 30 μM), purinergic A1 (16±1% inhibition at 30 μM), L type Ca++ channel (10±2% inhibition at 30 μM), Na+ channel (17±3% inhibition at 30μM), ATP-dependent K+ channel (31±1% inhibition at 30 μM)

2.6.2.4 Safety pharmacology

Summary: the effects of dronedarone were assessed in models of neurologic, cardiovascular, pulmonary , renal and gastrointestinal function.

Neurological effects: A single intravenous injection of 10 mg/kg caused a non-significant decrease in the activity level of mice. A single oral dose of ≥200 mg/kg caused a decrease in spontaneous motor activity in rats. A single oral dose of 800 mg/kg caused sedation.

Cardiovascular effects: The sponsor performed extensive pharmacological investigations into the effect of the drug on the cardiovascular system. A very few of these tests are summarized in the table below.

Summary of some Cardiovascular Safety Comparisons

Parameter studied	Comparator compound results	Dronedarone or metabolite result
Inhibition of atrial sodium channels	Amiodarone: 80±7% @30 μM	97±4% @ 3 μM
Inhibition of inward hERG (CHO cells)	Cisapride 100% @ 10 μM	94.4±1.8% @10 μM
β-adrenoceptor inhibition IC50 nM	Amiodarone 8650±2040 (±)propranolol 11.6±1.1	1755±360
Inhibition of inward hERG (CHO)	Cisapride 100% @ 10μM	SR35021A 91.8±3.7% @10μM
APD90 in anesthetized rats	Amiodarone 83% @ 30 mg/kg Cisapride 41% @ 30 mg/kg	39% @ 10 mg/kg. 60% of the rats experienced an AV block

Cardiovascular effects were also examined in anesthetized and conscious dogs. In anesthetized dogs, IV amiodarone was used as a comparator for intravenous dronedarone. Dronedarone caused approximately twice the decrease in heart rate compared to amiodarone based on percentage of means. Dronedarone also caused substantially greater increase in the PQ interval (42 vs 11, units not given) based on percentage of means. The conscious dogs received oral amiodarone or dronedarone. Plasma levels of drug were measured. There was no difference in plasma levels between 12.5 and 25 mg/kg (presented graphically, 0.3-0.4 nmol/ml) but there was an increase from 25 to 50 mg/kg/day (peaking at 3 nmol/ml). The sponsor showed a dose-related increase in heart rate (opposite to the decreases seen in toxicology studies): an increase of 27% at the LD of 12.5 mg/kg lasting for 45 minutes up to a 39% increase at the HD of 50 mg/kg lasting for 420 minutes. Dronedarone produced greater than usual changes in the heart rate and contractility in this study, also based on percentage of means. The results are summarized in the sponsor's table below. It could be questioned whether a larger sample size would have decreased the differences between the two drugs.

Sponsor's summary of dronedarone results

	12.5 mg/kg (n=5)		25 mg/kg (n=8)		50 mg/kg(n=6)	
	Control values	Maximal Var.%	Control values	Maximal Var.%	Control values	Maximal Var.%
HR(bpm)	75±7	+27(45)	75±4	+24* (330)	77±4	+39**(420)
DAP(mm HG)	79±5	-6	78±3	+6	81±6	-16(>420)
SAP(mmHG)	131±8	-8	126±3	-4	125±8	-17(>420)
MAP(mmHG)	96±6	-7	94±2	-4	96±6	+16
LVSP(mmHG)	138±7	-7	133±3	-7	137±5	-17*(>420)
LVEDP(mmHG)	12±3	-22	11±1	+17	14±2	-7
Cont(s^{-1})	32±3	+8	28±1	+9	26±1	-32**(>420)
Relax (s^{-1})	23±1	+16	22±1	+7	21±2	+7(375)

Control values were the mean±sem of the seven measurements before administration for all dogs of each group. Treatment-induced variations were calculated as percentage of means.
( ) total duration of effect in minutes
*p<0.05, **p<0.01 by the Mann Whitney U test

Sponsor's summary of amiodarone results

	25 mg/kg (n=6)		50 mg/kg(n=6)	
	Control values	Maximal Var.%	Control values	Maximal Var.%
HR(bpm)	77±4	+10	75±4	+2
DAP(mm HG)	84±4	-9	80±6	+8
SAP(mmHG)	131±5	-9	131±6	+3
MAP(mmHG)	99±4	-8	97±6	+5
LVSP(mmHG)	145±4	-6	139±9	-8
LVEDP(mmHG)	14±2	-22	14±2	+13
Cont(s^{-1})	29±2	+13	28±2	-13
Relax (s^{-1})	22±2	+14	21±1	+13

Control values were the mean±sem of the seven measurements before administration for all dogs of each group. Treatment-induced variations were calculated as percentage of means.
( ) total duration of effect in minutes
*p<0.05, **p<0.01 by the Mann Whitney U test

Pulmonary effects: were assessed in guinea pigs using whole body plethysmography. Theophylline was the positive control. At the highest dose of 100 mg/kg dronedarone caused a mild decrease in respiratory rate from 30 to 105 minutes after oral dosing (-11 to -16 mean change from baseline vs a change of -5 to -8 in the control group). Despite large variability, a doses of 30 mg/kg caused a depression of tidal volume of -6 to -23 mean change from baseline while theophylline caused a change from 30-60 minutes of -17 to -62 mean change from basleine.

Another study of both respiratory and cardiovascular effects following intravenous administration of dronedarone to anesthetized dogs showed dose-related effects on essentially

every parameter assessed. Mean blood pressure, heart rate, total peripheral resistance and contractility showed decreases with increasing dose. The PR interval increased as did the QT interval. Respiratory effects were also apparent with a dose-related increase in respiratory frequency and flow. Tidal volume showed a lot of variability. The results are summarized in tabular form on page 28 of this review. Oral, IV and intraduodenal effects are compared in the reviewer's table below

Intraduodenal administration of drug produced decreases in mean blood pressure and variable increases in heart rate. LV stroke volume and CO correspondingly increased with a decrease in total peripheral resistance. The respiratory changes were similar to those already recorded in that respiratory frequency and flow increased. Tidal volume again showed variability with a decrease at the HD.

Comparison of respiratory effects with different routes of administration of dronedarone (respiratory effects were not measured in dogs following oral administration)

	IV	Intraduodenal
Doses mg/kg	1,5	12.5, 25
Respiratory frequency (Cycles/min)	↑+9-15	↑+9-14
Respiratory flow(l/min)	↑up to 89%, parallel to respiratory frequency	↑51-127%, parallel to respiratory frequency
Tidal volume	↓~13% from 10-30 minutes	↓10-19%

Comparison of cardiovascular effects with different routes of administration of dronedarone

	Oral	IV	Intraduodenal
Doses mg/kg	12.5, 25, 50	1,5	12.5, 25
Heart rate	+45-420%	0- ↓29 bpm	+0-12 bpm
DAP mm Hg	+6 to -16		
SAP mm Hg	-4 to -17		
MAP mm Hg	-4 to +16	↓ to 32 mm Hg	↓ to 13 mm Hg
LVSP mm Hg	-7 to -17	↓parallel to blood pressure	↑ 27%
Contractility (s^{-1})	+9 to -32		
Cardiac output		↑early up to 35%	↑to 30%

The ECG changes of increased PR interval and increased QT are consistent with the toxicology studies. The variability of some results may be due to the vagaries of oral and intraduodenal absorption, and variations in individual metabolism. There is also a consideration that these tend to be acute, one exposure studies, versus the effects seen in the repeat dose toxicology studies.

Renal effects: After IV administration, females showed a dose-related increase in specific gravity (1.02-1.025, $p<0.01$) with no effect in males. Both sexes showed an increase in excreted K+ concentration (males 3-5 mM over control values; females 1-30 mM over control values). While creatinine clearance and concentration was unaffected in males, females showed a dose-related

increase in both parameters: Cr_{Cl} 28 to 33% and Cr_{conc} 1.7 – 2.7. Both sexes were also reported to have blood in the urine. Following oral administration there were some slight changes of questionable biological significance such a decrease in excreted creatinine in the HD of both sexes. The quantity of excreted potassium decreased in both sexes at the HD. Decreased creatinine clearance was seen in both sexes. Correspondingly the concentration of serum creatinine increased in both sexes. Serum sodium and potassium increased only in the females. Hematuria was not reported in this study as it was in the IV administration study. Alterations in creatinine and excreted electrolytes were also noted in the toxicology studies.

Gastrointestinal effects: Given orally to mice, dronedarone at the LD (100 mg/kg) and HD (1000 mg/kg) caused increases in intestinal transit time of 14% and 36% ($p \leq 0.05$) respectively. Given orally to rats, 100 mg/kg caused a decrease in gastric emptying of 10% while the HD of 300 mg/kg caused a decrease of 53%. Thus in these two species the same drug caused opposite effects upon the gastrointestinal system. Acid secretion was measured in rats after a single oral dose of 100 mg/kg dronedarone. There was a 13%(NS) increase in the volume of acid secretion.

INDIVIDUAL STUDIES

Neurological effects:
Effect of SR33589B on the central and autonomic nervous systems in male mice after intravenous administration. ***SNX0058*** June-July 1993. Male OF1 mice 10-12/group were given 0,3 or 10 mg/kg at an injection rate of 1 ml/min. Effect of the drug on central and autonomic NS was assessed by modified Irwin's test, body weight changes (7 day follow up) , body temperature, muscle tone and motor coordination and spontaneous motor activity. The behavior, body temp, and musculoskeletal parameters were observed 15, 30, 60 and 120 minutes after dosing. Spontaneous motor activity was performed 5 minutes after administration over a 30 minute period. There were no apparent differences in body weight and no unscheduled mortality was reported. No differences in behavior were recorded between the different groups. A slight decrease in body temperature was noted in all groups for the 2 hours of observation. No differences between groups were noted in the tests of motor coordination. There was a non-significantly lower level of activity in the 10 mg/kg group at the 3 timepoints of measurement.

SNX0054 *Effect of SR33589B on the central and autonomic nervous systems in male mice after oral administration. October-November, 1992*
Test A: doses of 0, 50, 100, 200, 400 and 800 mg/kg
Tests B,C,D: doses of 0, 100, 200 mg/kg The vehicle used for all tests was 5% gum Arabic

Male OF1 mice were used, 10-12/group. The tests were A. Behavior(modified Irwin's) and body weight (7 days) B. body temperature C. Muscle tone and motor coordination D. spontaneous motor activity. For A,B and C observations were performed at 30 , 60, 180 and 360 minutes. There was a 7 day follow-up for test A. Test D was performed at 30, 60 and 180 minutes after administration over a 30 minutes period for each evaluation time.

No unscheduled mortality was reported.

There was no significant difference in weight gain between the control group and doses up to an including 400 mg/kg. The 800 mg/kg group gained on average 4% less than the control group. The difference in rate of gain was apparent from day 3.
Doses ≥200 mg/kg caused a decrease in spontaneous motor activity. A dose of 800 mg/kg caused sedation.

Cardiovascular effects:
Effects of dronedarone on human cardiac sodium current. Comparison to amiodarone. ***CTT103.***

Human atrial myocytes obtained during surgery were dissociated and sodium currents obtained from whole cells, at room temperature by patch clamp technique. Sodium currents were obtained in the presence of TEA and 4-AP with low extracellular concentration of sodium ions (27 mM NaCl). Test substances were added to the extracellular solution and perfused on the cells for 7-10 minutes to obtain the maximum effect.

The sponsor's table is reproduced below:
Inhibition of percentages of I_{Na} by dronedarone and amiodarone

	0.3 µM	3 µM	30 µM
Dronedarone	23±10 [a]	97±4 [b,c]	
amiodarone		41±11[a,c]	80±7[b]

a: not significant (0.3µM dronedarone vs 3 µM amiodarone)
b: not significant (3µM dronedarone vs 30 µM amiodarone)
c: p<0.003 (3 µM dronedarone vs 3 µM amiodarone)

Dronedarone produced a greater inhibition of the atrial sodium channels at a lower concentration than amiodarone.

Effects on the hERG channel stably expressed in a mammalian cell line. PAT0076

Chinese hamster ovary (CHO) cells stably transfected to express the hERG channel were examined with the patch clamp technique. Dronedarone in 0.1% DMSO at concentrations of 0.01, 0.1,1 and 10µmol/l was added to the test system. Cisapride at 10 µmol/l was the positive control.

Summary of inhibition of inward tail of hERG as a percent of the vehicle control

	IC50	Drug concentration (µmol/l)		
		0.1	1	10
Dronedarone	531±27 nmol/l; (315±16 ng/ml)	15.9±5.8%	65.6±7.6	94.4±1.8%
cisapride				100%

Under the conditions of the assay, dronedarone caused an inhibition of the hERG channel at a level similar to that of cisapride.

Effects on the hERG channel stably expressed in a mammalian cell line. ***PAT0077***

Chinese hamster ovary (CHO) cells stably transfected to express the hERG channel were examined with the patch clamp technique. Amiodarone was used at concentrations of 0.01, 0.1, 1 and 5 µmol/l. Cisapride was again the positive control.

Summary of inhibition of inward tail of hERG as a percent of the vehicle control

	IC50	Drug concentration µmol/l			
		0.1	1	5	10
amiodarone	1.36±0.18µmol/ 928±123 ng/ml	15.0±4.8%	41.4±4.3%	75±4.5	
cisapride					100%

Under the conditions of the study amiodarone was less potent than dronedarone in inhibiting the Ikr channel based upon IC_{50} comparison.

*Interaction between SR33589B and Beta-adrenoceptor sites in rat cardiac membranes: in vitro study.****CTT0168*** *June 1994*

This study examined the effects of SR33589B in DMSO (10^{-8}M to 10^{-4}M) in competition, saturation and dissociation experiments on the specific binding of [^{125}I]-(-)iodocyanopindolol ([^{125}I]-(-)-CYP to rat cardiac membranes. Amiodarone and ±propranolol were used as comparators. The conditions used were Tris buffer (50 mM) pH7.4 containing 10mM $MgCl_2$ and cardiac membranes (100 µg protein) incubated for 1 hour at 37ºC. Total bound radioactivity was measured after filtration and rinsing. Specific binding was defined in the presence of 2µM(-)-alprenolol (dissociation was induced by this addition).

Dronedarone had an IC50 for this binding somewhere between that of amiodarone and ±propranolol (approximately 4 times the affinity of amiodarone). Both amiodarone and dronedarone showed non-competitive interaction with the beta-adrenoceptor sites.

The sponsor's table is reproduced below.

Sponsor's Summary of responses: Dose-response curves: IC_{50} nM

	SR33589B	Amiodarone	(±)propranolol
[^{125}I]-(-)-CYP	1755±360	8650±2040	11.6±1.1

n_H included between 0.86 and 0.93

Effect of chronic oral SR33589B administration on cardiac beta-adrenoceptor and adenylate cyclase activity in rat. ***685-4-043*** *June 1994.*

Male rats (10/group) were treated orally with SR33589B or amiodarone at 0(vehicle), 50, 100 or 150 mg/kg/day in gum arabic suspensions for 14 days. Measurements made included 1) β-adrenoceptor sites by [^{125}I]-(-)-iodocyanopindolol binding, 2) adenylate cyclase activity stimulated by GTP, GppNHp,3)±isoprenaline, 4)glucagon, 5) NaF and 6) forskolin in cardiac membranes.

Neither amiodarone nor dronedarone appeared to affect the catalytic or regulatory portion of the enzyme complex. However, both decreased the adenylate cyclase activity stimulated by isoprenaline and glucagons to approximately the same extent.

The sponsor's results are reproduced below.
Mean ±SEM unless otherwise specified.

Group	Adenylate cyclase activity (pmol cAMP/min/mg prot)						
	basal	GTP (0.01mM)	GppNHp (0.1mM)	NaF (10mM)	Forskolin (0.1mM)	Isoprenaline (1mM)	Glucagon (0.01mM)
control	14.8±0.9	25.8±1.7[a]	98±4[a]	103±5[a]	442±14[b]	60.3±1.6[b]	46.8±1.6[b]
SR33589B							
50 mg/kg	15.5± 0.9[a]	23.0±1.4	95±5	96±5	426±31	51.0±1.9[a]**	38.1±2.5*
100 mg/kg	15.6±0.7	24.3±0.6	99±4	113±8	490±20	51.0±2.4**	38.6±2.6*
150 mg/kg	15.0± 1.7[a]	23.5±1.1[a]	93±6	114±7	440±9	41.4±3.7***	33.3±2.8[b]***
Amiodarone							
50 mg/kg	15.8±1.1	24.9±1.3	98±3[a]	112±8	458±21	55.0±6.1	45.0±5.7
100 mg/kg	13.3± 0.8[a]	23.3±2.0[a]	86±6	93±2	402±33	43.8±4.5**	34.5±3.8[a]*
150 mg/kg	15.0±1.3	22.7±1.0	84±2	88±2[a]	406±28	37.8±3.2***	30.7±3.7**

*p<0.05, **p<0.01, ***p<0.001 compared to the control group. [a], one value rejected or not determined; [b], two values rejected

SR35021A: *Effects on the hERG channel stably expressed in a mammalian cell line PAT0082*

The hERG channel was transfected into Chinese hamster ovary (CHO) cells. The test material was dissolved in DMSO, applied at concentrations of 0.01, 0.1, 1 and 10 µmol/l and tested by patch clamp technique. Cisapride was used as positive control.

SR35021A blocked the hERG channel as summarized below and with an IC50 of 1.01±0.06 µmol/l.

Concentration of applied material (µmol/l)	0.1	1	10
SR35021A: Inhibition of hERG	4.8±2.9 %	50.6±3.5%	91.8±3.7%
Cisapride: inhibition of hERG			100%

Effects of SR35021A on the action of potential[sic] *characteristics of rabbit purkinje fibers.* ***685-4-054***

The isolated purkinje fibers were superfused with Tyrode's solution (36ºC) and stimulated at 60 beats/minute. The synthesized metabolite was tested at concentrations of 3 and 10 µM. AP parameters were evaluated before and at the end of the 30 and 60 minutes superfusion for 3µM SR35021A and at the time 25-60 minutes just before the occurrence of conduction disturbance for 10µM test article.

Results for the 2 different concentrations were taken at 2 different times due to conduction velocity disturbances.

Reproduction of sponsor's results

	AP variations (Δ%)							
	n	RP	APA	dV/dt max	APD50	APD70	APD90	CT
3µM(60 min)	5	0	-2	-11	-10*	-1	+3*	+4
10 µM(45±7 min)	4	-4*	-22**	-80*	+5	+3	+9	+37

*p<0.05, **p<0.01 versus control;Δ% =percentage variation of control value; RP=resting potential; APA= AP amplitude; dV/dT max= maximum rate of depolarization; APD=action potential duration at 50, 70 or 90% of depolarization; CT= conduction time

The sponsor did not offer an explanation as to the different times of determination for the different concentrations.

Reproduction of sponsor's results

	ERP/APD ratios				
	ERP (ms)	APD70 (ms)	APD90 (ms)	ERP/APD/70	ERP/APD90
Control n=4 3µM 60 min	236±14 244±15**	199±16 196±22	252±10 267±10	1.20±0.07 1.27±0.12	0.94±0.05 0.91±0.04
Control n=5 10µM 228 min	223±14 219±7	200±14 198±4	228±14 235±5	1.12±0.03 1.11±0.02	0.98±0.02 0.93±0.02

ERP= effective refractory period

In rabbit purkinje fibers, SR35021 caused a decrease in resting potential at 10 µM and an apparently dose related decrease in dV/dt max and AP amplitude. The sponsor concluded that the in vitro electrophysiological profile of SR35021A in rabbit purkinje fibers was similar to that of dronedarone.

Effect of SR33589 in comparison with amiodarone and other class III antiarrhythmic agents on action potential duration in anesthetized rats ***685-4-021*** *November 1991*

The effect of dronedarone and several class III antiarrhythmic agents (amiodarone, d-sotalol,UK68798, RS87337) on the action potential duration was measured in sodium pentobarbital anesthetized rats(SD) maintained with artificial ventilation. The drugs were given intravenously.

Dronedarone, amiodarone and D-sotalol caused dose-related increases in APD_{90} . At the highest dose of dronedarone, 3 out of 5 animals developed an A-V block that resulted in mortality. The sponsor's results are shown below.

Drugs i.v.	Dose (mg/kg)	APD_{90} (max Δ%)	HR (Δ%)	APDc (max Δ%/ $\sqrt{HR}$)
PEG/H_2O (4/1)	Control	+ 1	- 8	0.4
SR 33589 B	0.3	+14	- 6	5.6
A	1	+25	- 5	11.4
B	3	+27	- 9	9.0
A	10	+39 (60% AVB)	-11	11.8
AMIODARONE	1	+11	- 5	4.9
	10	+16	- 9	5.3
	20	+61	-23	12.7
	30	+83	-23	17.3
D-SOTALOL	1	+24	-13	6.7
	10	+31	-18	7.3
	30	+41	-23	8.5
UK 68798	0.01	+ 3	- 6	1.2
	0.1	+ 1	-13	0.3
RS 87337	1	+ 6	- 6	2.4
	10	+29	-27	5.6

SR33589B and amiodarone:
Electrophysiological actions in anesthetized dogs ***CTV0201***

Mongrel dogs (6/sex for amiodarone and dronedarone and 5/sex for control group) were given 5+5mg/kg amiodarone (aqueous solution) or 5+5 mg/kg dronedarone(1% PEG with water) intravenously in 2 injections at 60 minute intervals. Anesthesia was maintained with 0.8% α-chloralose.

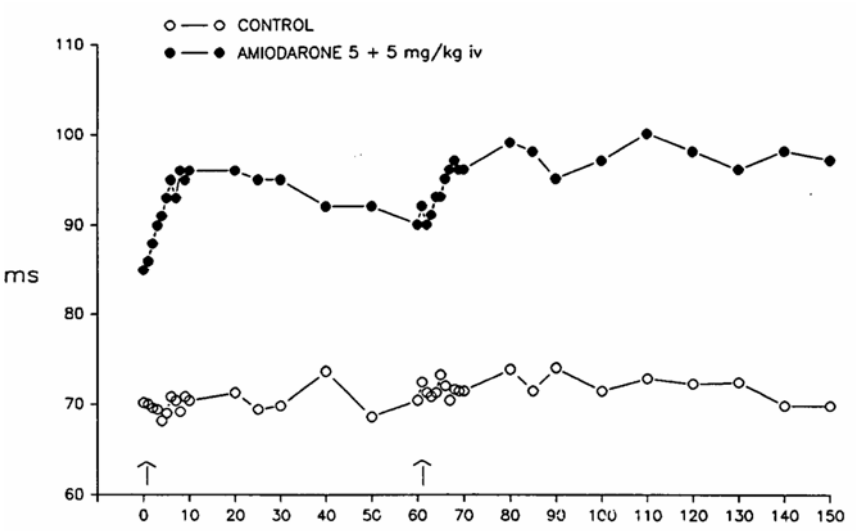
The sponsor's results are shown here.

NaCl 0.9 % (n = 5)					
Doses i.v.	4 ml		+ 4 ml		
Time (min)	10	50	+ 10	+50	+90
SCL	2	5	12	19	14
Heart rate	-4	-7	-12	-18	-12
AH	0	-2	2	4	-1
HV	4	3	2	4	6
WENCK	1	2	-1	2	5
ARP Func.	-2	1	1	0	0
Eff.	0	7	9	2	10
AVNRP Rel.	2	2	0	1	2
Func.	1	3	4	5	9*
Eff.	-2	3	3	-9	0
VRP Func.	2	5	4	8*	8*
Eff.	1	5*	3	6*	10*
L.II PQ	-2	0	2	1	2
QRS	1	3	4	4	4
QTb	3	8**	8	10*	14*
QTc	1	5	2	1	7

Dog	Amiodarone (n = 6)				
Doses i.v.	5 mg/kg		+ 5 mg/kg iv		
Time (min)	10	50	+ 10	+50	+90
SCL	13*	26	33	51*	57*
Heart rate	-12*	-19*	-23	-32*	-34*
AH	13	9	14	18*	15
HV	9	12	14	15	17
WENCK	31**	31*	58***	61**	81**
ARP Func.	13**	9**	17**	14*	12
Eff.	13*	10*	18***	14*	11
AVNRP Rel.	4	5	7*	5	5
Func.	19**	17***	35**	43**	44**
Eff.	26	19*	49*	64**	65*
VRP Func.	6	9**	15**	17**	17**
Eff.	6*	11**	17**	19**	20***
L.II PQ	11	7	12	12	12
QRS	-1	3*	4	4	5
QTb	5	13*	15*	24*	30*
QTc	-2	1	0	1	4

Dog	SR 33589B		(n = 6)		
Doses i.v.	5 mg/kg iv		+ 5 mg/kg iv		
Time (min)	10	50	+ 10	+50	+90
SCL	38***	48**	59***	59***	61**
Heart rate	-27***	-31***	-36***	-37***	-37***
AH	60**	49**	65***	51***	39***
HV	1	3	12	9	10
WENCK	83***	78***	112***	102***	91***
ARP Func.	15**	9**	11*	13	12*
Eff.	19	8	14	11	6
AVNRP Rel.	15	14	16	15	16
Func.	59**	44*	66**	53*	32
Eff.	105***	96**	125***	110***	100**
VRP Func.	7	8	13*	13	15*
Eff.	20**	22**	23**	25*	23**
L.II PQ	42*	35**	51**	42**	33**
QRS	4*	4	6	1	6
QTb	7*	17**	19**	19*	23**
QTc	-9**	-4	-6*	-6	-2

Some results were also presented graphically. There were some parameters where the control and treated groups started at different places. An example is shown below in the effect on AH interval.

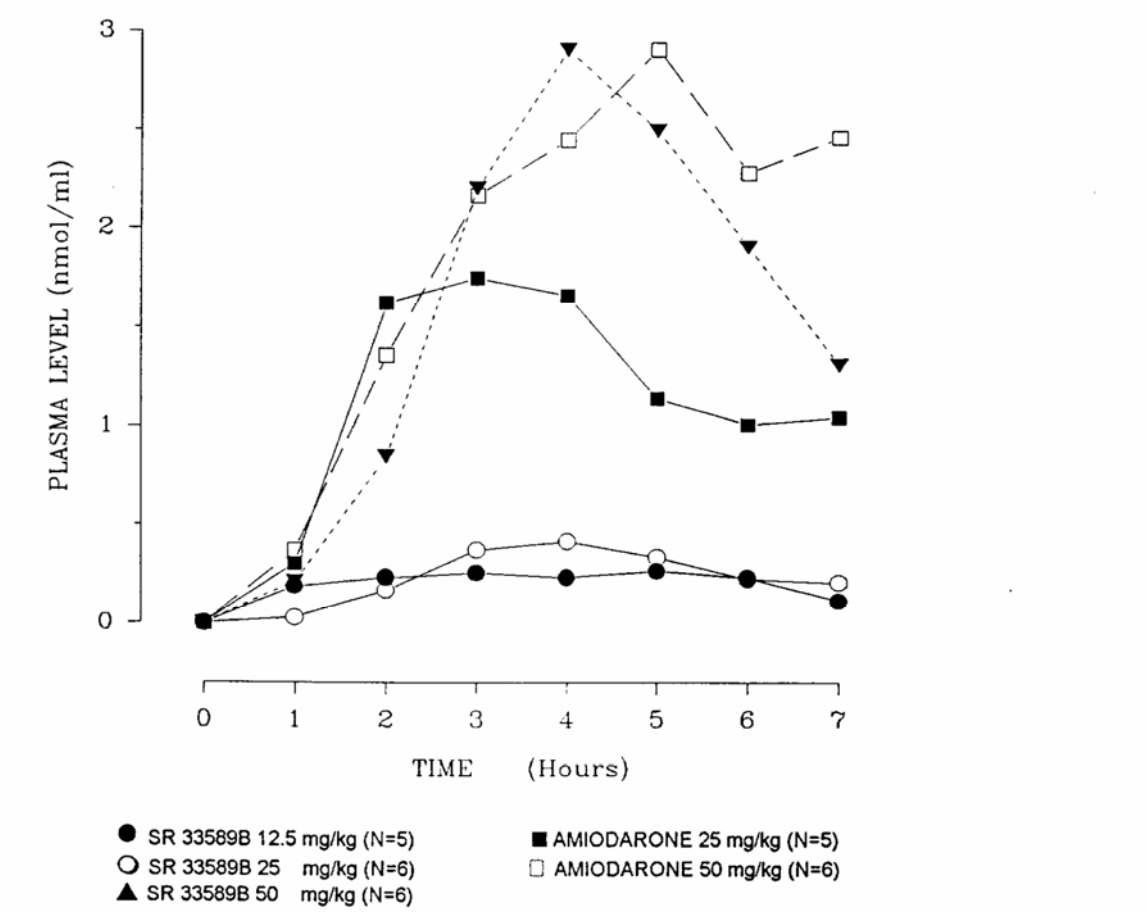


Both agents decreased HR and increased AH intervals. Wenckebach cycle time was also increased as was ARP, PQ and QTb intervals. Dronedarone appeared to affect PQ interval more than did amiodarone.

Hemodynamic study after oral administration of SR33589B in the conscious dog. Comparison with amiodarone. ***685-4-038*** *January, 1994*

Five to 8 mongrels per dose were given either SR33589B (12.5, 25 and 50 mg/kg single doses) or amiodarone (25 and 50 mg/kg single doses) in gelatin capsules. A variety of cardiovascular parameters were measured in these instrumented dogs both before and after drug administration. Effects were observed every 15 minutes after dosing for 7 hours.

Plasma level drug exposure was measured. There was no difference on the plasma levels of dronedarone after 12.5 and 25 mg/kg as shown below.



The sponsor's summary is reproduced below.

Sponsor's summary of dronedarone results

	12.5 mg/kg (n=5)		25 mg/kg (n=8)		50 mg/kg(n=6)	
	Control values	Maximal Var.%	Control values	Maximal Var.%	Control values	Maximal Var.%
HR(bpm)	75±7	+27(45)	75±4	+24* (330)	77±4	+39**(420)
DAP(mm HG)	79±5	-6	78±3	+6	81±6	-16(>420)
SAP(mmHG)	131±8	-8	126±3	-4	125±8	-17(>420)
MAP(mmHG)	96±6	-7	94±2	-4	96±6	+16
LVSP(mmHG)	138±7	-7	133±3	-7	137±5	-17*(>420)
LVEDP(mmHG)	12±3	-22	11±1	+17	14±2	-7
Cont(s^{-1})	32±3	+8	28±1	+9	26±1	-32**(>420)
Relax (s^{-1})	23±1	+16	22±1	+7	21±2	+7(375)

Control values were the mean±sem of the seven measurements before administration for all dogs of each group. Treatment-induced variations were calculated as percentage of means.
( ) total duration of effect in minutes
*p<0.05, **p<0.01 by the Mann Whitney U test

Sponsor's summary of amiodarone results

	25 mg/kg (n=6)		50 mg/kg(n=6)	
	Control values	Maximal Var.%	Control values	Maximal Var.%
HR(bpm)	77±4	+10	75±4	+2
DAP(mm HG)	84±4	-9	80±6	+8
SAP(mmHG)	131±5	-9	131±6	+3
MAP(mmHG)	99±4	-8	97±6	+5
LVSP(mmHG)	145±4	-6	139±9	-8
LVEDP(mmHG)	14±2	-22	14±2	+13
Cont(s^{-1})	29±2	+13	28±2	-13
Relax (s^{-1})	22±2	+14	21±1	+13

Control values were the mean±sem of the seven measurements before administration for all dogs of each group. Treatment-induced variations were calculated as percentage of means.
( ) total duration of effect in minutes
*p<0.05, **p<0.01 by the Mann Whitney U test

The MD of dronedarone caused a significant increase in HR with no significant effect on blood pressure. The HD, 50 mg/kg of dronedarone, caused an increase in HR with a trend of decreased blood pressure.
The doses of amiodarone used in this study did not produce any significant changes in the parameters studied. In some parameters, the variance became larger with time after dosing although no trend in effect was apparent.

Pulmonary effects: *Evaluation of the effects of an acute oral administration of SR33589B on respiratory parameters in unrestrained conscious guinea pigs using whole body plethysmography.* ***RCV0067*** Single oral doses of 10, 30 and 100 mg/kg dronedarone were given to 8 male Duncan-Hartley guinea pigs per group. Theophylline was the positive control. Animals remained in the plethysmograph for 4 hours after receiving drug. Respiratory parameters were obtained pre-drug, 15, 30, 45, 60 , 75, 90, 105, 120, 180 and 240 minutes after dosing. Venous blood was obtained at unspecified times from additional guinea pigs to determine plasma level drug concentration.

Plasma concentrations of drug and metabolite (ng/ml) at Tmax (120 minutes)

	10 mg/kg	30 mg/kg	100 mg/kg
SR33589	6.8	77.3	229.1
SR35021	1.1	13.3	68.4

The positive control produced robust responses on respiratory rate, minute volume, inspiratory time, expiratory time, peak inspiratory flow, peak expiratory flow and enhanced pause.
At the highest dose, dronedarone produced a very mild decrease in respiratory rate from 30 to 105 minutes. Tidal volume showed a great deal of variability. However, the MD and HD produced depression of tidal volume as did theophylline from 30 - 60minutes.
Dronedarone produced no discernible effects on minute volume, inspiratory time, expiratory time, peak inspiratory flow, peak expiratory flow, and enhanced pause.

Effect of SR33589B on the cardiovascular and respiratory functions in anesthetized dogs after intravenous administration. ***CVR0119***
An intravenous dose of 1-5 mg/kg was given in acetic/acetate buffer to 5 mongrel dogs per sex per group. Hemodynamics, myocardial function and respiratory system were assessed after single intravenous administration of drug to pentobarbital-anesthetized dogs. Hemodynamic, cardiac and respiratory parameters were recorded before administration and every 5 minutes from the 10th to the 40th minute then every 10 minutes to the end of the experiment (90 minutes). QTc was calculated according to Bazett's formula. Results were calculated relative to the control values.

There were significant effects on essentially every parameter.

parameter	1 mg/kg	5 mg/kg
Mean blood Pressure (mm Hg)	slight ↓ from the 50th minute reaching -12 mmHg by 90 minutes	Sudden transient↓ at 10 minutes(-28mm Hg) followed by return to baseline at 20 mins. Progressive ↓ from 40th to 90th minutes(-32mm). Most changes significant.
Heart rate (bpm)	unchanged	↓ from the 10th minute (- 17 bpm) until the end of study(-29bpm) Statistically significant from 50 mins
Cardiac output Ml/min	Moderate increase from 10th-50th minute(+30% on average)Signif at $p<0.05$ from 30-50 minutes.	↑from 10th min(+35%) until 40th min (+20%). ↓ after 70th min(-17% at end of experiment). Statistically significant from 10-20 minutes.
LV SV (ml)	Varied parallel to the changes in CO $P<0.05$ from 30-50 minutes	Statistically signif. ↑ from 10(51%) to 40 min (+35%). Return to baseline at 60 min.
LV pressure (mm Hg)	No signif. changes	Variations parallel to those in mean blood pressure. Signif ($p<0.01$) from 60-90 mins
LV contractility (Mm Hg/s)	↑(+10% on average) from 10-35 mins. ↑(+20% on average) from 40-70 mins.	↓ at 10 mins (-34%, NS) and approaching baseline at 30 mins. Progressive decrease after 50 mins of +35% on average from the 70th minute.
LV work (kg m/min)	↑from 10-50 minutes of +30% on average.	↑ from 15-35 minutes (max of 32% at 20 minutes). Progressive decrease after 50 mins, reaching -36%($p<0.05$) at 90 minutes.
Limb peripheral resistance (mm Hg)	No change	Sudden, transient ↓ of -22mm Hg at 10 minutes then return to baseline at 30 mins. A second ↓ after the 60th minute of 15 -20 mm Hg
Total peripheral resistance (dyn.s.cm-5)	↓ of -20% on average between 10-60 minutes then return to baseline	↓ from 10 mins (-43%, $p<0.001$) to 90 mins (-24%, $p<0.05$) Changes were significant throughout
ECG	Average +10% ↑ in PR interval primarily in the first 40 minutes.	↑RR interval throughout, progressive ↑ again from 60 minutes ($p<0.05$) ↑PR interval from 10-50 minutes (+10-+16% until 25 minutes) approaching baseline by 90 minutes ↑ QT interval at all points

QTc Interval by Bazette's formula (mean±SEM)

timepoint	Dronedarone mg/kg	
	1	5
Baseline	12.48±0.463	12.87±0.318
10	12.03±0.250	12.91±0.139
15	11.92±0.251	13.07±0.196
20	12.24±0.210	13.28±0.231
25	12.30±0.262	13.32±0.191
30	12.13±0.194	13.09±0.293
35	12.46±0.315	13.14±0.316
40	12.05±0.123	13.38±0.320
50	12.17±0.284	13.20±0.330
60	11.87±0.303	13.61±0.437
70	11.95±0.292	13.72±0.445
80	12.15±0.350	13.63±0.288
90	12.29±0.413	13.57±0.338

Summary of respiratory effects

parameter	1 mg/kg	5 mg/kg
Respiratory frequency (cycles/min)	↑ throughout with a maximum +9 cycles per min at 60 mins. Stat signif from 20-60 mins.($p<0.05$)	↑ from 10 minutes (+12 cycles/min, NS) to end (maximum +15 cycles/min at 35 mins, $p<0.05$) Approach towards baseline by 90 mins.
Respiratory flow (l/min)	↑ parallel to that in respiratory frequency Statistically signif ↑ from 30-90 mins. with max +89% at 60 mins	↑ parallel to that in respiratory frequency with a max of +72% at 30 mins. Significant from 30-50 mins)
Tidal volume (ml/cycle)	↓from 10 minutes -30 by ~ 13% ↑from 70-90minutes of ~10%	No change. Very variable measurements.

The single intravenous dose of 5 mg/kg caused a biphasic decrease in mean blood pressure and left ventricular contractility, a negative chronotropic effect and an increase in PR interval lasting 60-90 minutes after dosing. The lower dose of 1 mg/kg caused similar effects of a lesser magnitude.

Effect of SR33589B on the cardiovascular and respiratory functions in anesthetized dogs after intraduodenal administration. ***CVR0125***

Ten mongrel dogs (4 males and 6 females) were anesthetized with pentobarbital. Doses of 12.5 and 25 mg/kg were given via the intraduodenal route. Two different batches of the test article were given to 2 different sets of dogs (n=3 per group). Four dogs were given the high dose. The different parameters were recorded before dosing and after dosing at intervals of 5 minutes from the 10th to the 30th minute then at intervals of 10 minutes until the end of the experiment (150 minutes).

Summary of Cardiovascular Effects

parameter	12.5 mg/kg	25 mg/kg
Mean blood pressure (mm Hg)	↓ from 110 mins(-7mm Hg, p<0.05) thru end of study (-12 mm Hg, p<0.01)	Progressive ↓ from 70 mins reaching -13mm Hg at 110mins(p<0.05) persisting to end
Heart rate (bpm)	↑ from 30 mins (+11 bpm) to end (NS)	Variations from 30-70 mins (+12 bpm, NS) and from 110-130 (-12 bpm, NS)
Cardiac output (ml/min)	↑ from 25 mins(+13%, p<0.05) to 110 mins(+19, p<0.05). Max effect at 70 mins (+31%, p<0.001)	30-70mins avg ↑ of 30% (p<0.05-0.01). Max effect at 60 mins(+36%, p<0.01). Trend back to baseline from 110 mins.
LV stroke volume (ml)	Changes (NS) parallel to CO changes	↑20% from 10-70 mins. Max change at 60 mins (+27%, p<0.001) trend back to baseline
LV pressure (mm Hg)	Progressive ↓ from 110 mins to 150 mins, reaching -15 mmHg (p<0.01)	↑ from 10-50 mins (3-9 mm Hg) ↓from 100 min to end (-19 mm Hg, NS)
LV contractility (mmHg/s)	↑ from 30-70 mins (+14% , NS to max of +20%NS. Slight decrease below baseline after 120 mins.	↑ from 10-100 mins (10-11%). Maximum change at 50 mins(+33%). After 120 mins, values below baseline(-10%,NS)
LV work (kg m/min)	↑ from 25 mins(15%, p<0.05) to 90mins(17%, p<0.05). Max change at 70 mins (31%,p<0.001)	↑ from 10-70mins, signif from 30 mins(31%, p<0.05) to 60 mins (35%, p<0.01). Trending below basleine from 110 to end.
Limb peripheral resistance (mmHg)	No change	Avg ↓ of 10 mmHg from 50-130 mins (p<0.05). Max change at 90 mins (15 mm Hg, p<0.001)
Total peripheral resistance (dyn.s.cm-5)	Values below baseline within 10% except for 70 mins (16%, NS)	↓ from 10 mins (16%, p<0.05) to 130 mins (15%, p<0.05) Max change at 60 mins (-24%, p<0.01)
ECG	Increased HR	Increased HR

Respiratory Parameter Results

parameter	12.5 mg/kg	25 mg/kg
Respiratory frequency Cycles/min	↑ from 80 mins to end (≤4 cycles/min)	↑ from 10 mins (9cycles /min, p<0.05) to end of study (14 cycles/min, p<0.01 at 150 mins)
Respiratory flow (l/min)	↑ from 20 mins, signif from 70 mins (38%, p<0.05) to end of study(+74%,p<0.01)	↑ parallel to resp freq:+51%, p<0.05 at 10 mins to 127%, p<0.001 at 150 mins
Tidal volume(ml/cycle)	Individual variability	Values decreased 10-19% from 80 to 140 mins. NS

After a single intraduodenal administration there was a dose-related increase in cardiac output and a slight positive inotropic effect. Maximum effects tended to be noted 60-70 minutes after dosing. Decreased blood pressure was reported. Consistent with other studies, increased respiratory frequency and flow were also noted.

Renal effects:

Effect of SR33589B on the hydroelectric balance in rats after intravenous administration ***RS0040931005/ION0293.*** 1,3 and 10 mg/kg IV given to OFA rats (10/sex/group) .

Summary of effects

parameter	males	females
Specific gravity	No effect	Dose-related increase 1.020-1.025 sig p<0.1%
K+ concentration	↑ 68mM control; 75-73 mM	↑38mM control; 39-61 mM p<0.1%
K+ quantity	No change	↑ 28% (MD) and 46% (HD)
Creatinine conc (mM)	No change	Dose-related ↑; 1.6control, 1.7-2.7 P<0.1%
Creatinine quantity	No change	↑36%(MD), 50%(HD)
Creat Clearance ml/16h	↓at HD 11.5%	↑ at MD 28%, HD 33%
Blood in the urine	"moderate" at MD (9/10 rats) HD 6/10 "large", 4/10"moderate"	LD: 1/10 trace, 3/10 small MD: "Moderate" 10/10 rats HD: 2/10 moderate 8/10 large

Effect of SR33589B on the hydroelectric balance in rats after oral administration ***ION0217*** 10, 30 and 100 mg/kg was given to OFA rats (10/sex/group) as a single oral dose. Both sexes showed a slight, dose-related increase in specific gravity of questionable biological significance. There was a slight increase in excreted creatinine in the HD groups of both sexes. The quantity of excreted potassium decreased at the HD of both sexes. Creatinine clearance was decreased in both sexes. Correspondingly, the concentration of creatinine in the blood increased significantly in both sexes. Serum sodium and potassium increased only the females.
Unlike the intravenous administration study, blood was not reported in the urine under the conditions of this study.

Urinary parameters affected

parameters	males	females
16-hour urine vol(ml)	↓HD(26%) p<0.2%	↓HD(26%) p<0.1%
SG		
Proteins		
Ketone bodies		
Creatinine (mM)	↑at MD(11%), HD(19%) NS	↑LD(13%), MD(11%), HD(19%)
Potassium mM		↑10% at the HD
Potassium µmoles	↓HD(26%) p<1.2%	
Creatinine clearance ml/16hr	↓LD(1%),MD(6%), HD(26%) p<0.1%	↓LD(8%), MD(25%), HD(34%) p<0.1%

Effects of dronedarone on renal function in conscious normotensive rats following repeated oral administration ***PGD0133*** *January 2005*

Doses used were 0 (n=5 per sex, methylcellulose), 10 (n=3 per sex) and 30 mg/kg (n=5 per sex). Dronedarone was given orally to normotensive rats with surgically implanted renal blood flow probes. The animals were dosed once a day for 2 weeks. They were placed in metabolism cages for urine sampling after being water loaded (2% of body weight).
Renal blood flow was measured Days 0, 1,2,3,6,8,9,10,13 and 15. However, results from days 10 and 13 were not reported. Urine was collected days 0,7 and 14. The limited number of animals per group is due to 1)blood flow signals of poor quality and 2) several animals destroyed the external wire of the flow probe.
The results for essentially all parameters do not show any strong or clear patterns. At the same time, there is a great deal of variability, the groups are at very different starting points, and it would be easy to miss a subtle signal.

Gastrointestinal effects:

Effect of SR33589B on intestinal transit in mice after oral administration ***GIT0029***

Doses of 0(gum Arabic aqueous solution) 100, 300 and 1000 mg/kg were given orally to OF1 mice (10M/group). The effect of the drug on intestinal transit was assessed by measuring the length of intestine traveled by a charcoal meal in a 30 minute time period.

The low dose and the highest dose caused decreases in intestinal transit. The effect at the HD was statistically significant.

Effect of administration of SR33589B on intestinal transit in mice (mean±SEM)

group	Dose (mg/kg)	Length of intestine traveled by charcoal (%)	Variation [(a)](%)
Control	0	60±4	
SR33589B	100	69±2 (b)	+14
Control	0	63±4	
SR33589B	300	62±3	-1
Control	0	50±5	
SR33589B	1000(c)	68±4*	+36

(a)in relation to controls

(a) mean ±sem on 9 animals due to technical problem

(b) sedation;charcoal meal very diluted and in low quantity in the intestine

*p≤0.05

Effect of SR33589B on gastric emptying in rats after oral administration. ***GIT0030***

Doses of 0 (gum Arabic), 100 and 300 mg/kg were given orally to OFA rats (10F/group). Sixty minutes after receiving the drug, the effect on gastric clearance of a marker (phenol red) given in aqueous solution. Rats were euthanized 10 minutes after receiving the marker.

Doses of 0 (gum Arabic), 100 and 300 mg/kg were given orally to OFA rats (10F/group). Sixty minutes after receiving the drug, the effect on gastric clearance of a marker (phenol red) given in aqueous solution. Rats were euthanized 10 minutes after receiving the marker. Gastric emptying was evaluated as the difference in the total amount of phenol red administered and the amount remaining in the stomach after 10 minutes.

Effect of oral administration of SR33589B on gastric emptying in rats (mean±sem)

group	Dose (mg/kg)	Amount of phenol red emptied from the stomach (µg)	Variation (a) (%)
Control	0	442±28	
SR33589B	100	396±32	-10
Control	0	501±24	
SR33589B	300	234±37**	-53

(a) variation in relation to controls; **p≤0.01

Under the conditions of the study, the drug delayed gastric emptying. This is opposite to the effects in the mouse study in which gastric emptying was more rapid.

Effect of SR3389B on gastric acid secretion in rats after oral administration ***GIT0031***
SR33589B in 10% gum Arabic was given orally to fasted OFA rats. The effect of the test compound on gastric acid secretion was assessed by measuring the volume and pH of acid secretion in pylorus-ligated rats. Sixty minutes after treatment with the drug the animals were anesthetized and the pylorus ligated. The animals were euthanized 1 hour later.
SR33589B increased the volume and acidity of the secretions.

Dose (mg/kg)	Volume of secretion (µl)	pH of secretion	Total acid (µEq)	H+/ml (µEq/ml)
Control 0	279±71	2.66±0.22(b)	10.0±2.4(b)	36.2±5.0(b)
SR33589B 100 (a)	316±38 (+13)	2.39±0.09 (b) (-10)	14.3±2.3(b)	44.2±4.0(b) (+22)

(a) variations (%) in relation to controls
(b) results for 7 animals

While there were no statistically significant results, the one dose of drug caused an increased volume of more acidic secretions. A second dose would have made this study more informative (i.e., is the effect dose-related?).

<u>Abuse liability</u>: not done

<u>Other</u>:

Effects of chronic oral SR33589B administration on plasma thyroid hormone levels in rat. Comparison with amiodarone. ***685-4-013***
Male Wistar rats (7 groups of 10 animals) were dosed with 50, 100 or 150 mg/kg amiodarone or 50, 100 or 150 mg/kg of dronedarone given as an oral suspension in 5% aqueous gum arabic. The rats were dosed once a day for 14 days. T3, T4 and rT3 were measured by RIA kits.

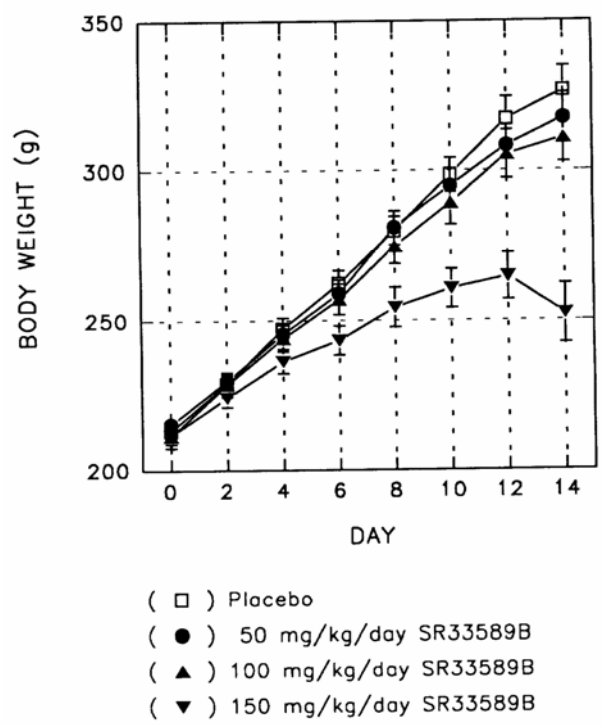
Dronedarone caused a decrease in T4 at the highest dose and a decrease in the T4/T3 ratio. Amiodarone caused a decrease in T4 and T3 and an increase in rT3. The results are shown below in the sponsor's summary.

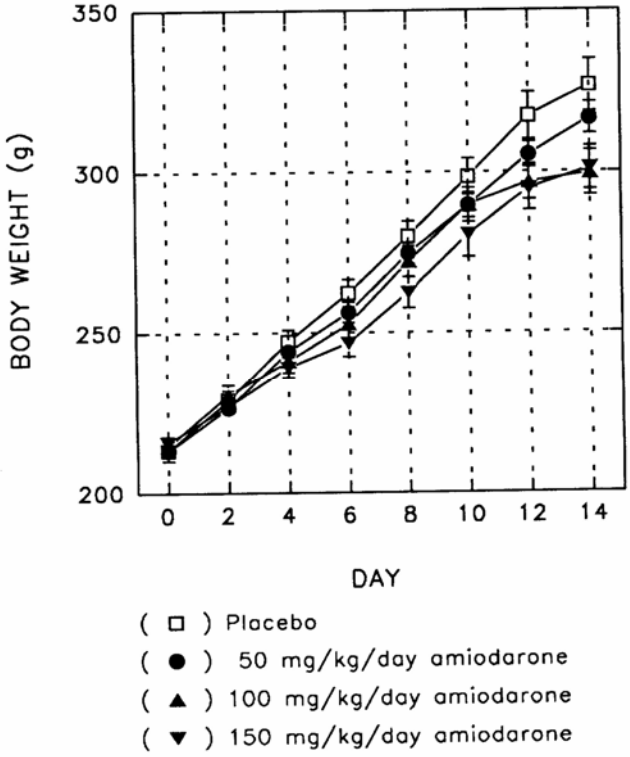
Effects of orally administered dronedarone and amiodarone on body weight

group	Body weight (g)	Product plasma concentrations (nmol/l)
Control	327±25(10)	
SR33589B 50 mg/kg	318±26 (10)	0.17±0.03 (7)[a]
SR33589B 100 mg/kg	311±24 (9)	0.17±0.05(8) [b]
SR33589B 150 mg/kg	252±31*** (10)	0.82±0.37(10)
Amiodarone 50 mg/kg	316±16(10)	0.49±0.17(10)
Amiodarone 100 mg/kg	300±22 (10)	2.05±0.41(10)
Amiodarone 150 mg/kg	301±21(10)	2.58±1.11(10)

**p<0.01, ***p<0.001 compared to control group; (n)number of determinations

[a] No detectable levels of SR33589B in 3 rats (<0.017 nmol/ml)





[b] No detectable levels of SR33589B in 1 rat (<0.017 nmol/ml)

Effects of orally administered dronedarone and amiodarone on thyroid hormone levels

group	T4 (ng/ml)	T3 (ng/ml)	rT3 (pg/ml)	T4/T3 ratio
Control	54±5(10)	0.93±0.10(9)	60±13(9)	58±3(9)
SR33589B 50 mg/kg	56±12(10)	0.98±0.17(10)	61±22(10)	57±6(10)
SR33589B 100 mg/kg	49±9(9)	0.76±0.12(9)	63±17(9)	62±4(8)
SR33589B 150 mg/kg	35±9***(10)	0.76±0.18(10)	48±14(10)	46±6***(10)
Amiodarone 50 mg/kg	62±10(10)	0.94±0.10(8)	133±21***(10)	66±11(8)
Amiodarone 100 mg/kg	61±11(10)	0.81±0.15(10)	210±21***(9)	69±10**(10)
Amiodarone 150 mg/kg	50±9(10)	0.73±0.09**(10)	222±48***(10)	75±2***(10)

**p<0.01, ***p<0.001 compared to control group
(n)number of determinations (in duplicate for T4, T3, rT3 measurements)
[a] No detectable levels of SR33589B in 3 rats (<0.017 nmol/ml)
[b] No detectable levels of SR33589B in 1 rat (<0.017 nmol/ml

The highest dose of dronedarone caused a decrease in body weight gain apparent from the 6th day.

In this study, the highest dose of dronedarone caused a marked decrease in bodyweight gain while the highest dose of amiodarone had little effect on body weight. Amiodarone had minimal effect on T4 levels, caused a decrease in T3, an increase in rT3 and finally an increase in the ratio of T4/T3. It is questionable whether 2 weeks is sufficient time to assess thyroid hormone effects. A question that usually arises is whether there is an absolute effect on the production of hormone or whether there is a change in the time in circulation. The usual argument is that thyroid effects seen in the rat are not relevant to the human due to the differences in half life between the species. A study of 28 days duration using radiolabels to track the effects of the drugs on the biological half-lives of the thyroid hormones would have been preferable. Also, other studies with this drug have shown an endocrine signal in the females. In the interests of investigating that signal and the potential relevance to humans both sexes should have been evaluated.In this study there was minimal detected effect on thyroid hormones except for those induced by treatment intolerance (a sick euthyroid effect?) found at a maximally tolerated dose. However, that is not necessarily a complete description of the thyroid effects of dronedarone when administered over a longer time period.

Phospholipid content of lung and liver in rats treated orally for 14 days with SR3389B and amiodarone ***685-4-040***

Seven groups of 10 male Wistars/group were treated orally for 14 days with doses of 50, 100 and 150 mg/kg/day. Twenty-four hours after the end of treatment the rats were anesthetized and blood and tissues collected. Lipids were extracted from plasma and from tissues (lung and liver)

Again, the high dose of 150 mg/kg/day caused a decrease in body weight apparent from the 6th day. There was however a dose-related decrease in body weight with both drugs.

Effect of dronedarone treatment on body and tissue weight

	vehicle	SR33589B		
		50	100	150
Body weight	326.6±8.1(10)	317.5±8.3(10)	310.8±8.1(9)	252.3±9.9***(10)
Lung/body weight x 100	0.472±0.027(10)	0.478±0.012(10)	0.475±0.016(8)[a]	0.450±0.013(9)[a]
Liver/body weight x 100	4.46±0.13(10)	4.48±0.08(10)	4.09±0.08(9)	3.82±0.09***(10)

Mean ±sem of (n) animals
[a]: lung weight not determined in 1 rat
***:p≤0.001

Effect of amiodarone treatment on body and tissue weight

	vehicle	amiodarone		
		50	100	150
Body weight	326.6±8.1(10)	316.4±4.9(10)	299.6±6.9(10)	301.1±6.7(10)
Lung/body weight x 100	0.472±0.027(10)	0.442±0.011(10)	0.477±0.017(10)	0.499±0.013(10)
Liver/body weight x 100	4.46±0.13(10)	4.42±0.09(10)	4.70±0.09(10)	4.77±0.15(10)

Mean ±sem of (n) animals
[a]: lung weight not determined in 1 rat
***:p≤0.001

The results of the lipid content are shown below. The sponsor's table has been divided for greater clarity.

Effects of orally administered drug on plasma lipids

	SR33589B(mg/kg/day)			
	Vehicle (0)	50	100	150
Proteins mg/ml	61.6±0.07	63.0±0.7	61.8±0.9	61.4±1.3
Phospholipids (nmol/mg/prot)	36.6±1.5	35.1±1.3	35.3±1.6	35.1±1.3
Total cholesterol Nmol/mg prot	11.8±0.7	11.4±0.8	13.8±0.5	12.5±0.6
Free cholesterol Nmol/mg prot	7.5±0.9	8.8±0.8	10.8±0.8	9.3±0.8
Esterified cholesterol nmol/mg prot	4.4±0.8	2.6±0.7	2.9±0.5	3.2±1.1
Total cholesterol/ phospholipids	0.33±0.02	0.33±0.02	0.39±0.02	0.36±0.01
Compound nmol/mg prot		0.0027±0.0002[a]	0.0028±0.0002[b]	0.0136±0.0021

mean±sem
[a] no detectable levels of SR33589B in 5 rats (<0.17 nmol/ml plasma)
[b] no detectable levels of SR33589B in 1 rats (<0.17 nmol/ml plasma)
***p≤0.001

Effects of orally administered drug on plasma lipids

	amiodarone (mg/kg/day)			
	vehicle	50	100	150
Proteins mg/ml	61.6±0.07	63.4±0.6	61.3±0.7	62.9±0.7
Phospholipids (nmol/mg/prot)	36.6±1.5	40.9±1.6	35.1±2.1	41.2±1.9
Total cholesterol Nmol/mg prot	11.8±0.7	14.0±0.7	17.6±0.8***	18.3±1.0***
Free cholesterol Nmol/mg prot	7.5±0.9	8.9±0.5	13.1±0.9***	14.8±0.7***
Esterified cholesterol nmol/mg prot	4.4±0.8	5.2±0.7	4.5±0.7	3.6±1.2
Total cholesterol/ phospholipids	0.33±0.02	0.34±0.02	0.52±0.04***	0.44±0.01***
Compound nmol/mg prot		0.0077±0.0009	0.0337±0.0024	0.0410±0.0058[c]

mean±sem
[c] one value rejected
***p≤0.001

Effects of orally administered drug on tissue lipids

	SR33589B(mg/kg/day)				Amiodarone (mg/kg/day)		
	Vehicle (0)	50	100	150	50	100	150
Proteins mg/ml	207.2 ±2.5	205.5 ±2.7	216.4 ±4.0	223.0 ±5.4	215.2 ±5.6	210.9 ±3.0	218.5 ±2.1**
Phospholipids (nmol/mg/prot)	156.1 ±4.5	151.6 ±4.4	178.2 ±4.5**	162.6 ±4.4	149.9 ±6.0	175.3 ±6.1	187.6 ±3.4***
Total cholesterol Nmol/mg prot	22.92 ±0.84	23.50 ±0.86	23.21 ±0.81	22.9 ±0.91	21.85 ±1.05	22.43 ±0.72	20.71 ±0.89
Total cholesterol/ phospholipids	0.15 ±0.01	0.16 ±0.01	0.13 ±0.01	0.14 ±0.01	0.15 ±0.01	0.12 ±0.01	0.11 ±0.01***
Compound nmol/mg prot		0.0069 ±0.0011[b]	0.0060 ±0.0008[c]	0.1581 ±0.0343[d]	0.0845 ±0.0071	0.197 ±0.0033	0.246 ±0.036

mean±sem
[a] no detectable levels of SR33589B in 5 rats (<0.17 nmol/ml plasma)
[b] no detectable levels of SR33589B in 1 rats (<0.17 nmol/ml plasma)
***p≤0.001

There are small but statistically significant changes in serum phospholipids and cholesterol following amiodarone treatment. These changes are slightly greater than those seen with dronedarone. There is some variability of tissue levels. How sensitive a measure of a subtle effect are these parameters? One test that was not done was histopathology or electron microscopy, which might have been better able to detect low grade or early changes.

2.6.2.5 Pharmacodynamic drug interactions

2.6.3 PHARMACOLOGY TABULATED SUMMARY

[pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the sponsor] The tables as provided by the sponsor were of poorly scannable or transferable quality and could not be used without producing a "Compressed File Virus" corruption of this review.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.8 **2.6.4.1 Brief summary** The absorption, distribution, metabolism and excretion of dronedarone was evaluated in CD-1 mice, Sprague-Dawley rats, New Zealand White rabbits, Beagles and Macaca fasicularis monkeys. There was also some examination of the effect of dronedarone on the CYP450 system. Oral administration studies were conducted using a suspension of drug in 0.6% methylcellulose or, for dogs, gelatin capsules. Intravenous administration studies with formulations of PEG400/sodium acetate buffer or mannitol/sodium phosphate were carried out in rats, dogs and macaques.

The oral bioavailability is relatively low: 14-22%. The volume of distribution is large, 12 to 66 l/kg with a moderately high systemic clearance of 2-4 l/h/kg. The apparent terminal half-life after oral dosing is from 2-7 hours.

In all species studied, dronedarone was highly protein bound (>99%). The drug stays primarily in the plasma, not the red blood cells. There is wide tissue distribution (lung, liver, spleen, kidney, myocardium) including crossing the placental barrier and entering milk. Radioactivity has also been identified in the brain, indicating that either drug and/or its metabolites cross the blood brain barrier. Low levels of radioactivity persisted after 336 hours in the liver, spleen and testis. Melanin binding was also demonstrated.

The drug is extensively metabolized and the sponsor's diagram of the proposed metabolic scheme can be found in the conclusion of this section. N-debutylation leads to SR35021, an active metabolite and the main circulating species in mice. A carboxylic acid derivative, SR90154, has limited pharmacologic activity and is one of the main circulating metabolites in rats and dogs.

The main route of excretion after both oral and intravenous administration is via the feces. There is a minor amount excreted in the urine. Aliquots of urine treated with β-glucuronidase indicate that there is little if any conjugation of the metabolites.

2.6.4.2 Methods of Analysis

[see under individual study reviews]

Determination of SR33589 and its N-debutyl metabolite (SR35021) in mouse plasma by HPLC-UV following liquid/liquid extraction. ***DOS0320*** The sponsor determined a linear range of 0.04-1.0 mg/l with a limit of detection 0.020 mg/l and a limit of quantitation of 0.04 mg/l. Within day variability (CV) was from 3.0-6.6% at the LOQ for SR33589 and from 3.0-5.3%. Reproducibility over 5 days (CV) was <20% for both parent and metabolite.

Validation of an electrospray LC-MS/MS detection method for the quantitative analysis of SR33589 and its metabolite SR35021 in mouse plasma following a Disk SPE (96 well plate) extraction. ***DOS0465*** The linear range was determined to be 1 – 2000 ng/ml. The limit of detection was not determined and the limit of quantitation was reported to be 1 ng/ml. The assay variability (CV) was determined to be ≤5% for each of the four standard concentrations of parent drug.

Validation of an LC/MS-MS detection method for the quantitative analysis of SR33589 and its metabolite SR35021 in rat plasma following a Disk SPE (96 well plate) extraction ***DOS0444.*** The linear range of the assay was determined to be 0.5-1000 ng/ml for both SR33589 and SR35021. The limit of detection was not determined. The limit of quantitation was 0.5 ng/ml for both chemicals.

HPLC-UV assay of SR33589 and its N-debutyl metabolite, SR35021, in rat plasma samples ***DOS0150***

Rat plasma collected with sodium heparin was spiked with 0.125 µg of SR34193 (internal standard) and the test compounds, water/methanol and sodium acetate buffer. After vortexing the mixture was allowed to stand on the extraction column. SR33589, SR35021 and the internal standard were eluted, dried under nitrogen and re-solubilised. Aliquots were injected onto the HPLC system.

The retention times listed indicate good separation of the peaks:
SR33589- approx 7.3 min
SR35021- ~5.9 min
SR34193~10.8 min

Limit of detection: 0.01 mg/l for SR33589 and SR35021
Limit of quantitation: 0.02mg/l for SR33589 and SR35021

It was also determined that the SR33589 and SR35021 did not bind to glass or plastic material in contact with plasma or water/methanol solution.

The extraction efficiency was calculated at 0.02, 0.2 and 1 mg/l using plasma samples spiked with known amounts of SR35021A and SR33589B and SR34193. The same concentrations were used to determine precision and accuracy of the assay method.

Long term stability of SR33589 and SR35021 in frozen rat plasma. ***SPP0010***
SR33589 plasma standards were prepared at 0.059, 0.197 and 0.690 mg/l concentration levels and SR35021 at 0.059, 0.197 and 0.692 mg/l. Six determinations of SR33589 and SR 35021 were made at each level at 24 months. At each period a daily calibration curve was performed using validated batches of the two chemicals. Concentrations were determined using HPLC-UV analysis. There was a slight decrease in concentration over 24 months for both chemicals.

Mean concentration (SD) of five determinations

SR33589		
theoretical	After 24 months	Variation range (%)
0.059	0.053±0.002	-10.2
0.197	0.194±0.003	-1.5
0.690	0.697±0.039	-1.6
SR35021		
0.059	0.053±0.002	-10.2
0.197	0.193±0.003	-2.0
0.692	0.714±0.030	+3.2

The samples were relatively stable (variation range <20%) when stored at -18ºC in the dark over 24 months.

Long term stability of SR33589 and SR35021 in frozen dog plasma ***SPP0011***
SR33589 and SR35021 plasma standards were prepared at 0.050 and 0.400 mg/ml concentration levels. Five determinations of SR33589 and SR35021 were made at each level at 3 and 16 months. At each period a daily calibration curve was performed using validated batches of SR33589 and SR35021. Concentrations were determined by HPLC-UV detection.

Mean concentration (SD) for 5 determinations

SR33589		
theoretical	After 16 months	Variation Range%
0.050	0.049(0.002)	-2.0
0.400	0.407(0.015)	+1.8
SR35021		
0.050	0.041(0.001)	-18.0
0.400	0.370(0.012)	-7.5

The samples were relatively stable (variation range <20%) when stored at -18ºC in the dark for 16 months.

Radioachemical stability and binding to glass and plastic of 14C labeled 33589B in vehicles used for animal studies. ***SFA0002***

Male and female Sprague-Dawley rats used for excretion balance and distribution studies were given 30 mg/kg p.o. (in methylcellulose) or 10 mg/kg i.v. (PEG400/sodium acetate) of SR33589B. The radioactivity administered was 1.11 MBq (30 µCi/kg) for both sexes and routes of administration. The radiochemical purity was determined to be 99.9%.

Radiochemical stability was assessed over 48 hours after preparation and storage either at room temperature or at 4ºC and reported as "good".

The sponsor provided a summary of the concentrations of 14C labeled SR33589B dissolved in formulations as a function of the sampling time. This is reproduced below.

Transfer number	Time (minutes)	Oral formulation		Intravenous formulation	
		Glass	plastic	Glass	plastic
0	0	237.26	244.64	222.18	217.13
1	10	232.83	227.99	211.24	207.51
2	20	212.60	248.82	215.69	219.52
3	30	224.61	217.20	208.62	219.23
4	40	228.88	235.91	214.09	207.34
5	50	212.78	222.90	216.63	213.22
6	60	222.10	226.99	213.26	217.10
At t=60, after last transfer, binding to container accounted for(% of what not defined)		6.39%	7.22%	4.01%	0.01%

2.6.4.3 Absorption

Pharmacokinetics and absolute bioavailability of SR33589B following single 10 mg/kg intravenous and 30 mg/kg oral administration of (carbonyl-14C)-SR33589B to male and female Sprague-Dawley rats. ***Abs0102***

Three animals/sex/sampling time/route. Radioactivity: 1.1×10^3 KBq/kg
Sampling times:

IV: 0, 0.083, 0.05,1,2,3,4,5,6,8,10, 24, 32, 48 and 72 hours
PO: 0,0.5, 1, 1.5, 2,3,4,6,8, 10, 24, 32, 48 and 72 hours.

Plasma levels of SR33589B and SR35021 were determined.

Pharmacokinetic Summary

	intravenous		oral	
parameters	male	female	male	Female
Co(mg/l)	0.72	1.03		
Cmax(mg/l)			0.19	0.18
Tmax(hour)			4.0	4.0
$T_{1/2}$(h)	6.1	12.5	6.4	6.6
$AUC_{0\text{-}10h}$ (mg h/l)	1.74	1.75	1.15	0.96
$AUC_{0\text{-}inf}$ (mg hr/l)	2.28	2.64		
Cl(l/h.kg)	4.4	2.3		
Vd(l/kg)	38.5	66.2		
F%			22	18

The concentrations of SR35021 were very low. Only Cmax and Tmax were determined.

Mean(SD) values for SR35021

	PO		IV	
	males	females	males	females
Cmax (mg/l)	0.052(0.046)	0.030(0.030)	<0.020	<0.020
Tmax (h)	4.0	4.0		

Pharmacokinetic profiles of SR33589B and SR35021 following a single (30 mg/kg) oral or (5 mg/kg) intravenous infusion administration of SR33589B or SR35021A to Beagles. ***Abs0209***

Two dogs per sex, approximately 2 years of age were used.
Sampling times:

IV: 0.083, 0.25, 0.5, 1,2,3,4,6,8,10,24,32,48,54,72 and 96 hours post-dose
PO: 0.5,1,1.5,2,3,4,6,8,10,24, 32,48, 54, 72 and 96 hours post-dose.

Plasma level determination of parent drug and SR35021 was assessed by HPLC-UV.

Summary of pharmacokinetic parameters

	SR33589B		SR35021	
	Intravenous	oral	Intravenous	oral
$AUC_{0\text{-}Clast}$ (mg.h/l)	2.309±1.278	1.672±2.810	0.614±0.215	0.181±0.028
$AUC_{0\text{-}inf}$ (mg.h/l)	2.50±1.287	3.363±3.719*	0.713±0.235	NC
$Cl_{0\text{-}inf}$ (l/h.kg)	2.374±1.005		7.628±2.479	
$Cl_{0\text{-}inf}$ (l/h)	29.421±12.367		92.038±30.757	
Vd(l/kg)	12.016±5.591		23.658±7.653	
$T_{1/2}\beta$(h)	3.4±0.7	3.8±0.0*	2.2±0.3	
$MRT_{(0\text{-}inf)}$(h)	3.570±0.973		2.426±0.421	
tmax		3.55±1.94		1.70±0.56
Cmax(mg/l)		0.241±0.349		0.071±0.043
F%		14±13*		

*two values

After oral administration, SR35021 was quantifiable in only 1 animal due to limitations of assay sensitivity. There was substantial inter-animal variability in the plasma concentrations and subsequent pharmacokinetic parameters. Both parent drug and the active metabolite showed a large volume of distribution as well as plasma clearance.

The pharmacokinetics of SR33589 following a single 1 mg/kg intravenous administration of (carbonyl-14C)-SR 33589B to male Macaca [sic] monkeys. ***ABS0103***

Four males were given 1.85 $x10^3$ KBq/kg.
Sampling times: 0.083, 0.25, 0.5, 1,2,3,4,6,8,10,24, 48, 120 and 168 hours.

SR35021 was not detected.

SR33589B PK parameters (mean ±SD)

Co(mg/l)	0.163(0.045)
T1/2(h)	1.94(0.49)
AUCobs(mg.h/l)	0.154(0.061)
AUC 0-inf (mg h/l)	0.233(0.085)
Cl(l/h.kg)	4.92(2.35)
Vd(l/kg)	12.81(3.45)

2.6.4.4 Distribution

Quantitative tissue distribution and excretion balance of (carbonyl-14C)SR33589B following single oral administration (30 mg/kg) to the male Sprague-Dawley rat. ***DIS0045***

Eighteen males received drug in a methylcellulose suspension containing 0.37MBq/ml.
The tissues of 3 animals per time point were analyzed at 1,4,8,24,96 and 168 hours post-dose.

The highest concentration of radioactivity was reported for the small intestinal contents followed by the large intestinal contents. After that, the liver showed the greatest concentration.

TABLE 4 : MEAN TISSUE CONCENTRATIONS OF THE RADIOACTIVITY OBSERVED AFTER SINGLE 30 mg.kg^{-1} ORAL ADMINISTRATION OF (carbonyl-^{14}C)SR 33589B TO MALE SPRAGUE-DAWLEY RATS.
(Results expressed as mg Eq.SR 33589B.kg^{-1} of tissue and normalized to a theoretical dose of 30 mg.kg^{-1}).

TIME (h)	MEAN 1	MEAN 4	MEAN 8	MEAN 24	MEAN 96	MEAN 168
WEIGHT(g)	269	268	259	263	264	261
ADM.DOSE (mg.kg^{-1})	30.30	30.55	29.71	30.24	30.04	30.00
BRAIN	0.15	0.23	0.15	0.058	0.10	ILQ
LUNGS	22	47	20	0.44	0.091	ILQ
LIVER	51	39	8.4	1.4	0.40	0.12
HEART	7.5	9.0	2.6	0.15	0.068	ILQ
KIDNEYS	14	18	6.5	0.46	0.17	ILQ
TESTICLES	0.16	0.65	0.63	0.40	0.31	0.17
OESOPHAG.	18	18	2.5	0.28	0.21	ILQ
STOMACH	79	27	2.2	0.13	0.051	ILQ
SML INT.	121	83	11	0.43	0.15	ILQ
CAECUM	2.6	18	26	0.90	0.095	ILQ
COLON	2.3	11	14	0.63	0.11	ILQ
RECTUM	2.0	5.4	38	0.61	0.12	ILQ
FLAT BONE	1.5	3.1	1.2	0.36	0.69	ILQ
BONE SURF	1.3	2.6	0.91	0.22	0.35	ILQ
SALIV G.	5.1	12	6.3	0.082	ILQ	ILQ
THYMUS	1.7	5.6	4.2	0.25	ILQ	ILQ
PANCREAS	7.5	17	7.9	0.52	ILQ	ILQ
SPLEEN	9.4	14	5.0	0.19	ILQ	ILQ
PROSTATE	2.0	6.0	5.5	0.19	ILQ	ILQ
BLADDER	2.7	5.1**	5.1	ILQ	ILQ	ILQ
EYES	0.52	1.0	0.47	ILQ	ILQ	ILQ
THYROID	9.8	12	3.6	ILQ	ILQ	ILQ
ADRENALS	16	28	11	ILQ	ILQ	ILQ
SPINAL C.	0.16	0.29	0.30	ILQ	ILQ	ILQ
B. MARROW	4.5	11	4.6	ILQ	ILQ	ILQ
HYPOPHYS.	4.0	20	12	2.2	ILQ	ILQ
HARDER GL	30	8.4	10	4.3	1.1	0.40
MUSCLE	2.9	5.1	2.1	ILQ	ILQ	ILQ
WHITE FAT	2.1	5.8	3.8	0.20	ILQ	ILQ
BROWN FAT	8.7	14	3.1	0.17	ILQ	ILQ
SKIN	1.6**	3.3	1.8	0.13	ILQ	ILQ
PLASMA	1.4	1.9	0.39	0.022	ILQ	ILQ
TOT.BLOOD	1.1	1.5	0.30	ILQ	ILQ	ILQ
GAST.CT	42	7.9	0.88	0.032	ILQ	ILQ
S.INT.CT	229	200	55*	1.6	0.13	0.017
L.INT.CT	0.12	75	85*	1.9	0.069	ILQ
CARCASS	1.8	4.2	2.3	0.17	0.090	ILQ

Summary of radioactivity at specific time points

organ	Mg Eq SR33589B.kg^{-1} of tissue		Ct 1/c pl	$T_{1/2}$ (h)
	Ct1	Ct2		
Lungs	22	ILQ	15	31
Liver	51	0.12	35	41
Kidneys	14	ILQ	9.4	50
plasma	1.4	ILQ	1.0	4

Ct1 = 1 hr after dosing
Ct2=168 hr after dosing=last measurement
Cpl= plasma concentration 1 hour after administration

The maximum concentration in most tissues was seen at 4 hours after dosing except for the liver, stomach and contents, small intestine and contents, and Harderian glands. The named tissues showed maximum concentration at the first sampling point of 1 hour. Cecum, colon, rectum and associated contents showed maximum concentration at 8 hours post-dose. At 96 hours post-dose the highest concentration was reported for the "flat bone."

Tissue distribution after a single (30 mg/kg) oral administration of (^{14}C-carbonyl) SR335589B to the female Sprague-Dawley rat ***DIS0198***

Seven female rats, 1 animal/time point, were given a single dose of drug as a solution in methyl cellulose containing 3.70 MBq/kg. Sampling times were 1,4,8,24,96, 168 and 336 hours post-dosing.

The text of the report states that highest radioactivity levels were observed in gut content. This was not apparent in the data presented. It can be said that the radiolabeled drug was rapidly distributed to the tissues sampled and was cleared by 168 hours after dosing. Liver, spleen, lung and kidney showed the highest levels of drug-associated label.

. Quantitative tissue distribution by Liquid Scintillation Counting : tissue concentrations expressed as mg Eq/kg of tissue

SAMPLING TIMES (hours)	1	4	8	24	96	168	336
Blood	0.624	0.678	1.141	UDL	UDL	UDL	UDL
Plasma	0.651	0.719	1.087	0.129	UDL	UDL	UDL
Brain	0.140	0.132	0.309	UDL	UDL	UDL	UDL
Kidney	4.502	8.056	15.945	0.464	0.089	UDL	UDL
Liver	15.007	15.829	20.091	1.466	0.175	0.101	UDL
Lung	2.509	12.231	22.136	0.735	UDL	UDL	UDL
Muscle	0.727	1.710	5.171	0.189	UDL	UDL	UDL
Myocardium	1.611	3.637	6.149	0.188	UDL	UDL	UDL
Spleen	5.113	21.346	20.643	0.629	UDL	UDL	UDL
Thymus	0.782	2.195	7.772	0.529	UDL	UDL	UDL
White fat	3.184	*	6.895	0.366	UDL	UDL	UDL

* technical problem
UDL = under detection limit

. Half live estimation

No half-life value was determined

Tissue distribution of radioactivity following a single (30 mg/kg) oral administration of (Carbonyl-^{14}C) SR33589B to the pregnant Sprague-Dawley rat ***DIS0231***

Pregnant rats (3/sampling time/day of gestation) were used. The drug was suspended in methyl cellulose with 0.1398 MBq/mg. Sampling times were 2,6, 24 and 48 hours for blood, plasma and tissues at day 9 and day 18 of gestation. Analysis was by quantitative whole body radioluminography (QWBRLG) and liquid scintillation counting (LSC).

Gestation Day 9: Drug was rapidly distributed to all tissues analyzed. There was an increase in radiolabel in the embryo from 2 to 6 hours. Drug-associated label was reported for the ovaries, mammary gland and uterus also. The sponsor's results are shown below.

. Mean tissue concentrations on day 9 of gestation (results expressed as mg Eq. non salified compound/ (n=3 animals /sampling time except when indicated between brackets).

Sample times	2 hours		6 hours		24 hours		48 hours	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Blood	1.557 (*)	0.435	1.542 (*)	0.338	ND	NC	ND	NC
Brain	UDL	NC	UDL	NC	ND	NC	ND	NC
Harder's gland	3.100	0.728	15.667	2.122	6.704	1.343	1.677	0.299
Kidney	15.037	4.143	22.490	4.494	1.308 (*) (n=2)	NC	ND	NC
Liver	41.920	12.099	35.305	7.366	2.771	0.321	0.667 (*)	0.054
Lung	14.476	4.874	36.097	3.165	1.000 (*)	0.273	ND	NC
Mammary gland	4.030	1.747	10.061	1.083	ND	NC	ND	NC
Myocardium	7.840	2.258	11.899	2.449	ND	NC	ND	NC
Ovaries	6.251	2.479	9.476	2.217	1.066 (*) (n=1)	NC	ND	NC
Plasma [1]	0.940	0.199	1.107	0.338	0.163	0.103	UDL	NC
Spleen	19.140	5.060	35.430	6.754	1.369 (*)	0.272	ND	NC
Thymus	2.692	0.884	10.980	1.883	1.016 (*)	0.328	ND	NC
Uterus	2.662	0.298	6.738	1.102	1.057 (*) (n=1)	NC	ND	NC
Embryo	4.659	1.065	10.148	1.398	0.941 (*) (n=1)	NC	ND	NC

UDL = Under detection Limit LOD = 0.495 mg Eq./kg
(*) = Under Quantification Limit LOQ = 1.650 mg Eq./kg
NC = Not calculated
ND = Not determined (No measured data because under the background noise of the detector system)
[1] = values from LSC counting

The data for gestation day 18 show similar results

Sample time	2 hours		6 hours		24 hours		48 hours	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Blood	2.844	0.270	2.503	0.496	ND	NC	ND	NC
Brain	UDL	NC	0.611 (n=2) (*)	NC	UDL	NC	ND	NC
Harder's gl.	7.472	1.448	21.636	3.588	7.900	0.246	3.523	1.076
Kidney	27.017	2.160	29.642	6.389	1.329 (*)	0.182	ND	NC
Liver	86.207	4.212	47.073	12.695	2.184	0.131	1.028 (*)	0.166
Lung	34.649	1.898	59.396	7.950	1.812	0.268	ND	NC
Mammary gl.	8.751	0.644	18.592	2.088	1.768	0.071	0.703 (n=2) (*)	NC
Myocardium	16.627	0.837	14.922	2.944	ND	NC	ND	NC
Ovaries	17.575	0.646	12.126	3.476	0.563 (n=2) (*)	NC	ND	NC
Plasma [1]	1.657	0.023	1.120 (n=2)	NC	0.080 (n=2)	NC	UDL	NC
Spleen	33.253	3.824	45.214	6.059	1.642 (*)	0.194	ND	NC
Thymus	7.242	0.612	16.753	2.237	2.312	0.469	ND	NC
Placenta	10.041	0.393	9.544	2.870	0.623 (n=2) (*)	NC	ND	NC
Decidua	7.815	1.904	21.950	2.652	8.617	0.721	6.532	NC
Trophoblast	12.492	0.854	17.692	0.428	3.562	0.497	2.819 (n=2)	NC
Fetus	UDL	NC	0.534 (n=1) (*)	NC	UDL	NC	ND	NC
Fetus liver	0.888 (*)	0.017	1.546 (*)	0.199	UDL	NC	ND	NC

UDL = Under detection Limit LOD = 0.495 mg Eq./kg
(*) = Under Quantification Limit LOQ = 1.650 mg Eq./kg
NC = Not calculated
ND = Not determined (No measured data because under the background noise of the detector system)
[1] = values from LSC counting

After a single oral dose of [carbonyl-^{14}C]SR33589B to pregnant Sprague-Dawley rats, detectable transfer of drug-associated radioactivity to the embryo was demonstrated. There was also significant uptake of radioactivity by smooth muscle – containing structures (uterine wall and decidua) and by the trophoblastic area (area of exchange between fetus and female).

Table (5.1) 4 - Mean tissue to maternal plasma ratios after a single (30 mg/kg expressed as non salified compound) oral administration of [Carbonyl-^{14}C] SR33589B to the pregnant Sprague-Dawley rat on day 18 of gestation
(n = 3 animals /sampling time except when indicated between brackets)

Sample time	2 hours		6 hours		24 hours		48 hours	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Blood	1.713	0.143	1.823 (n=2)	NC	NC	NC	NC	NC
Brain	NC	NC	0.663 (n=2)	NC	NC	NC	NC	NC
Decidua	4.688	1.099	21.848 (n=2)	NC	113.145 (n=2)	NC	NC	NC
Fetus	NC	NC	0.417 (n=2)	NC	NC	NC	NC	NC
Fetus liver	0.537	0.017	1.425 (n=2)	NC	NC	NC	NC	NC
Harder's gl.	4.488	0.823	21.850 (n=2)	NC	108.888 (n=2)	NC	NC	NC
Kidney	16.278	1.091	21.456 (n=2)	NC	20.248 (n=2)	NC	NC	NC
Liver	52.028	2.313	31.167 (n=2)	NC	30.971 (n=2)	NC	NC	NC
Lung	20.907	1.017	50.430 (n=2)	NC	27.952 (n=2)	NC	NC	NC
Mammary gl.	5.274	0.326	17.547 (n=2)	NC	24.600 (n=2)	NC	NC	NC
Myocardium	10.026	0.369	11.078 (n=2)	NC	NC	NC	NC	NC
Ovaries	10.602	0.260	8.011 (n=2)	NC	9.917 (n=2)	NC	NC	NC
Placenta	6.067	0.293	1.000 (n=2)	NC	1.000 (n=2)	NC	NC	NC
Plasma	1.000	NC	6.102 (n=2)	NC	8.192 (n=2)	NC	NC	NC
Spleen	20.015	2.056	36.817 (n=2)	NC	23.006 (n=2)	NC	NC	NC
Thymus	4.363	0.313	16.194 (n=2)	NC	35.490 (n=2)	NC	NC	NC
Trophoblast	7.538	0.476	15.733 (n=2)	NC	53.529 (n=2)	NC	NC	NC

Investigation of possible affinity of total radioactivity in melanin containing tissue following a single oral (30 mg/kg) administration of [^{14}C-carbonyl]-SR33589B to pigmented rats. ***DIS0407***

Male Lister Hooded rats, 3 per timepoint, received drug in a methylcellulose suspension with 3.49µCi/mg of radiolabel. Eye, liver, uveal tract and skin (pigmented and non-pigmented) were sampled at 24, 96 and 336 hours after dose administration. Analysis was by QWB autoradiography.

The highest concentrations were observed at 24 hours for all tissues assessed. The uveal tract showed the greatest levels of radioactivity. Unfortunately the retinal pigment epithelium was not also analyzed (or reported). Pigmented skin showed detectable levels of radio-label while there were undetectable amounts in the non-pigmented skin. Overall the data is suggestive that the drug binds to melanin.

Summary of radioactivity in melanin-containing tissue

	Timepoint (ng Eq unsalified compound/g ±SEM)		
	24 h	96h	336h
Eye	14530±6940	3405±1716	2299±519
Liver	1428±209	94	BLQ
Skin(non-pigmented)	BLQ	BLQ	BLQ
Skin (pigmented)	1306±125	1229±238	BLQ
Uveal tract	49840±9676	18501±9289	12590±3523
LOQ	340±82	424±95	126±14
Whole blood (LSC)	45±5	BLQ	Blq
Plasma (LSC)	47±14	BLQ	Blq
LOQ	39	39	39
	Timepoint (% administered±SEM)		
	24h	96h	336h
Eye	0.056±0.027	0.020±0.001	0.009±0.002
Liver	0.232±0.034	0.046	NC
Uveal tract	0.035±0.007	0.019±0.001	0.009±0.002

Tissue distribution after a single (3 mg/kg) intravenous administration of (^{14}C-carbonyl) SR33589B to the male Sprague-Dawley rat. ***DIS0140***

Seven rats, 1 per sampling time, were given an intravenous injection of dronedarone containing 3.70 MBq/kg radioactivity. Sampling times were 1,4,8, 24, 96, 168 and 336 hours after dosing. The highest concentrations of radioactivity were seen in the lung. Half-life values were estimated for the liver, spleen and testes (69.8, 102.5 and 65.6 hours respectively).

The highest drug-associated radioactivity levels were observed in the lungs, hypophysis(data not shown), pineal body(data not shown), adrenal gland(data not shown), gastric wall, gut content and pancreas over the 1-4 hour sampling period. Radioactivity levels decreased from 8-24 hours. Radioactivity was found during that period in liver, spleen, kidney, Harder's gland, adrenal gland and testis.
At 168 hours, radioactivity was still observed in liver, spleen, adrenal, kidney and testis. Residual radioactivity was reported to still be present in blood, liver, spleen and testis. Although the sponsor specifically cited the hypophysis and pineal gland, I found only textual references to these sections.

This is more persistent radioactivity than was seen after oral administration to the female SD rat.

. Quantitative tissue distribution by Liquid Scintillation Counting : tissue concentrations expressed as mg Eq/kg of tissue

SAMPLING TIMES (hours)	1	4	8	24	96	168	336
Blood	0.195	0.108	0.036	0.032	0.078	0.080	0.078
Plasma	0.207	0.150	0.054	0.008	UDL	UDL	UDL
Brain	1.774	0.408	0.083	0.022	UDL	UDL	UDL
Kidney	3.774	1.896	0.738	0.146	0.053	0.026	UDL
Liver	4.454	2.461	1.524	0.453	0.076	0.037	0.007
Lung	12.273	6.282	1.074	0.063	0.009	UDL	UDL
Muscle	1.473	0.933	0.200	0.019	UDL	UDL	UDL
Myocardium	2.034	0.903	0.292	0.034	UDL	UDL	UDL
Spleen	4.718	2.717	0.831	0.110	0.044	0.024	0.012
Testis	0.214	0.249	0.172	0.118	0.038	0.015	0.004
Thymus	1.948	1.621	0.730	0.042	UDL	UDL	UDL
White fat	2.105	2.050	1.097	0.109	0.007	UDL	UDL

UDL = under detection limit

In Vitro Binding of [^{14}-carbonyl]- SR33589B to the Plasma Proteins of Rat, Mouse and Rabbit. ***LPR0873***

Plasma was obtained from male Sprague-Dawley rats, male CD-1 mice and female NZW rabbits. Pooled plasma was spiked with radiolabeled drug (specific activity of 3.47 MBq/mg (93.9 µCi/mg)) at concentrations of 50, 100, 500, 1000, 5000 and 10, 000 ng/ml. The mixtures were incubated at 37ºC for 2 hours at which time it was assumed that equilibrium was reached. Binding was determined by equilibrium dialysis.

Stability of the [^{14}C-carbonyl]- SR33589B in plasma was determined for each species after incubation at 37ºC for 2 hours by chromatographic analysis at concentrations of 100 and 1000 ng/ml during the equilibrium dialysis experiment.

Aliquots of plasma were extracted with methanol and dried under N_2. Reconstituted samples were subject to chromatographic analysis.

In all species, at all concentrations tested, [14C-carbonyl]-SR33589B was highly bound (>99%) to the plasma proteins. Over the tested range of 50-10,000 ng/ml, no concentration dependence was observed. Saturation of protein binding was also not observed.

In vitro binding of SR33589B to rat, dog, monkey maccaca and human plasma proteins. ***LPR0508***

Binding to rat, dog, monkey and human plasma proteins was studied by equilibrium dialysis carried out at 37ºC. Time to reach equilibrium and the diffusion of the compound through the dialysis membrane were studied in triplicate at 5 concentrations (0.001, 0.05, 0.1, 0.5 and 10 mg/l) and 5 times of incubation (0.5, 1,2,3 and 4 hours). Stability of SR33589B in human plasma was checked by HPLC analysis after incubation of samples for 2 and 4 hours at a concentration of 10 mg/l.

The drug was shown to be stable in the plasma under the conditions of the study for the timepoints and concentration examined. At all tested concentrations protein binding was >99.5% for rat, dog, macaque and human by equilibrium dialysis techniques. Using ultrafiltration, there was a suggestion of concentration dependence in the human plasma, the only data shown.

[SR33589B] mg/l	0.001	0.1	10
$F_{b,}$ human SD	87.52 (31.18)	99.15 (0.47)	99.14 (0.05)

In Vitro Binding of [^{14}C- Carbonyl]- SR35021A to the Plasma Proteins of Rat, Dog, Mouse, Rabbit and Human ***LPR0876***

Plasma was collected from male Sprague-Dawley rats, male Beagles, male CD-1 mice, female NZW rabbits, and male Caucasians. Radiolabeled drug was tested at concentrations of 50, 100, 500, 1000, 5000 and 10,000 ng/ml for 2 hour incubations at 37ºC.

Similar to the parent drug, under the conditions of the study the metabolite was highly protein bound in the species studied. At all concentrations tested, protein binding was reported as ≥98.7% across species.

BLOOD DISTRIBUTION AND PHARMACOKINETICS OF RADIOACTIVITY FOLLOWING SINGLE ORAL (30 MG/KG) OR INTRAVENOUS (10 MG/KG) ADMINISTRATION OF ^{14}C-LABELLED SR 33589B TO MALE AND FEMALE SPRAGUE DAWLEY RATS ***Study LPR0046***

Three animals/sex/sampling time/route were used. Oral doses were given in a suspension of 0.6% methyl cellulose. Intravenous doses were given as a solution in PEG400/sodium acetate buffer. Sampling times were:

IV: 0, 0.083, 0.5, 1,2,3,4,6,8,10,24,32, 48 and 72 hours

PO: 0, 0.5, 1, 1.5, 2,3,4,6,8,10, 24, 32, 48 and 72 hours.

Plasma was analyzed by direct liquid scintillation counting. Blood was analyzed by combustion prior to LSC.

Distribution of blood radioactivity results expressed as % in plasma : mean (SD)

Oral administration		
Time (h)	male	female
0.5	83(13)	(73(3)
1	71(11)	73(5)
1.5	72(7)	72(5)
4	69(5)	78(2)
10	77(17)	84(6)
Intravenous administration		
Time (h)	male	female
0.083	40(3)	60(25)
0.5	49(5)	57(7)
1	43(10)	63(20)
4	61(1)	78(24)
10	64(6)	71(2)

Mean pharmacokinetic parameters of plasma radioactivity

	oral		intravenous	
parameters	male	female	male	female
C_0 (mg Eq/l)			1.16	1.25
Cmax(mg Eq/l)	1.89(0.38)*	2.32(0.78)*		
Tmax (hour)	3	4		
$T_{1/2}$ (hour)	24.4	15.3	30.8	13.5

* standard deviation

The circulating half life was shorter in females than males following both routes of administration.

Blood distribution and pharmacokinetics of radioactivity following single oral (25 mg/kg) or single intravenous (2.5 mg/kg) administration of 14C-labeled SR33589B to male Beagle dogs. ***LPR0048***

Four males per route of administration were studied. The oral dose was administered as a suspension of 0.6% methyl cellulose with. The intravenous material was prepared in PEG400/sodium acetate. The radioactivity administered by either route was 1.85 x 10^3 KBq/kg. Sampling times were:

Oral: 0, 0.5,1,1.5, 2,3,4,6,8,10, 24, 32, 48, 54, 72, 96, 120 and 168 hours.

IV: 0, 0.083, 0.25, 0.5, 1, 2,3,4,6,8, 10, 24, 32, 48, 120 and 168 hours.

Plasma was analyzed by direct LSC. Blood was subject to combustion prior to LSC.

Percentage of radioactivity in plasma: Mean (SD)

Time (hours)	oral	Intravenous
0.083		52.6(6.2)
0.5	67.9(8.8)	53.3(6.7)
1	74.9(5.1)	57.1(3.3)
4	62.7(3.1)	51.9(10.8)
10	58.6(13.0)	49.7(2.3)
24	62.3(29.9)	49.9(18.5)
48	52.9(39.1)	27.5(11.7)

Pharmacokinetic parameters of plasma radioactivity: mean (SD)

	oral	intravenous
Cmax(mg Eq/l)	2.63 (1.27)	
Co (mg Eq/l)		0.62(0.11)
Tmax (hour)	2.38(1.11)	
$T_{1/2}$ (hour)	11.45(5.26)	35.33(7.02)

The half- life was longer with intravenous administration. In the previous report using rats, intravenous administration also had a half life as long or longer than that found using oral administration. The sponsor presumed the shorter t1/2 after oral vs IV administration to be due to lower levels of absorption and therefore a more rapid decrease to circulating levels below the limits of detection.

Blood distribution and pharmacokinetics of radioactivity following single intravenous (1mg/kg) administration of 14C-labelled SR33589B to male Macaca monkeys. ***LPR0047***

Four male Macaca fascicularis were used. SR33589B in aqueous solution of mannitol and monobasic sodium phosphate was used to deliver a dose of 1 mg/kg with radioactivity of 1.85×10^3. Blood and plasma were collected at 0, 0.083, 0.25, 0.5, 1,2,3,4,6,8,10,24, 48, 120 and 168 hours. Analysis was by combustion and LSC.

Distribution of blood radioactivity
(% in plasma ±SD)

Time (hour)	%plasma
0.083	51.54±6.40
0.5	47.39±6.60
1	44.42±6.99
4	44.23±7.21
10	50.34±12.12
24	64.51±9.56

PK parameters of plasma radioactivity

	Mean(SD)
C0 (mg Eq/l)	0.328(0.071)
T1/2(hour)	66.9(6.0)

A long circulating half-life is seen in the macaque following intravenous administration.

Fetal tissue distribution of radioactivity following a single (100mg/kg) oral administration of (Carbonyl-14C) SR33589B to the pregnant Sprague-Dawley rat. ***DPK0054***

Two pregnant females were used per sampling time. Blood, plasma and tissues were collected at 6 and 24 hours after dosing on GD18. The animals received a single oral dose of 90 mg/kg (non-salified compound) in 0.6% methylcellulose with 3.9±0.084 MBq/kg.

As shown in the sponsor's table below, radioactivity was well represented in the female reproductive tract, placenta and fetal liver. At 24 hours after dosing there was a greater concentration of radiolabel in the mammary gland than in the myocardium. The radioactivity levels in the uterus had not declined from 6 hours. It appears that there may be retention of drug or accumulation in the uterus and possibly other parts of the reproductive system.

Distribution pattern

Sampling times (h)	Tissues
6	• In pregnant females : Adrenal gland > Spleen > Liver > Lung > Kidney > Mammary glands > Harder's gland > Myocardium > Hypophysis > Ovary. Blood and brain radioactivity close to the background noise of the detector. • In fetal area : Trophoblast > Placenta > Uterus (uterine wall and/or decidua) > Fetus > Fetal liver > Amniotic fluid
24	• In pregnant females : Harder's gland > Lung > Thymus > Mammary glands > Liver > Myocardium. Blood and brain radioactivity close to the background noise of the detector. • In fetal area : Trophoblast > Uterus (uterine wall and/or decidua) > Placenta. Fetus, fetal liver and amniotic fluid radioactivity levels close to the background noise of the detector.

. Individual and mean tissue concentrations on day 18 of gestation (results expressed as mg Eq. non salified compound/kg).

Sampling times (h)	6			24		
Animal number	CA28	CA39	Mean value	CA32	CA40	Mean value
Blood	2.868(*)	3.923(*)	3.396(*)	1.339(*)	UDL	1.339(*)
Liver	64.046	89.05	76.552	7.801	16.898	12.350
Mammary gland	19.249	34.825	27.037	5.504	15.782	10.643
Ovaries	14.405	26.516	20.461	2.132(*)	4.883	3.508(*)
Plasma [1]	2.107	3.055	2.581	0.281	0.697	0.489
Uterus [2]	12.628	34.552	23.590	28.999	23.673	26.336
Trophoblast	20.673	39.093	29.883	10.881	15.624	13.253
Placenta	11.038	17.847	14.443	1.528(*)	5.837	3.683(*)
Amniotic fluid	UDL	UDL	NC	UDL	UDL	NC
Fetus	UDL	2.659(*)	2.659(*)	UDL	UDL	NC
Fetal liver	2.355(*)	3.703(*)	3.029(*)	ND	ND	ND

UDL = Under detection limit
(*) = Under quantification limit
[1] = Values issued form LSC
[2] = Uterine wall and/or decidua
NC = Not calculated
ND = Not determined
LOD = 1.205 mg Eq./kg
LOQ = 4.018 mg Eq./kg

Placental transfer of radioactivity after a single oral (60 mg/kg expressed as unsalified compound) administration of [^{14}C-Carbonyl]-SR33589B to the pregnant New Zealand rabbit (Quantitative Whole Body Autoradioagraphy) ***PLT0037***

One pregnant NZW rabbit was used per timepoint. After receiving a single oral dose of radio-labeled material, sagittal whole body sections were taken through each animal at 4, 24 and 48 hours. The sections were analyzed by quantitative whole body autoradiography.

Maternal radioactivity at several timepoints

Maternal tissue Sample	Timepoint		
	4 h	24 h	48 h
Amniotic fluid	Blq	Blq	Nd
Blood	1383	Blq	Blq
Deciduas	944	764	Nd
Liver	36853	3686	1203
Ovaries	1024	950	599
placenta	2179	861	Nd
Trophoblast	2800	908	Nd
Uterus	1086	472	Nd
Uterine luminal fluid	blq	blq	nd

Fetal radioactivity at several timepoints

Fetal tissue Sample	Timepoint		
	4 h	24 h	48 h
Whole fetus	Blq	Blq	Blq
Blood	Blq	Blq	Nd
Brain	Blq	Blq	Nd
Eye	Blq	Blq	Nd
Gastric content	Blq	744	636
Gut content	762	16338	55588
Kidney	Blq	Blq	Nd
Liver	Blq	Blq	Nd
lung	Blq	Blq	Nd
Muscle	Blq	Blq	Nd
Myocardium	Blq	Blq	Nd
tissue	Blq	Na	Blq
loq	375	367	470
Whole blood (LSC)	1454	117	Blq
Plasma (LSC)	1974	299	Blq
loq	75	75	75

Lsc= liquid scintillation counting

This small sample size study provided evidence of fetal exposure to maternally administered drug in that the concentration of radioactivity in the fetal gastric contents increased over the course of the study. Is this present due to movement from fetal blood through a liver capable of making bile?

Toxicokinetic study, complementary to the study for effects on embryo-fetal development in the rabbit. ***DIV0914***

Three mated female New Zealand White rabbits per group were given oral doses of 0, 20, 60 or 200 mg/kg/day of dronedarone in 0.6% methylcellulose from GD6 to GD18. Blood samples were drawn the first and last day of dosing at 0, 1,2,4,8 and 24 hours after dosing. At time or euthanasia, 4 females were not pregnant: 1 LD f, 1 MD f and 2 HD f. We do not know if these were early or late losses or other.

Summary of TK parameters Days 6 and 18 of gestation

day	Dose Mg/kg/day		Tmax hour	Cmax Ng/ml	AUC_{0-24} Ng h/ml
GD 6	20	Mean ±SD	1	14.3±8.1	87.5±11.4
		CV%		57	13
GD 6	60	Mean ±SD	1	60.7 (n=1)	461.8
		CV%		NA	
GD 6	200	Mean ±SD	4	323.0±170.4	4497.2±2469.7
		CV%		53	55
GD 18	20	Mean ±SD	1	5.2±1.1	60.6±9.3
		CV%		21	15
GD 18	60	Mean ±SD	4	46.1	532.2
		CV%		NA	
GD 18	200	Mean ±SD	8	775.3±85.6	13852.7±3827.8
		CV%		11	28

Based on this small sample size it can be said that oral dosing produced systemic exposure in the pregnant rabbits used for this study.

2.6.4.5 Metabolism

Interspecies variability in SR33589B metabolism by hepatic microsomal fractions ***MIV0143***

Hepatic microsomal fractions were obtained from Swiss CD1 mice, Sprague-Dawley rats, Hartley guinea pigs, New Zealand rabbits, Beagle dogs, Yucatan minpigs, macacca and baboon primates and humans. After a 60 minute incubation ± NADPH, the samples were analyzed for parent drug and some metabolites. In the absence of NADPH SR33589B did not disappear and metabolites did not appear. With NADPH, numerous metabolites were reported. These were numbered based on elution order.

The percentages of biotransformation under the conditions of the study were

species	Primary metabolites	% of biotransformation
Swiss CD1 mouse	6,8	35.7
SD rat	1,6	39.8±5.6
Hartley guinea pig	6,8	43.3
NZW rabbit	6,8	40.9±1.9
Beagle	1,6	54.5±7.5
Yucatan minipig	1,8	50.3±12.0
Macacca monkey	1,8	79.5±2.1
Baboon	1,8	78.8±2.0
Caucasian human	1,8	41.8±14.9

Metabolite 8 = SR35021

Profile and identification of plasma, urine and fecal metabolites following a single and repeated oral administration (75 mg/kg/day) of [14C]-SR33589B to male Swiss CD1 mice. ***MET 0462***

Drug was administered as a suspension in 0.6% methyl cellulose. Mice received either a single dose or repeated daily dosing over 14 days.
Blood/plasma samples collected: pre tx days 1,7,10 and 14
Days 1 and 14: 0.5, 2,4,8 and 24 hours after dosing
Urine, feces and cage washes: 24 hour fraction after dosing days 1,7,10 and 14
Samples were analyzed by HPLC-MS with radioactivity detection and HPLC/MS/MS for identification.

Excretion data for total radioactivity

sample	period	Amount as mg-Eq	% of daily excreted radioactivity
urine	Day 1: 0-24	0.70	3.32
	Day 7: 0-24	0.96	3.56
	Day 10: 0-24	1.07	4.50
	Day 14: 0-24	1.09	4.68
feces	Day 1: 0-24	20.4	96.7
	Day 7: 0-24	26.0	96.4
	Day 10: 0-24	22.7	95.5
	Day 14: 0-24	22.2	95.3

PK parameters for total radioactivity, SR33589 and SR35021 in plasma

sample	day	Tmax hours	T1/2 hours	Cmax	AUCτ	AUC	R_{ac}*	R_{AUC} SR/TR**
radioactivity	1	2	2.9	5850		33500		
	14	2	4.4	5890	43400		nc	
SR33589B	1	0.5	2.1	1400	8390	8390		0.25[a]
	14	0.5	2.4	1930	8120		0.97	0.19[b]
SR35021	1	2	2.2	991	6150	6150		0.18[a]
	14	2	2.3	1010	7580		1.23	0.17[b]

*accumulation ratio between day 14 and day 1; **ratio SR33589/total radioactivity
[a]calculated from AUC on Day 1; [b]calculated from AUCτ on day 14

Under the conditions of the study, there was no detected change in pharmacokinetic parameters from day 1 to day 14. Greater than 90% of the radioactivity was recovered primarily in the feces regardless of duration of dosing. There was no qualitative change in the metabolite profile over the course of the study either.

Plasma, urinary, tissue and fecal metabolites following single and repeated oral administrations (10 mg/kg/day) of [^{14}C]SR33589B to male Sprague-Dawley rats. ***RME0003***

Rats received either a single oral dose or repeated dosing for 14 days.
Samples collected:
Plasma: day 1 pre-tx, 0.5, 1,2,4,8,12,18,24,48,72,120 and 168 hours after treatment
Days 7 and 10: pre-tx
Day 14: pre-tx, 0.5, 1,2,4,8,12,18, 24, 48, 72, 120 and 168 hours after tx
Urine, feces: 24 hour fractions over 7 days after the day 1 dosing
24 hour fractions after dosing on day1,6, and 9 and daily over 7 days after dosing on day 14.
Tissues: lung, myocardium and liver collected 4 hours and 24 hours after dosing on day 24

The sponsor stated that due to low specific radioactivity, no interpretable radiochromatograms for plasma could be obtained. Qualitative metabolic profiles were based on a reconstructed ion chromatogram during MS analysis. Qualitative differences from day 1 to day 14 were not detected under these conditions. HPLC radiochromatograms for urine showed similar metabolic profiles for both days of analysis. The hydroxyl-SR35021 metabolite was the main excreted compound in urine, increasing from 22% on day 1 to 35% day 14 of all radioactive peaks detected. Unchanged parent drug was not reported as a significant presence in the urine. However, in the feces, unchanged drug accounted for ~5%(day6) and ~12%(day 1) of all radioactive peaks. Peaks 8 and 9, mono-hydroxy SR35021 derivatives, were the main excreted species in the feces. Peak 8 accounted for 11-17% of total excreted compound and peak 9 accounted for 20-27% of all detected peaks.

tissue	Primary species	amount
Liver	Peak 9 :mono-hydroxy SR35021	24% of all radioactive peaks
Lung	UD:SR33589B Peak 21: SR35021	Relative percentages not given
myocardium	UD:SR33589B Peak 21: SR35021	Relative percentages not given

The main routes of biotransformation were thus reported as:
Hydroxylation and oxidation of parent compound
N-debutylation leading to SR35021 and subsequent hydroxylation/oxidation
Oxidative deamination leading to SR90154 and subsequent hydroxylation
Cleavage between benzofuran ring and carbonyl group yielding benzoic acid derivatives

The plasma radiochromatograms were reported as of poor quality but that a conclusion had been reached that there were no qualitative changes between day 1 and day 14. The two main metabolites were postulated as a benzoic acid and propionic acid (SR90154).

No qualitative or quantitative differences were reported for day 1 to day 14. Parent drug was not detected in the urine samples. The main metabolite reported was OH-SR35021. The main excreted compounds identified in the feces were SR33589B, SR35021 and 2 hydroxylated SR35021 isomers.

Both SR33589B and SR35021 were found (as well as other metabolites) in the lung, liver and myocardium.

Profile and identification of plasma metabolites following single oral (30 mg/kg) or single intravenous (10 mg/kg) administration of ^{14}C-labeled SR33589B to male and female Sprague-Dawley rats ***Met0138***

Three rats/sex/route/sampling time were given single oral or intravenous doses of ^{14}C-SR33589B. Oral doses were suspended in 0.6% methyl cellulose. Intravenous doses were dissolved in PEG400/sodium acetate 0.01M, pH 4.9. Plasma was sampled at the following times:

Oral: 0, 0.5, 1,1.5, 2,3,4,6,8,10, 24,32,48 and 72 hours.
IV: 0, 0.083, 0.5, 2,3,4,6,8,10,24, 32,48 and 72 hours.

Samples were analyzed by HPLC with UV, radioactive and MS detection. Plasma samples after 10 hours were not analyzed due to low radioactivity concentrations.

In both sexes, parent drug was detected up to the 10-hour sampling time. After oral treatment, metabolite 1, a carboxylic acid derivative due to N-dealkylation, not the parent drug, was the predominant circulating species in either sex. In males, this metabolite comprised 70% (relative percentage but relative to what is not clear) at 0.5 hours down to 16% at 10 hours. In females this metabolite comprised 42% (relative percentage) at 0.5 hours and 84% at 10 hours.

After intravenous administration, SR33589B was the main compound found in males at all times and in females up to 2 hours after dosing. The relative percentage in males ranged from 88% at 0.083 hours to 43% at 4 hours and back up to 60% at 10 hours. In female the relative percentage of SR33589B ranged from 86% at 0.083hours down to 30% at 10 hours.

Profile and identification of urinary metabolites following a single oral (30 mg/kg) or intravenous (10 mg/kg) administration of ^{14}C-labelled SR33589B to male and female Sprague-Dawley rats. ***Met0139***

This is the analysis of urinary metabolism from the preceding report. Sampling times for urine were 0-6, 6-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. Analysis was by HPLC with UV, radioactive and MS detection. For each administration route and each sex, the urinary metabolite profile was performed at random on one animal over a 0-48 hour period of collection.

After oral administration the parent drug was not detected in either sex except in the 24-48 hour fraction. The sponsor did not offer an explanation for this. The possibility of column contamination is one consideration. Parent drug was extensively metabolized in both sexes although more radioactive peaks were reported for the females than the males. The same major compound was reported for both sexes. That was the mono-N-debutyl-hydroxy (on the benzofuran ring). Enzymatic hydrolysis produced little change, suggesting that most radioactive

peaks were excreted in the free form. No major qualitative differences in the urinary profile were reported regardless of sex or route of drug administration.

Profile and identification of biliary metabolites following single oral (30 mg/kg) or intravenous (10 mg/kg) administration of 14C labeled SR33589B to male and female Sprague-Dawley rats.
MET0140
Bile duct cannulated rats, 5/sex/route were used. Samples were collected 0-1, 1-3, 3-6, 6-24 and 24-48 hours. Analsysis was by HPLC with UV, radioactive and MS detection.

Biliary excretion as a percent of the administered dose was greater in both sexes following intravenous dosing. Parent drug was not detected in either sex or after either administration route. Part of the sponsor's summary is reproduced below.

Period (hours)	oral		intravenous	
	male	Female	male	Female
0-1	0.25 ±0.15	0.30±0.07	5.41±1.44	3.93±2.06
0-24	36.68±9.16	41.82±3.92	69.25±3.15	60.79±8.66
0-48	43.24±11.12	45.67±4.05	71.97±3.59	66.01±8.02

Some of the biotransformation identified included taurine, glucuronide and sulfo-conjugates, butyric acid derivatives, O-propanoic acid derivatives, various hydroxylations.

Profile and identification of plasma, urine and fecal metabolites following a single oral administration (60 mg/kg) of [14C]-SR33589B to the female New Zealand white rabbit.
MET0533

Two groups of 4 females/group. Plasma was collected pre-tx,1,2,4,8,12,24,48 and 72 hours after administration. Urine, feces and cage washes: 24 hour fractions before dosing and daily for 72 hours. Analysis was HPLC with UV, radioactivity and MS detection.

The majority of drug-associated radioactivity was excreted in the feces: 69% of the given dose in the first 24 hours and a cumulative total of 88% by 72 hours. Nine percent of the given dose was recovered in the urine by 24 hours. This changed only minimally by 72 hours.
The pharmacokinetic parameters calculated are summarized below:

parameter	blood	Plasma
Cmax (µg-Eq/g)	1.53±0.413	0.874±0.178
Tmax (hours)*	3[1-4]	2.5[1-4]
$T_{1/2}$ (hours)	4.35±0.45	4.18±0.497
T_{last} (hours)*	12[4-24]	12[8-24]
AUC_{last} (µg-Eq.h/g)	7.40±1.10	6.04±1.33
AUC (µg-Eq.h/g)	NC	NC

*median[range]

Summary of main metabolites

matrix	Metabolites
plasma	SR33589B 4%, keto-and hydroxyl SR33589B 21%, keto and hydroxyl-N-debutyl SR33589B 19%, OH-propionic acid derivative SR90154 17%
urine	Main metabolites corresponded to the main metabolites in plasma. Parent drug not identified
feces	Keto and hydroxyl-N-debutyl SR33589B 5%, keto and hydroxyl SR33589B 24%, SR33589B 12%

Profile and identification of plasma, urinary and fecal metabolites following single and repeated oral administrations (15 mg/kg/day) of [14C-carbonyl]-SR33589B to male dogs. ***RME0009***

Dogs received a single dose and then daily oral dosing for 14 days with a 35 day washout period.
Blood samples were collected before treatment days 1,7,10 and 14
Day 1: 0.5, 1,2,4,8,24,48,72,96,120,144 and 168 hours post-dosing
Day 14: 0.5, 1,2,4,8,24,48,72,96, 120, 144 and 168 hours after dosing.
Urine, feces and cage washes: 24 hour fraction after dosing on days 1,7, 10,and 14 by 24-hour fractions over 168 hours after dosing days 1 and 14.

Qualitative differences were not reported between days 1 and 14.

Summary of main metabolites per matrix

matrix	metabolite	% of total detected compounds in matrix	
		Day 1	Day 14
plasma	SR90154	31%	41%
	SR33589	19%	20%
\			
urine	Dihydroxy-SR33589	20%	13%
	Monohydroxy-SR35021	20%	17%
	Parent compound not seen		
feces	SR33589	7%	6%
	Dihydroxy-SR35021	21%	16%
	Monohydroxy-SR35021	20%	22%

Profile and identification of plasma metabolites following a single oral (25 mg/kg) or a single intravenous (2.5 mg/kg) administration of (14C)-SR 33589B to male dogs. ***MET0237***

Sampling times after oral dosing were 0, 0.5, 1,1.5, 2,3, 4,6,8, 10, 24,32, 48, 54, 72, 96, 120, 168 hours. Sampling after intravenous dosing: 0, 0.083, 0.25, 0.5, 1,2,3,4,6,8,24,32,48, 120 and 168 hours.

After single oral administration to male dogs the main circulating metabolite was O-propanoic SR33589 accounting for 23% at 10 hours to 74% (1 hour) of all detected metabolites. SR33589 and SR35021 were detected as minor metabolites.

After single intravenous administration to male dogs, unchanged drug was detected as the main circulating compound over the first 10 hours accounting for 19%- 76% of all detected metabolites.

Profile and identification of urinary metabolites following single oral (25 mg/kg) and intravenous (2.5 mg/kg) administrations of (14C)-SR33589B to male dogs. ***MET0238***

Sampling times for urine were 0-6, 6-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. Aliquots of urine were treated with β-glucuronidase to assess conjugation.

The same qualitative profiles were obtained with both routes of administration but with quantitative differences. At the time of the report, the structures of the urinary metabolites had not been confirmed.

Profile and identification of plasma metabolites following single intravenous (1 or 8 mg/kg) administration of 14C-labelled SR33589B to male macaca monkeys ***MET0141***

Four males received drug in mannitol/monobasic sodium phosphate solution (group 1) and 2 males received drug in PEG/sodium acetate solution (group 2). Blood (plasma) samples were collected for group1 at 0, 0.083, 0.25, 0.5, 1,2,3,4,6,8,10,24, 48,120 and 168 hours. Samples were collected from group 2 at 0, 2,6 and 24 hours.

One main radioactive peak was detected with HPLC retention time corresponding to that of SR33589. Other minor peaks were detected that included SR35021 and a carboxylic acid formed by deamination and oxidation of the parent compound.

Profile and identification of urinary metabolites following single intravenous (2.5 or 8 mg/kg) administration of 14C-labelled SR33589B to male macaca monkeys. ***MET0142***

Four males were in group 1 and 2 males in group 2. Both groups received drug formulated in PEG/sodium acetate. Sampling times for group 1 were 0-6, 6-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168hours. Group 2 was sampled from 0-24 hours.

Parent compound was not detected in the urinary samples at any time point or at either dose. Enzymatic analysis showed that the metabolites were not conjugated. The main peaks were mono- or di- hydroxylated on the benzofuran ± mono or di-N-debutylation. Final characterization of the metabolites had not been completed at the time of writing of the report.

Effects of SR33589B repeated oral administration (375,450 mg/kg/day) during 14 days on various liver monooxygenase activities in CD-1(ICR)BR mouse. ***TIN0089***

Animals from the tk satellite group, 10/sex/group and 3 pools of 2 animals/sex/group corresponding to 0,1, and 2 hours post-dose for the enzyme evaluation (6 animals per group) were used. They were treated daily for 14 days. Liver samples were collected at time of necropsy and microsomes prepared.

Activity CYP450 involved (nanomoles product/min/mg of protein)	Effect: in males		
	0	375	450
7-ethoxyresorufin O-dethylase CYP1A			
7-pentoxyresorufin O-dealkylase CYP2B	0.074	0.110	0.166*
Aminopyrine N-demethylase CYP2C-3A			
Aniline hydroxylase CYP2E			
Erythromycin N-demethylase CYP3A	4.29	8.20*	8.64*

*p<0.05

Activity CYP450 involved (nanomoles product/min/mg of protein)	Effect: in females		
	0	375	450
7-ethoxyresorufin O-dethylase CYP1A			
7-pentoxyresorufin O-dealkylase CYP2B			
Aminopyrine N-demethylase CYP2C-3A	9.92	11.81	12.40
Aniline hydroxylase CYP2E			
Erythromycin N-demethylase CYP3A	3.51	5.36*	6.70*

*p<0.05

A significant dose-related increase in erythromycin N-demethylase was observed in both sexes (CYP3A).

Effects of a 2-week repeated oral administration of SR33589B (30, 70 and 160 mg/kg/d) on various liver enzyme activities in Sprague-Dawley rats. ***TIN0045***

Ten animals/sex/group and 5 animals/sex for enzyme evaluation. Animals were treated daily for 2 weeks with drug administered as a suspension in 0.6% methylcellulose.

Activity CYP450 involved (nanomoles product/min/mg of protein)	Effect in males			
	0	30	70	160
7-ethoxyresorufin O-dethylase CYP1A				
7-pentoxyresorufin O-dealkylase CYP2B				
Aminopyrine N-demethylase CYP2C-3A	3.86	3.81	4.19	2.47*
Aniline hydroxylase CYP2E	0.71	0.80	0.93*	0.68
Erythromycin N-demethylase CYP3A				

*p<0.05

Activity CYP450 involved (nanomoles product/min/mg of protein)	Effect in females			
	0	30	70	160
7-ethoxyresorufin O-dethylase CYP1A				
7-pentoxyresorufin O-dealkylase CYP2B				
Aminopyrine N-demethylase CYP2C-3A	2.88	2.04*	2.11*	2.64
Aniline hydroxylase CYP2E				
Erythromycin N-demethylase CYP3A	1.42	1.26	1.18	1.85*

*p<0.05

No consistent dose-related effects were seen. Erythromycin N-demethylase showed a slight and statistically significant increase in the HD females. Amino-N-demethylase activity showed a statistically significant decrease at the LD and MD and a non-significant decrease at the HD. The inconsistency and small magnitude of effects make it unlikely that they are of biological significance.

Effect of a 2-week repeated oral administration of SR33589B (25, 60 and 140 mg/kg/d) on various liver enzyme activities in Beagle dogs. ***TIN0046***

Three animals /sex/group received drug daily for 14-15 days.

There were no discernible effects on the liver/bodyweight ratio or CYP450 content expressed as nanomoles/mg protein. There were minimal and non-significant effects upon enzyme activity.

Under the conditions of the study, 2 weeks of exposure to the drug caused no detectable changes in the CYP450 enzymes examined.

2.6.4.6 Excretion

Pharmacokinetics and excretion balance after single and repeated oral (10 mg/kg/day) administration of [14C-carbonyl]-SR33589B to male Sprague-Dawley rats. ***RDS0008***
Animals used:
5 males for excretion after single oral dose
5 males for excretion following multiple oral doses
33 males for plasma kinetics after single oral dose
42 males for plasma kinetics after multiple oral doses

Whole blood and plasma samples were obtained :

Day1: 0.5, 1,2,4,8, 12,24,48,72,120 and 168 hours
Day 6: 24 hours after dosing
Day 9: 24 hours after dosing
Day 13: 24 hours after dosing
Day 14: 0.5, 1,2,4,8,12,18, 24,48, 72, 120 and 168 hours after dosing.

Urine, feces and cage wash samples:
After single dosing: 0-24 hours and 24 hour fractions up to 168 hours after dosing
After single and repeated dosing: 24 hours post-dose 1, 24 hours post dose 6, 24 hours post dose 9, 24 hours post-dose 13 and 24 hour fractions until 168 h post-dose 14.

Expired air: 0-24 and 24-48 hours post single dose.

Summary of PK parameters for male rats

compound	Tmax (hour)	Cmax (ng/ml) or ng Eq/ml	AUC_{last} ng h/ml	T1/2 h
Radioactivity day 1	4	204	1606	3.0
Radioactivity day 14	2	398	2421	2.7
SR33589 day 1	1	17.5	110	2.4
SR33589 day 14	1	38.0	252	2.6
SR35021 day1	8	2.8	24	Nc
SR35021 day14	4	9.8	70	2.4

After a single dose, 76% of the radioactivity was excreted in the feces after 24 hours. Cumulatively 93% of the radioactivity was excreted in the feces after 168 hours. 2.4% was excreted in the urine after 24 hours. This did not change cumulatively over 168 hours.
The same findings occurred after repeat dosing. Cumulatively, 114% of the administered radioactivity was excreted by 168 hours after the last dose while 3.3% was excreted in the urine over the same time frame. Terminal half-lives were similar between radioactivity, parent drug and metabolite. There was a tendency to higher AUC values over the 14 day study period.

In the text of the report it was noted that mean concentration of total radioactivity in the heart, liver and lungs was ~13, 5 and 20 times higher respectively at 4 hours post dose day 14 than at 24 hours post dose day 1. Tissue accumulation was thus indicated although definitive studies to confirm and quantify this have not been performed.

Excretion balance following a single oral (30 mg/kg) or a single intravenous (10 mg/kg) administration of 14C-labelled SR33589B to male and female Sprague-Dawley rats. ***EBA0056***

After a single dose of drug, samples were collected as follows:

Urine: 0-6, 6-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 hours
Feces: 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 hours
Carcass: 168 hours

Oral administration: Results expressed as % of the dose given

	urine	feces	carcass	Total
Male 0-24 hrs	4.94±0.88	66.85±2.32		
Male 0-168	5.61±1.11	71.81±2.71	12.87±1.38	90.30±3.47
Female 0-24hr	4.60±0.60	65.92±5.73		
Female 0-168hr	5.25±0.72	72.33±6.60	15.72±2.29	93.29±5.43

Intravenous administration: Results expressed as % of the dose given

	urine	feces	carcass	Total
Male 0-24 hrs	5.05±0.54	70.94±7.98		
Male 0-168	6.18±0.62	78.75±9.40	5.00±2.18	89.93±11.07
Female 0-24hr	5.05±1.18	74.42±5.74		
Female 0-168hr	6.52±1.18	86.83±4.91	5.26±2.23	98.61±6.59

Consistent with other studies, radioactivity was primarily excreted via the feces.

Enterohepatic recirculation of radioactivity following a single intravenous (10 mg/kg) administration of [^{14}C]-SR33589B to male Sprague-Dawley rats. ***MET0464***

Route of administration was either a single intravenous dose to bile-duct cannulated animals (grp 1) or single intraduodenal administration to bile-duct cannulated animals of pooled bile from grp 1. Samples collected were urine, bile, feces and cage washes over 24 hours after dosing. These were analyzed for total radioactivity.

Mean±SEM excretion for total radioactivity over 0-24 hours after dosing in male Sprague-Dawley rats

sample	Intravenous (n=4)	Intraduodenal (n=5)
Urine	6.77±1.57	2.09±0.08
Feces	7.00±0.84	67.1±3.60
Bile	64.1±6.55	9.16±0.32
Cage washes	0.34±0.10	0.01±0.01
total	78.2±6.74	78.4±3.59

After intravenous administration, the main route of elimination was the bile, accounting for about 64% of the administered radioactivity. SR33589 was reported to be detectable at less than 1%. Most recovered compounds were reported to be free forms. Two radioactive peaks were excreted as conjugated derivatives: a taurine conjugate and a glucuronide peak. The sum of these was approximately 9% of all radioactive peaks detected. The main radioactive peaks were reported to correspond to mono- and dihydroxylated derivatives of SR35021.

When the bile from the intravenously-dosed animals was collected and injected intraduodenally into another group of rats, the main route of elimination was again the feces. The main peaks recovered included a taurine conjugate (~20% of detected peaks), an hydroxylated SR35021 (~13%) and an hydroxyl-propionic acid derivative (~12% of detected peaks).

Pharmacokinetics and excretion balance after single and repeated oral (15 mg/kg/day) administration of[14C-Carbonyl]SR33589B to male dogs. ***RDS0009***

A single day of treatment was followed by 14 days of daily treatments. Urine and feces were collected predose and at 24 hour intervals up to 168 hours post-dose. Whole blood and plasma were collected pre-dose and at 0.5, 1,2,4,8, 24,48, 72, 96, 120, 144 and 168 hours post-dose.

For the repeated dosing protocol, urine, feces and cage wash were collected for the periods 0-24 hours on dosing days 7 and 10 and for 0-168 hour post-dose after day 14 at 24 hour intervals. Whole blood and plasma were collected pre-dose days 7, 10 and 14 and at intervals following dosing on day 14.

Mean±SEM PK parameters for total radioactivity

day	Tmax (h)	Cmax (ngEq.h/ml)	T1/2 (h)	AUC0-τ (ngEq.h/ml)
1	2(1-2)	2090±114	5.1±0.3	9933±329
14	2(1-2)	1450±126	14.6±1.1	10194±683
Mean±SEM PK parameters for SR33589				
1	1.5[1-2]	199.3±25.2	4.0±0.1	893±157
14	2[1-2]	246.9±53.7	4.4±0.4	1479±359
Mean ±SEM PK parameters for SR35021				
1	2[1-2]	22.4±4.2	1.7±0.1	NC
14	2[1-2]	29.0±6.2	2.2±0.1	148±38

Single dose: Mean±SEM excretion of total radioactivity as % of administered dose

		urine	feces	Cage wash	Total
Day 1	0-24 h	3.34±0.15	73.86±2.89	1.49±0.04	78.69±3.02
	0-168 h	3.74±0.12	90.83±1.01	2.12±0.06	96.68±0.88
Repeat dose: mean±SEM excretion of total radioactivity as % of daily administered dose					
Day 7	0-24h	3.36±0.28	80.21±6.33	0.45±0.03	84.02±6.33
Day 10	0-24h	3.21±0.33	76.44±11.07	0.62±0.15	80.28±28
Day 14	0-24h	3.00±0.24	76.68±2.92	0.65±0.04	80.33±2.69

Total radioactivity was greater than SR33589 concentration. Unchanged drug seemed to account for 9-14% of total circulating radioactivity. From day 1 to day 14 there was an increase in AUC_{0-t} of 1.6x with minimal increase in Cmax. SR35021 accounted for approximately 1/10 the value of SR33589 (0.8- 1.4% of total radioactivity). Following either single or repeat dosing, feces was the main route of excretion with urine accounting for only 3-4% elimination.

*Excretion balance following single oral (25 mg/kg) or single intravenous (2.5 mg/kg) administration of 14C-labelled SR33589B to male Beagle dogs.**EBA0092***

Urine and feces were collected as follows:
Urine: 0-6, 6-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 hours
Feces: 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 hours

Oral administration: values as % of the dose given ±SD

	0-24hours	0-48 hours	0-168 hours
Urine	3.32±1.93	5.53±2.49	6.35±3.18
Feces	32.73±32.79	58.83±35.28	78.33±10.39
total	36.05±33.84	64.36±33.33	84.68±10.63
Intravenous administration			
Urine	4.20±1.59	5.00±1.41	5.42±1.46
Feces	26.56±19.30	55.46±4.07	64.75±5.83
total	30.77±20.27	60.46±4.26	70.17±5.54

Consistent with other studies, excretion, even after IV administration, was mainly through the feces. By 168 hours approximately15- 30% of the radiolabel had not yet been excreted.

Excretion balance following a single intravenous (2.5 mg/kg) administration of 14C-labelled SR33589B to male macaca monkeys. ***EBA0057***

Four male Cynomologous monkeys received IV boluses of radio-labeled drug. Urine and feces were collected as follows:

Urine: 0-6, 6-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 hours
Feces: 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 hours

Intravenous administration: values expressed as % of the given dose ±SD

	urine	feces	Total
0-24h	2.9±1.6	9.1±10.1	12.1±8.9
0-72h	3.8±1.9	77.8±6.9	81.6±5.8
0-168h	4.2±2.1	84.6±5.0	88.8±4.9

Consistent with other studies, the main route of excretion was via the feces. Compared to other species, there was less excretion within the first 24 hours in this small sample-size study. Again consistent with other studies in other species, excretion was not complete at 168 hours after dosing.

The secretion of total radioactivity in milk of lactating albino rats following a single oral (30 mg/kg) administration of [^{14}C-carbonyl]-SR33589B. ***MIL0003***

The dams received a single oral dose on day 11 after parturition. Plasma, milk and pups gastric content was sampled 2, 4 and 24 hours post dose.

The secretion of total radioactivity in milk of lactating albino rats following a single oral (30 mg/kg) administration of [^{14}C-carbonyl]-SR33589B

	Timepoint (ngEq unsalified compound/g SEM))		
	2h	4h	24h
Milk	3814	5614	110±17
Plasma	1539±299	1362±154	Blq
Pup gastric contents	Blq	873±63	3531±226
Milk:plasma ratio	2.3	4.6	3.3

At all points of determination there was a greater concentration of drug in milk compared to plasma. Total radioactivity was also found in the stomachs of pups. From the information in this study it can be said that the drug and/or its metabolites find their way into the milk. It can't be determined from available material if there is an active secretion or sequestration process.

2.6.4.7 Pharmacokinetic drug interactions : None submitted

2.6.4.9 Other Pharmacokinetic Studies: no other studies submitted

2.6.4.10 **Discussion and Conclusions** The absorption, distribution, metabolism and excretion of dronedarone was evaluated in CD-1 mice, Sprague-Dawley rats, New Zealand White rabbits, Beagles and Macaca fasicularis monkeys. There was also some examination of the effect of dronedarone on the CYP450 system. Oral administration studies were conducted using a suspension of drug in 0.6% methylcellulose or, for dogs, gelatin capsules. Intravenous administration studies with formulations of PEG400/sodium acetate buffer or mannitol/sodium phosphate were carried out in rats, dogs and macaques.

The oral bioavailability in rats and dogs is relatively low: 14-22%. The volume of distribution is large, 12 to 66 l/kg with a moderately high systemic clearance of 2-4 l/h/kg. The apparent terminal half-life after oral dosing is from 2-7 hours.

In all species studied, dronedarone was highly protein bound (>99%). The drug stays primarily in the plasma, not the red blood cells. There is wide tissue distribution (lung, liver, spleen, kidney, myocardium) including crossing the placental barrier and entering milk and bile. Radioactivity has also been identified in the brain, indicating that either drug and/or its metabolites cross the blood brain barrier. Low levels of radioactivity persisted after 336 hours in the liver, spleen and testis. Melanin binding was also demonstrated.

The drug is extensively metabolized and the sponsor's diagram of the proposed metabolic scheme can be found below. N-debutylation leads to SR35021, an active metabolite and the main circulating species in mice. A carboxylic acid derivative, SR90154, has limited pharmacologic activity and is one of the main circulating metabolites in rats and dogs.

The main route of excretion after both oral and intravenous administration is via the feces and via the bile in rat and dog. There is a minor amount excreted in the urine. Aliquots of urine treated with β-glucuronidase indicate that there is little if any conjugation of the metabolites.

2.6.4.10 Tables and figures to include comparative TK summary

PK parameters for SR33589B and SR35021 after single oral and IV doses

Species/route	Rat/po	Rat/iv	Dog/po	Dog/iv	Macaque/iv
Dose mg/kg	30	10	30	5	1
dronedarone					
Parameters					
Tmax (h)	4.0	Na	3.55	Na	Na
Cmax ng/ml	190-180	Na	241	Na	Na
AUC Ng.h/ml	1150-960	1740-1750	3360	2500	233
T1/2 h	6.4-6.6	6.1-12.5	3.8	3.4	1.9
Cl (l/hr/kg)	Na	4.4-2.3	Na	2.4	4.9
Vz (l/kg)	Na	38.5-66.2	Na	12.0	12.8
F%	22-18	Na	14	Na	Na
SR35021					
Tmax(h)	4.0	Na	Nd	Na	Na
Cmax ng/ml	52-30	Na	Blq	Na	Na
AUC ng.h/ml	nd	nd	nd	nd	nd

Metabolites in main toxicological species compared to metabolites in human plasma following oral administration of ^{14}C-dronedarone

Metabolite name	species				
	mouse	rat	rabbit	dog	human
Dronedarone	P12%, f	P,f,b	P4.4%,f	P19%,f	P10%,f
SR35021	P19%,f	P,f	P1.1%,u,f	P,f	P30%,u,f
SR90154	P9%,f	P,f,b	P5.5%,f	P31%,f	
Dronedarone derivatives					
Monohydroxy-SR35589	P17%,f	P,u	P8.4%,u,f	P17%,u,f	4.8%,u,f
Dihydroxy-SR35589	P4%,f	U,f		P15%,u,f	P5.8%u,f
Trihydroxy-SR35589	T			T	P0.7%,u,f
Monohydroxy-keto-SR35589			P21%,u,f		p1.1%,f
SR35021 derivatives					
Monohydroxy-SR35021	P3%,u,f	P,u,f,b	P1.8%,u,f	P11%,u,f	P4.7%,u,f
Dihydroxy-SR35021	P10%,u,f	U,f,b	P3.3%,u,f	P7%,u,f	P4.9%,u,f
Keto-SR35021	T	T		T	P0.9%,u,f
Monohydroxy-keto-SR35021	P7%,u,f	U,f,b	P19%,u,f	u	P2.5%,u,f

% of total radioactivity circulating in plasma at 2hours in mouse and dog, over 0-24 hours in rabbit and at 4 hours in human

b:bile, f:feces,p:plasma,u:urine, T: metabolite detected in trace amounts in at least one biological matrix

Because of the striking thrombotic effects in the intravenous toxicology studies, the metabolites seen after oral administration were compared with those seen after intravenous administration. I came to the conclusion that the parent drug has prothrombotic properties.

Male and female rats

After single oral administration	After single IV administration
SR90154 males 16-70% of total circulating radioactivity females 39-89% SR33589 males 11-45% of total plasma radioactivity females 4-26%	SR33589 was main circulating species up to the 10th hour after dosing

Dogs

Single oral administration	Single IV administration
O-propanoic acid SR33589 derivative: main circulating metabolite over 1st 10 hours (23-74% of all detected metabolites) SR33589 minor SR35021 minor Compound of unknown structure minor	SR33589 main circulating metabolite over 1st 10 hours (19-76% of all detected metabolites) SR35021 was not positively identified O-propanoic acid SR33589 derivative minor

Macaques

Single oral administration	Single IV administration
Not done	SR33589 62-100% of total radioactivity SR35021 minor SR90154 minor

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

[pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the sponsor] Tables provided by the sponsor were of poorly scannable/transferable quality. Use of the sponsor's tables produced a "Compressed file virus" corruption of this review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Elizabeth Hausner
3/3/2006 03:08:15 PM
PHARMACOLOGIST
Elizabeth Hausner

Albert Defelice
3/6/2006 08:15:18 AM
PHARMACOLOGIST

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: *Summary of Single Dose Toxicology*: The single dose toxicology studies were conducted in mice and rats. Death was not seen following single oral doses up to 2000 mg/kg in both sexes of mice and rats. Clinical signs associated with doses ≥1500 mg/kg , the lowest dose evaluated, were prostration, hematuria and ptyalism. Following bolus intravenous administration of 15-20 mg/kg, death was seen in both sexes of mice and rats. For both sexes and species, an LD50 for intravenous administration of SR33589B can be estimated to be between 15-20 mg/kg.

Summary of Repeat Dose Toxicology: The repeat dose oral administration studies were conducted in rats and dogs. Mice were used in the 3 month dose-ranging study and the 2 year carcinogenicity study. In dogs and rats, the same target organs of toxicity were identified: the gastrointestinal system and biliary tree, the kidney, the reproductive system of both sexes and the thyroid. The long term rodent students identified angiomatous changes in both mice and rats. Changes were also reported in the heart which included AV block in both species, decreased heart rate, increased PR interval and increased T wave amplitude (dogs). Increased heart weight was inconsistently reported. The effects on the heart and ECG are expected from the pharmacology. There is also a question whether the increases in heart weight may contribute to some of the ECG alterations.

Ptyalism was seen in both rats (≥30 mg/kg) and dogs (≥45 mg/kg). At doses of ≥70 mg/kg in rats, ptyalism was associated with histological changes of epithelial hyperplasia and hyperkeratosis of the esophagus and stomach. Erosive and ulcerative lesions were seen in the glandular stomach. Histolopathological findings in the liver included necrotic foci. Biliary fibrosis and hyperplasia were also reported. The histological findings from the esophagus and stomach are characteristic of what may be seen in response to an irritant substance. This is consistent with the irritant and prothrombotic effects seen in the intravenous administration studies. The histological findings are also to be expected from the variable clinical chemistry changes seen in serum triglyceride, cholesterol, AST and ALT. Dogs showed clinical signs of vomiting and diarrhea. Histological changes in the gastrointestinal system included necrotic foci in the liver. The pancreas showed inconsistent changes in both species including serous dedifferentiation. Sometimes the overall effects in the animals could be attributed to chronic sympathetic stimulation ("stress") as demonstrated in increased serum glucose, changes in circulating electrolytes, adrenal hyperplasia, splenic lymphoid atrophy and accelerated thymic involution. However, chronic sympathetic stimulation does not account for all reported changes. The single dose safety pharmacology studies are supportive of the changes reported in the toxicology studies and are not likely attributable to "stress".

Inconsistent hematologic changes were seen. Hemoconcentration was apparent in the two-week rodent study with an accompanying decrease in reticulocytes percent in both sexes. The absolute number of reticulocytes decreased in females(~0.5x) and increased in males (~4x). For the most part, hematology changes across studies were mild, consisting of decreases in RBC, PCV and Hb that while statistically significant were of questionable biological significance.

Effects upon the renal system were typically manifested in the serum chemistry and urinalysis without associated histological findings. Serum urea was increased in the 2 week rat study (160 mg/kg) in both sexes. In the 2 week rat study a dose-related increase in serum sodium and potassium was seen in both sexes (doses ≥30 mg/kg). In the 3 month study, increased serum urea, increased serum creatinine and increased serum sodium (≥5 mg/kg/day) were seen in both sexes and increased serum potassium in the females only (≥5 mg/kg). Serum creatinine and inorganic P were increased in the 6 month rat study (≥50 mg/kg).

Decreases in excreted electrolytes were seen in the 2-week rat study(160 mg/kg), the 2-week dog study (≥25 mg/kg), the 3-month dog study (decreased sodium excretion at 17.5 mg/kg, 60 mg/kg) and the 1-year

dog study. In the 1-year study urinary sodium and potassium were decreased at 45 mg/kg (HD) in the males. Urinary potassium was decreased in the drug-treated females in a non-dose related pattern. Urinary sodium was increased in the HD females days 86 and 177 but decreased day 363. Urinary creatinine excretion was decreased in the HDm and all groups of drug-treated females with a dose-response. Kidney weight was inconsistently increased, usually at the HD in both species.

Foamy macrophages were reported in various organs in rats. At doses ≥5 mg/kg (3 month study) foamy macrophages were reported in the lungs, tracheobronchial lymph nodes, popliteal lymph nodes and mesenteric lymph nodes. At doses ≥17.5 mg/kg (3 month study) foamy macrophages were also reported in the ileum and the femoral bone marrow. Electron microscopy indicated that the macrophages contained lipids. The sponsor then referred to the foamy macrophages as due to dyslipidosis.

Because of the similarity to amiodarone, effects upon the thyroid were given special consideration. Thyroid hormone levels were measured in several studies. Findings or trends from those studies are summarized below. It may be seen that effects do not necessarily follow a strict dose-response and are not always very profound.

14 day safety pharmacology study in rats

Effects of orally administered dronedarone and amiodarone on thyroid hormone levels

group	T4 (ng/ml)	T3 (ng/ml)	rT3 (pg/ml)	T4/T3 ratio
Control	54±5(10)	0.93±0.10(9)	60±13(9)	58±3(9)
SR33589B 50 mg/kg	56±12(10)	0.98±0.17(10)	61±22(10)	57±6(10)
SR33589B 100 mg/kg	49±9(9)	0.76±0.12(9)	63±17(9)	62±4(8)
SR33589B 150 mg/kg	35±9***(10)	0.76±0.18(10)	48±14(10)	46±6***(10)
Amiodarone 50 mg/kg	62±10(10)	0.94±0.10(8)	133±21***(10)	66±11(8)
Amiodarone 100 mg/kg	61±11(10)	0.81±0.15(10)	210±21***(9)	69±10**(10)
Amiodarone 150 mg/kg	50±9(10)	0.73±0.09**(10)	222±48***(10)	75±2***(10)

**p<0.01, ***p<0.001 compared to control group
(n)number of determinations (in duplicate for T4, T3, rT3 measurements)
[a] No detectable levels of SR33589B in 3 rats (<0.017 nmol/ml)
[b] No detectable levels of SR33589B in 1 rat (<0.017 nmol/ml

3 month rat tox

Summary of thyroid tests, day 98

	Male: dose mg/kg/day			
	0	5	17.5	60
TSH ng/ml	9.6±0.89	10.1±1.1	10.3±0.92	11.3±1.7
T3 nM	1.02±0.06	0.81±0.09	0.97±0.04	0.78±0.05
T4 nM	34.34±1.79	31.03±1.68	35.72±0.83	31.93±1.54
	Female			
TSH ng/ml	6.7±0.43	5.9±0.20	6.9±0.44	8.4±0.56
T3 nM	1.43±0.05	0.91±0.03***	0.96±0.04***	0.99±0.04***
T4 nM	35.66±2.47	34.15±1.07	31.89±1.37	34.52±1.17

***p<0.1%

6 month rat tox

Summary of Thyroid hormone changes

Dose mg/kg	T3 (nM)		T3 (nM)	
	M Day 185	M day 245	F Day 185	F Day 245
0	0.98±0.04	0.72±0.05	0.82±0.04	0.96±0.06
2	0.97±0.04		1.24±0.06***	
10	0.91±0.06		1.12±0.05***	
50	0.80±0.04*	0.62±0.035	0.82±0.06	0.66±0.05**

*<1.8%, **0.2%, ***0.1%

3 month oral toxicity in the dog

Summary of thyroid hormone effects

Males				
Dose in mg/kg	0	5	17.5	60
T3 nM day 89	1.48±0.151	1.21±0.011	1.36±0.084	0.93±0.077**
T4 nM day 89	36.84±3.569	26.64±1.303*	32.11±1.730	27.44±2.609

Summary of thyroid hormone effects

Females				
Dose in mg/kg	0	5	17.5	60
T3 nM day 89	1.60±0.105	1.44±0.192	1.27±0.246	0.64±0.097**
T4 nM day 89	43.18±4.103	37.69±5.273	40.27±4.242	24.47±1.942*

1 year oral tox in the dog

Summary of thyroid hormone effects

Males				
	Dose mg/kg			
	0	5	15	45
T3 nM day 365	1.34±0.062	1.35±0.070	1.02±0.075	0.72±0.055***
Females				
T3 nM day 365	1.32±0.057	1.12±0.139	1.11±0.086	0.74±0.028***

* 1.0%<p≤5.0%; **0.1%<p≤1.0%; ***p≤0.1%

From the 1-year dog study

Study No.: TXC0970 (Continued)

Dose (mg/kg/day)[a]	**0**		**5**		**15**		**45**	
No. of Animals on Study	**M**: 5	**F**: 5	**M**: 5	**F**: 5	**M**: 5	**F**: 5	**M**: 5	**F**: 5
Clinical Chemistry (Day 90, 181, 365) (continued)								
Inorganic phosphate (mM)[b] **(Day 90)**	NAD	1.39	NTRC	1.22	NTRC	1.23	NTRC	1.01*
Immunoglobulins G (mg/L)[c]								
Day 181	4140	NAD	3955	NTRC	4018	NTRC	8100**	NTRC
IgGs and IgMs (day 181, 365)	NA	NA	NTRC	NTRC	NTRC	NTRC	NTRC	NTRC
Hormone levels[d]								
T3 (mM)								
Day 90	1.24	1.20	1.22	1.15	1.17	1.17	**1.04**	**0.94***
Day 181	1.15	1.26	0.91	1.08	**0.83**	**1.09**	**0.95**	**1.05**
Day 365	1.34	1.32	1.35[b]	1.12	**1.02****	**1.11**	**0.72*****	**0.74*****
T3/T4 ratio								
Day –7	0.040	0.037	0.037	0.034	0.036	0.029**	0.034	0.027***
Day 90	0.039	0.035	0.039	0.031	0.034	0.029*	0.035	0.024***
Day 181	0.034	0.034	0.034	0.023	0.026	0.023	0.035	0.024
Day 365	0.051	0.039	0.051[b]	0.031	**0.035****	**0.029****	**0.027 *****	**0.022*****

Abbreviations: NTRC = No treatment related changes; NAD = no abnormality detected

Histopathology from the various rat toxicology studies typically report increased columnar thyroid follicular epithelium, generally accepted as indicative of hyperplasia. However, the 2-year carcinogenicity studies do not report any hyperplasia, adenoma or carcinoma of the thyroid gland.

Amiodarone, as an iodinated drug, inhibits in vivo the 5'-monodeiodination of T4 in the rat liver. Male and female Sprague-Dawley rats given 5,16 or 50 mg/kg/day of amiodarone orally in the 2 year carcinogenicity studies had an increased incidence of thyroid follicular cell hyperplasia, adenomas and carcinomas when compared with the control groups. The B6C3F1 mice who received the drug in the 2 year studies did not show an increase in thyroid follicular cell hyperplasia or tumors. In published literature, amiodarone has been reported to decrease T3 levels and increase T4 and rT3 levels.

A side-by-side comparison of the effects of amiodarone and dronedarone on 5'-monodeiodination of T4 might have been useful information. Other than the measurement of thyroid hormone levels, no further examination of dronedarone's effect on thyroid metabolism was made.

Another consideration is drug effect on the half-life of thyroid hormones. Half-life can be shortened or lengthened due to changes in metabolism as evidenced in hyperthyroidism and hypothyroidism (Goodman and Gilman, "Thyroid and Anti-thyroid Drugs"9th edition). Something that would have been very helpful in this NDA is a radiolabel (^{125}I-iodine) study to determine if there were any changes in the metabolism of the thyroid hormones. For example, if there was a more rapid conversion to rT3, a biologically inactive form, or if circulating half-lives were altered.

An unexplained phenomenon was alteration in weight of eyes and brain, seen inconsistently in several, but not all, studies in dogs and rats. This is summarized in the reviewer's table below. Because the weight of both these organs is protected, finding changes is a flag. The sponsor does not address these findings. Histological findings were not reported in association with the weight changes. Possible explanations include 1)collection techniques 2)weighing techniques 3) fluid (blood, CSF, intracellular fluid) content,

which bears upon collection technique 4) pharmacologic effect and 5) random chance. Variations in normal thyroid metabolism may also contribute to increased size of the eyes.

Reviewer's Summary of Eye and Brain Weights

2 week rat oral toxicity study				
Doses mg/kg	0	30	70	160
Males: eyes g/kg	0.778±0.023	0.845±0.029	0.803±0.04	1.141±0.07***
Males : brain g/kg	5.96±0.17			8.08±0.41***
Females: eyes g/kg	1.149±0.045	1.038±0.027	1.027±0.047	1.443±0.082***
Females : brain g/kg	8.19±0.160	7.69±0.118	7.41±0.142	9.78±0.202***
3 month rat				
Doses mg/kg				
Males : Eyes g/kg	0.662	0.720*	0.672	0.685
Females : Eyes g/kg	1.010±0.03	0.994±0.02	0.977±0.02	1.008±0.03
6 month rat				
Doses mg/kg	**0**	**2**	**10**	**50**
Males: eyes g/kg	0.647±0.014	0.670±0.018	0.652±0.021	0.700±0.027
Males : brain g/kg	3.77±0.080	3.75±0.091	3.79±0.111	3.98±0.169
Females: eyes g/kg	1.092±0.026	1.168±0.031	1.101±0.019	1.075±0.030
Females : brain g/kg	6.30±0.148	6.58±0.146	6.37±0.124	6.16±0.165
2 week mouse study				
Doses mg/kg	0	450	600	
Males : brain g/kg	0.5005±0.014	0.4942±0.015	0.4720±0.016	
Females : brain g/kg	0.4983±0.014	0.4980±0.013	0.4843±0.018	
Eye data not present in report				
3 month mouse study				
Doses mg/kg	**0**	**50**	**150**	**450**
Males : brain g/kg	0.5016±0.008	0.5125±0.009	0.4932±0.009	0.4796±0.011
Females : brain g/kg	0.5524±0.010	0.5327±0.009	0.5460±0.008	0.5459±0.009
Eye data not present in report				

Reviewer's Summary of Normalized Eye and Brain Weights continued

Two week dog study				
Doses used	**0**	**25**	**60**	**140**
Males: eyes g/kg	1.047±0.10	1.026±0.01	1.192±0.01	1.008±0.04
Females: eyes g/kg	1.154±0.113	1.229±0.023	1.080±0.09	1.188±0.08
Males: brain g/kg	6.57±0.83	6.99±0.10	7.39±0.20	6.77±0.22
Females: brain g/kg	7.05±0.45	7.74±0.07	7.57±0.74	8.38±0.87
3 month dog study				
Doses used				
Males: eyes g/kg	1.1	1.11	1.002	1.265
Females: eyes g/kg	1.01	1.156	1.081	1.324*
Males: brain g/kg	7.27	7.5	7.3	7.87
Females: brain g/kg	6.45	7.36	7.43	9.02
1 year dog study				
Doses used				
Males: Brain g/kg	5.72±0.485	5.91±0.387	6.22±0.359	7.6±0.449*
Females: Brain g/kg	6.44±0.349	6.35±0.442	6.46 ±0.428	7.69±0.413

Genetic toxicology:

Dronedarone has been tested in the Ames assay, the mouse lymphoma, HPRT in Chinese hamster V79 cells, unscheduled DNA synthesis (in vitro) and a human lymphocytogenetic study.
The sponsor dismissed the positive results in the HPRT Chinese hamster cell assay as being within the range of historical controls.

Study #, Assay	Concentrations	Results
CEL0593 Ames assay	Preliminary: 94, 469, 938, 2345,4690µg/plate Genotox: 4.7, 9.4, 47, 94, 235 µg/plate	No increase in revertants
CEL0709 Ames assay	Preliminary (T98): 4.7, 9.4, 47, 94, 235, 469 µg/plate Genotox: 9.4, 23, 47, 94, 164 µg/plate	TA98 +S9 showed a repeatable increase (NS) in revertants. A full dose response was not shown due to the level of toxicity at the concentrations tested.
LYM0125 Mouse lymphoma	3hr ±S9: 9.37, 18.75,37.5, 75, 150, 300 µg/ml 24 hr-S9: 0.1, 0.25, 0.5, 1,2,4 and 5 µg/ml 3hr-S9: 2.5, 5, 7.5, 10, 12.5, 15 µg/ml 3hr+S9: 10, 15, 20, 25, 30, 35 µg/ml 24 –S9: 0.5, 1,1.5, 2,2.5, 3 µg/ml 3hr+S9: 17.5, 20, 22.5, 25, 27.5, 30µg/ml	No indication of increased mutation frequency in the data as presented.
685-3-008 HPRT in Chinese hamster V79 fibroblasts	1st±S9: 2.5, 5,10,25,50, 100 µg/ml 2nd –S9: 1,2.5,5,10, 17.5 µg/ml 2nd+S9: 5,10,17.5,25,37.5 µg/ml	With S9, statistically significant increases in mutants were seen in 3 repeat assays
DNA0001 in vitro DNA repair assay in primary culture rat hepatocytes	1, 2.5, 5, 10, 25 µg/ml	No evidence of unscheduled DNA synthesis in the data as presented
CEL0536 in vitro DNA repair assay in primary culture rat hepatocytes	Cytotoxicity study: 1,5,10,50,100, 250 µg/ml DNA repair study: 1,5,10,25 µg/ml	No evidence of unscheduled DNA synthesis in the data as presented
MAF0018 Lymphocyte cytogenetic study	Prelim ±S9: 25, 50, 100, 200, 600 µg/ml Main –S9: 1.25, 2.5, 5,10,15,20 µg/ml Main+S9: 6.25,12.5, 25,35,40,45 µg/ml	
MUT0046 Mouse micronucleus	Single oral dose of 2000 mg/kg	No evidence of increased micronuclei as presented

Carcinogenicity: The Executive CAC found the following to be drug-related: histiocytic sarcomas in male mice, mammary adenocarcinomas in female mice and the hemangiomas in male rats. The full details may be found in the minutes of the Exec CAC meeting (Appendix C in NDA_partIV_Appendices), the Pharmacology/Toxicology review of the studies (Appendix B NDA_partIV_Appendices) and the CDER statistical review by Jialu Zhang, Ph.D.

Carcinogenicity study finding	Sponsor's response to CA study findings
Vasoproliferative lesions in mesenteric lymph nodes	'…the incidence of hemangioma was much higher than that described for other SD rats in the literature. It thus seems that the strain used in our study exhibited an increased susceptibility to…this lesion, and that …dronedarone results in an increase of this spontaneous pathology." P 35 of Nonclinical Overview
Histiocytic sarcoma	"Changes were observed at a low incidence, and the relevance of such marginal findings remains equivocal since this could be the result of normal variation or represent a weak carcinogenic response;… No chemical products are known to induce histiocytic sarcoma in rats; in mice, 3 compounds are known to cause such changes…There was no increase in the frequency of other lymphoreticular tumors in both carcinogenicity studies." P 35 of Nonclinical Overview
Mammary adenoma and adenocanthoma in female mice	"Changes were not associated with target organ toxicity" "Tumors were limited to 1 sex, species and HD group…The proven prolactin-dependent pathogenesis of rodent tumors(24) is different from that in humans…" P 36 of Nonclinical Overview

The sponsor submitted with the NDA a narrative summary from a "Scientific Advisory Panel" (SAP) provided by Experimental Pathology Laboratories, a contract pathology laboratory. The SAP gave their opinion on the relevance to humans. They concluded that dronedarone did not pose a carcinogenic risk for humans.

My response to the arguments provided:
Vasoproliferative lesions: An increase in spontaneous lesions is considered a positive carcinogenicity finding.

Histiocytic sarcoma: The foundation of the sponsor's argument is a 1990 report (Squire) stating that at that time, no chemical had been shown to increase the incidence of histiocytic sarcoma in rats. However, 3 NTP reports (1993, 1996 and 1997) did demonstrate that there were 3 chemicals causing increases in histiocytic sarcoma in mice. Why are these relevant arguments and how does a 16-year old report have any relationship to the current drug? The report states that histiocytic sarcomas are rare in mice until 12 months of age and cites historical control data that was published by Haseman et al in 1986. Given the change in laboratory animal genetics and husbandry conditions, we may question the relevance (historical controls are usually requested to be the most recent possible) of these findings to a contemporary study. The report notes that "Except for receptor mediated (hormonal) carcinogens, the SAP knows of no nongenotoxic chemicals that have been shown to cause mesenchymal neoplasms when administered systemically, other than tetrafluoroethylene which was not extensively tested for genotoxicity by the NTP." This seems to be saying that hormonal mechanisms have been shown to cause increased incidence of histiocytic sarcomas. The SAP comes to the conclusion that "The relevance of histiocytic sarcoma in mice to humans is unknown since an analogous neoplasm is extremely rare in humans." The final decision that the finding did not represent a significant risk to humans was based upon the postulated margin of safety at the highest dose and the recommended therapeutic dose.

Mammary gland adenocarcinoma in female mice: The sponsor states that "In the absence of concurrent changes in ovaries, pituitary gland or adrenal gland, the mechanism leading to the increased numbers of mammary tumors in the current study is unknown. …The morphology of the neoplasms is species specific and dissimilar to mammary tumors observed in humans. Mammary gland tumors are generally considered to be associated with elevated prolactin levels, In humans, mammary gland neoplasms are not related to prolactin levels." Even though it is stated that the mechanism behind the tumors seen is unknown, an assumption was made that it must be

a) prolactin
b) unrelated to humans

I find the assumptions in the absence of mechanistic data to be disturbing. In the two studies where prolactin was measured, it was unchanged in one study and in the other study showed a **dose-related decrease.** There were no measurements of prolactin in the carcinogenicity study.

I find it very disturbing that the view of prolactin being unrelated to human mammary carcinogenesis was presented in isolation by the SAP. A 5 minute search using PubMed and the terms

"mammary neoplasia" AND prolactin
"mammary adenoma" AND prolactin
"mammary carcinoma" AND prolactin

produced over 100 references and a substantial body of research making a case for the role of prolactin(PRL) in 1)higher risk of human breast cancer independent of estradiol/other sex hormone levels 2)a decreased time to human breast cancer recurrence 3) an increase in human metastatic disease and 4) increased mortality. A not-exhaustive examination of the literature showed a few recent publications claiming that prolactin is luteotrophic in rodents but not humans and the mechanism of prolactin-induced rodent mammary carcinogenesis is argued to not be relevant to humans. But these publications appear to ignore the epidemiologic, clinical, molecular and transgenic research regarding prolactin and human mammary carcinogenesis. An exhaustive examination of this subject is beyond the scope of this review. However, there are several reviews in the scientific literature making a case for rodent mammary tumors being significant for human carcinogenesis and again I am disturbed that the Scientific Advisory Panel is either unaware of this research or chooses not to mention it. If they find the research flawed to the point where it is unsupportive of the argument that PRL is involved in human mammary carcinogenesis, a statement to that effect would have been appropriate in the interests of fairness and full disclosure.

Because many of the drugs prescribed for psychoses and schizophrenia cause increased prolactin levels, I asked Lois Freed, Ph.D., Supervisory Pharmacologist for the Division of Neuropharmacological Drugs how that Division handles drugs where mammary tumors are seen in the carcinogenicity studies. Dr Freed replied that if a sponsor wishes to claim that the tumors are prolactin based, they are required to show increased circulating

prolactin levels. These increases typically are not subtle but may be 50 to 100 fold over normal levels. Also, the risk-to-benefit ratio is part of the consideration for approval where prolactin-related mammary tumors have been reported.

One final comment on the carcinogenesis findings. A hormonal mechanism could explain all 3 of the tumor findings. The sponsor seems to be arguing for 3 different tumors caused by 3 different mechanisms of action. While this is possible, it seems a lower probability than one drug with one mechanism.

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Reproductive toxicology: The sponsor has already stated in their proposed labeling (and I do not disagree with this) that dronedarone is teratogenic in rats. In a preliminary study, no maternal toxicity was noted in dams at doses of 10, 20, 40 and 80 mg/kg/day with the exception of a mild decrease in body weight gain from GD6-GD10. Maternal toxicity was seen at the HD. Two dams that received 160 mg/kg/day died while the food consumption and body weight gain was greatly decreased. There were skeletal, visceral

and external malformations in 17 out of 18 fetuses. At 80 mg/kg/day, with no maternal toxicity, skeletal malformations similar to those seen at 160 mg/kg were reported for 15 out of 48 (~30%) of the fetuses. The main rat embryo-fetal toxicity study used doses of 0,10, 30 and 100 mg/kg/day. The HD animals gained 57% less body weight throughout the treatment period. No maternal toxicity was seen in the LD and MD groups. In the HD group, 198 out of 221 fetuses had abnormalities that affected external morphology, all major organ systems and the skeleton. While there were no reported anomalies in the MD group, there were reports of unilateral anophthalmia and unilateral microphthalmia in the LD group. Were these coincidental? While the sponsor did not consider the drug to be teratogenic in rabbits, skeletal abnormalities were seen at all doses in the definitive study, including the LD (20 mg/kg) with no maternal toxicity. Two fetuses from different litters of the LD, were grossly abnormal. One had a proboscis, microcephaly, both ears pointing forwards, cyclopia, agenesis of the lower jaw and mouth and an enlarged and misshapen larynx. The other had a large, misshapen larynx, central displacement of both eyes with partially open eyelids, enlarged snout with agenesis of nares and agenesis of lower jaw with no mouth. The sponsor felt that these were not drug-related. While I am not sure of this, there is agreement between reviewer and sponsor that the drug is teratogenic.

Another issue that appeared was an effect upon female cyclicity. This manifested in a number of toxicology studies with the drug-treated females paused in diestrus. In the reproductive toxicology studies where multiple analyses were made, prolonged cycles, irregular cycles and acyclicity were seen in the drug-treated females. Effects upon the weight of the uterus and ovaries were also seen in several studies. An interesting point is that these effects were reported in studies where the females were exposed to drug for ≤3 months. These effects are summarized in the reviewer's tables below.

Female cyclicity data

2 week rat oral toxicity				
Doses mg/kg/day	0	30	70	160
Estrus cycle phase:				
Diestrus	1	5	4	8
Proestrus	2	2	0	0
Estrus	0	0	1	0
Metestrus	7	3	5	0
3 month oral toxicity				
Doses mg/kg/day	0	5	17.5	60
Estrus cycle phase:				
Diestrus	4	10	8	10
Proestrus	1	1	2	1
Estrus	1	2	3	1
Metestrus	9	2	2	3
6 month oral toxicity study in rats : no data provided				

Female Cyclicity Summary Continued

Segment I Reproductive Toxicity Study				
Doses mg/kg/day	0	10	30	100
FER250: Estrous Cycles Arithmetic number (percent)				
Regular 4 or 5 day cycle	6(100)	4(67)	5(83)	6(100)
Irregular cycle [a]	0	1(17)	1(17)	0
Acyclic [b]	0	1(17)	0	0
FER0297				
Doses mg/kg/day	0	10	30	100
4 day estrous cycle	20(91)	18(82)	10(45)[b]	11(50) [b]
4/5 day estrous cycle	1(5)	2(9)	4(18)	9(41)[b]
5 day estrous cycle	0	0	4(18)	0
Irregular λ	1(5)	0	0	1(5)
Acyclicψ	0	2(9)	4(18)	1(5)

[a] At least one cycle of two, 3, or six-10 days
[b] At least 10 days without estrous
λ at least one cycle of 2,3 or 6-10 days
ψ at least 10 days without estrous

Female reproductive organ weight summary

2 week oral toxicity study in rats				
Doses mg/kg	0	30	70	160
Pituitary mg/kg	66.2±2.54			74.2±4.31
Uterus g/kg	2.46±0.24	2.26±0.24	1.97±0.15	1.49±0.12*
Ovaries mg/kg	440±30	416±19	449±18	451±34
3 month oral toxicity study in rats				
Dose mg/kg	0	5	17.5	60
Uterus g/kg	2.252±0.17	2.12±0.17	2.397±0.24	1.84
Ovary mg/kg	298±19.5	289±16.5	303±11.1	334±12.5
6 month oral toxicity study in rats				
Dose mg/kg	0	2	10	50
Uterus day 191 Day 246	2.474±0.16 2.322±0.21	2.686±0.20	2.226±0.21	1.973±0.12 2.25±0.11
Ovary day 191 Day 246	324±14.7 346±38.2	312±12.2	345±12.1	347±16.4 265±39.1
Dog 2 week oral toxicity study				
Dose mg/kg	0	25	60	140
Uterus g/kg	0.437±0.13	0.572±0.10	1.375±0.14	1.876±0.55
Ovaries mg/kg	102±8.4	108±16.1	161±9.6*	161±7.9*
Dog 3 month oral toxicity study				
Dose mg/kg	0	5	17.5	60
Uterus g/kg	0.359±0.0413	0.493±0.0540	0.880±0.3553	0.407±0.0661
Dog 2 week IV toxicity study				
Uterus g/kg	0.46±0.19	0.971±0.54	1.29±0.53	1.26±0.56
Ovaries (mg/kg)	66±12	114±37	121±32	156±54

Special toxicology: Special toxicology covered 1) hemolytic potential in vitro 2) phototoxicity and photoallergy and 3)immunological effects
Hemolytic potential was assessed in baboon and human blood. In the human study (HEM0015), after 30 minutes of incubating drug and blood, the 0.5% (LD), 0.9%(MD) and 1.4% (HD of undiluted formulation) hemolysis seen with the drug slightly exceeded that seen with the vehicle (0.2%). After 2 hours of incubation, only the HD produced more hemolysis (5.1%) than did the vehicle (3.3%). None of the in vitro hemolysis studies provided standard curves to allow the reader to assess the range of measurement of the assay.

The sponsor decided not to pursue the intravenous indication for dronedarone. For completeness, the majority of intravenous administration toxicology studies were reviewed. The sponsor identified the liver as the target organ of toxicity, poor local tolerability and venous thrombosis and phlebitis as secondary to the intravenous administration. I agree with the sponsor's assessments. Poor tolerability was seen in rats, dogs and macaques, the three species in which intravenous dosing was tried. Consistent with oral dosing, changes were seen in the serum and excreted electrolytes. In the dog studies, changes were seen in the weight of the female reproductive tract (see above). In the macaques, dose-dependency for the thrombotic effects was reported as lacking. Increased PR and QT as well as AV block were reported in the dogs and macaques. The macaques seemed to be very sensitive to the adverse effects. In the 2-week IV dosing study, dose-related increases in tissue irritation were seen at ≥1 mg/kg. The damage included profound gross and microscopic changes of hemorrhage, inflammation, thrombosis and muscle necrosis. Not presented in the summary tables but mentioned in the text were reports of changes in the veins of the axilla, cases of vascular rupture, segmental venous necrosis and muscular and dermal hemorrhagic infiltration. There was further mention of local opportunistic infections, a few cases of widespread necrosis of the crural muscle with inflammatory, septic, edematous and hemorrhagic changes sometimes associated.

Three studies were conducted in guinea pigs to examine the potential for phototoxicity, photoallergy and photosensitization associated with tissue storage. After one dose of drug and UVA +UVB irradiation, a phototoxic response was noted in 8/10 animals at 100 mg/kg and in 8/10 animals at 200 mg/kg. The reactions were graded 1-2 on a scale of 0-4 with 0 being no reaction. The score 2 was listed as well-defined erythema, pale pink. The studies did not provide evidence of photoallergy.

Dronedarone's structural similarity to amiodarone, which has a black box warning for pulmonary hypersensitivity pneumonitis or interstitial alveolar pneumonitis, may well

have been the impetus for the immunotoxicology studies. In the Toxicology Summary, p.230/465 the sponsor describes some of the changes seen as classical health deterioration, to include: lymphoid atrophy of the thymus (involution) or lymph nodes, fatty involution of the bone marrow and necrosis or hemorrhage in the adrenal cortex. Dyslipidosis was characterized by foamy macrophage infiltration of the thymus, spleen and lymph nodes as well as the non-lymphoid tissues of liver, lung and intestine. These signs may also be taken as potential immune system effects.

According to the Guidance on Immunotoxicology Evaluation of Investigational New Drugs, evaluation of potential immune system effects may include serum globulin levels (immunosuppresion), hematology differential, immune system-related organ weights and their histopathology. The most widely accepted method of experimental evaluation of immune system function is the effect on immune response to a T-cell dependent immunogen. This was in fact the method the sponsor used in the 4-week oral toxicity study in the rat.

Assessment of potential immunotoxicity included A) 3-month and 6-month rat toxicity studies: measuring IgG and IgM concentrations and examining lymphocyte subpopulations (6-month study only). B) 3-month and 1-year dog toxicity studies: IgG and IgM concentrations, lymphocyte subpopulations and lymphoblast transformation tests (1-year study only). A 4-week immunotoxicity study using male rats at doses of 2,10 and 50 mg/kg/day (the doses from the 6-month study) evaluated bone marrow cellularity, hematology, selected lymphocyte subpopulations and functional assessment of IgG and IgM blood levels in response to stimulation from keyhole limpet hemocyanin (KLH). There was no apparent difference in primary or secondary response as measured by anti-KLH titers. The lymphoblastic transformation study did show decreases in cpm of ^{3}H-thymidine with corresponding decreases in the standard error of the mean for the measurements. The variability of the various assays was discussed with Ken Hastings, Ph.D. of the Immunotoxicity Committee. Dr Hastings confirmed that these assays typically show a great deal of variability. It is further possible to obscure positive results by using a positive control that is extremely potent. However, in the lymphoblastic transformation assay as an example, a decrease in cpm with a decrease in sem may in fact indicate significant results. A summary of the results from the various immunotoxicity assays was shared with Dr Hastings (email communication). His feeling was that the results from the 3 month rat study were possibly indicative of a subclinical infection. The effects overall were mild enough that issue was not one of significance.
The data specifically pertaining to the immunotoxicology is summarized below (the same material that was provided to Dr Hastings).

3 month rat study

Summary of lymphocyte populations: mean %±SEM and (mean absolute ($10^3/mm^3$))

	Males: dose (mg/kg/day)			
	0	5	17.5	60
CD4+	44.7±5.5	52.8±4.2	51.7±4.9	52.9±3.7
CD8+	3.5±0.9 (0.26)	4.6±0.9 (0.28)	6.3±1.1 (0.39)	6.2±1.0 (0.42)
B	27.0±2.8(2.07)	19.8±1.3(1.21)	18.7±1.2*(1.19)	23.5±1.5 (1.54)
	Females (mg/kg/day)			
CD4+	62.6±1.9	62±2.7	62.8±2.8	61.3±3.5
CD8+	5.5±0.8	6.8±1.1	7.4±1.1	7.6±1.54
B	18.9±0.7	18.7±1.5	16.3±0.7	19.4±2.6

IgM was increased at the HD for males and in females showed a dose-related increase.

Summary of Immunoglobulin findings day 103

	Males: dose (mg/kg/day)			
	0	5	60	160
IgM mg/l	1170±52	1162±34	1166±39	1319±49
	Females			
IgM mg/l	1150±29	1191±49	1268±56	1500±35***

***p<0.1%

Rat 6 month toxicity study

	IgG mg/l		IgM mg/l	
	males	females	males	females
vehicle	10242±593	11027±645	1199±47	1213±41
10 mg/kg	10211±899	10557±1159	1296±44	1253±41
30 mg/kg	13318±1150*	10196±855	1390±41*	1474±44***

*1.0%<P<5.0%, ***P≤0.01%

There were no apparent findings of significance in either the lymphocyte subpopulation analysis or the bone marrow cellularity.

Lymphocyte subpopulations (%) day 185

MALE	CD4+	CD8+	B	Total
Levene	8.6% NS	>10% NS	6.8% NS	>10% NS
1-ANOVA	0.4% **	>10% NS	>10% NS	>10% NS
Group 0 : Vehicle				
n = 30	(5)	(5)	(5)	(5)
mean	23.6	7.8	42.5	73.9
SEM	2.26	0.85	6.16	6.47
Group 1 : SR 33589B 2 mg/kg				
n = 20	(5)	(5)	(5)	(5)
mean	40.0	10.6	34.1	84.7
SEM	3.33	1.48	1.28	3.58
Test/group 0 <0.1%***				
Group 2 : SR 33589B 10 mg/kg				
n = 20	(4)	(4)	(4)	(4)
mean	34.1	9.4	38.3	81.7
SEM	3.65	1.19	4.08	2.63
Test/group 0 5.3% NS				
Group 3 : SR 33589B 50 mg/kg				
n = 30	(5)	(5)	(4)	(4)
mean	32.3	10.1	40.1	82.9
SEM	1.24	0.89	3.05	3.27
Test/group 0 9.7% NS				

Lymphocyte subpopulations (%) day 185 (Cont'd)

FEMALE	CD4+	CD8+	B	Total
Levene	>10% NS	>10% NS	8.6% NS	3.3% *
1-ANOVA	>10% NS	>10% NS	>10% NS	---
Group 0 : Vehicle				
n = 30	(5)	(5)	(5)	(5)
mean	51.3	12.6	26.2	90.0
SEM	3.00	1.27	0.95	3.09
Group 1 : SR 33589B 2 mg/kg				
n = 20	(5)	(5)	(5)	(5)
mean	48.6	10.5	23.5	82.6
SEM	3.51	1.65	3.34	1.96
Test/group 0				7.8% NS
Group 2 : SR 33589B 10 mg/kg				
n = 20	(5)	(5)	(5)	(5)
mean	45.2	9.0	24.5	78.7
SEM	3.16	1.37	3.04	1.83
Test/group 0				1.4% *
Group 3 : SR 33589B 50 mg/kg				
n = 30	(4)	(4)	(4)	(4)
mean	50.3	11.1	25.2	86.5
SEM	1.76	1.46	1.80	1.14
Test/group 0				>10% NS

Table (5.5.3) 2.
Microscopy: lymph nodes - End of treatment (6 months)
(mesenteric, popliteal, retromandibular and tracheobronchial lymph nodes)

Group	0		1		2		3	
Test compound	Vehicle		SR33589B		SR33589B		SR33589B	
Dose (mg/kg/day)	-		2		10		50	
Sex	M	F	M	F	M	F	M	F
No. of animals: end of study	20	20	20	20	19	20	20	19
sacr. during study					1			1
Mesenteric lymph node								
- Macrophage infiltration								
very slight	4	10	8	8	-/4	6	1	-/7
slight	7	5	7	7	-/7	10	12	1/7
moderate	1	1	-	1	-/2	-	2	-/2
Popliteal lymph nodes								
- Macrophage infiltration								
very slight	3	5	3	5	-/6	7	2	-/7
slight	4	-	1	3	1/1	4	3	1/2
moderate	-	-	-	-	-/-	-	3	-/-
Retromandibular lymph node (examined on opportunity)								
- Macrophage infiltration								
very slight or slight	3	9	-	-	-/-	-	2	1/6
moderate or marked	1	1	-	-	-/-	-	3	-/1
Tracheobronchial lymph node								
- Very slight or slight medullary plasmocytosis	2	-	-	-	-/1	1	3	-/3

3 month dog study

Table (5.4.2) 1.
Lymphocyte subpopulations (%) day 85

MALE	T	B
Levene	2.6% *	>10% NS
1-ANOVA	---	>10% NS
Group 0 : EMPTY CAPSULE		
n = 4		
mean	76.7	12.4
SEM	1.60	2.33
Group 1 : SR 33589B 5 mg/kg		
n = 4		
mean	79.0	11.1
SEM	0.89	1.32
Test/group 0 >10% NS		
Group 2 : SR 33589B 17.5 mg/kg		
n = 4		
mean	74.4	10.8
SEM	7.98	3.17
Test/group 0 >10% NS		
Group 3 : SR 33589B 60 mg/kg		
n = 4		
mean	81.5	9.1
SEM	2.43	0.98
Test/group 0 >10% NS		

Table (5.4.2) 1
Lymphocyte subpopulations (%) day 85 (Con

FEMALE	T	B
Levene	>10% NS	>10% NS
1-ANOVA	>10% NS	>10% NS
Group 0 : EMPTY CAPSULE		
n = 4		
mean	79.9	10.6
SEM	2.31	1.67
Group 1 : SR 33589B 5 mg/kg		
n = 4		
mean	81.5	11.2
SEM	2.54	2.56
Group 2 : SR 33589B 17.5 mg/kg		
n = 4	(3)	(3)
mean	80.7	10.9
SEM	1.62	1.72
Group 3 : SR 33589B 60 mg/kg		
n = 4		
mean	84.1	8.0
SEM	2.84	2.71

The absolute numbers of lymphocytes do not show any consistent pattern and are not shown here.

Immunoglobulins : Class day 89

MALE	IgG mg/l	IgM mg/l
Levene	>10% NS	>10% NS
1-ANOVA	>10% NS	>10% NS
Group 0 : EMPTY CAPSULE		
n = 4		
mean	24500	1123
SEM	1936.5	248.7
Group 1 : SR 33589B 5 mg/kg		
n = 4		
mean	23500	1010
SEM	4092.7	149.8
Group 2 : SR 33589B 17.5 mg/kg		
n = 4		
mean	17375	945
SEM	1477.3	121.8
Group 3 : SR 33589B 60 mg/kg		
n = 4		
mean	20125	1215
SEM	2065.3	205.5

Table (5.4.3) 21
Immunoglobulins : Class day 89 (Cont'd)

FEMALE	IgG mg/l	IgM mg/l
Levene	>10% NS	>10% NS
1-ANOVA	>10% NS	>10% NS
Group 0 : EMPTY CAPSULE		
n = 4		
mean	16000	905
SEM	1779.5	119.5
Group 1 : SR 33589B 5 mg/kg		
n = 4		
mean	18625	1033
SEM	1313.0	87.7
Group 2 : SR 33589B 17.5 mg/kg		
n = 4		
mean	16250	838
SEM	1701.7	106.2
Group 3 : SR 33589B 60 mg/kg		
n = 4		
mean	17125	1010
SEM	1663.0	163.9

One year dog study

Summary of Immunoglobulin levels (Mean ±SEM)

Males				
Dose mg/kg	0	5	15	45
IgG mg/l day 181	4140±90	3955±112	4018±126	8100±653**
IgG mg/l day 365	11822±2994	10418±3014	8298±2470	5612±322
IgM mg/l day 181	1165±156	805±117	840±80	884±119
Females				
IgG mg/l day 181	4342±184	4112±85	4744±666	6392±1614
IgG mg/l day 365	5726±993	6100±1073	5400±1678	4344±245
IgM mg/l day 181	1303±258	885±117	1090±246	1119±260

*1.0%<p≤5.0%; **0.1%<p≤1.0%; ***p≤0.1%

Lymphoblastic transformation test: PHA (cpm) day 359 in males

Dose group mg/kg	Without mitogen	Conc. 1	Conc. 2	Conc. 3
Empty capsule	274±54	12834±3308	14479±4869	15634±6456
5	266±16	12077±2375	14071±2897	15614±3172
15	197±13	7793±1700	10161±2810	9963±2887
45	296±44	8001±1936	9340±2289	9858±3397
PWM: day 184				
Empty capsule	239±36	6322±2093	6985±2065	9670±2600
5	217±32	7541±1465	7757±1702	10316±2317
15	259±37	5377±680	5258±700	7648±1100
45	294±44	5263±728	5663±614	8109±492
PWM: day 359				
Empty capsule	330±50	6468±2747	6203±2250	9010±3722
5	363±43	7514±1400	9113±2368	11573±2641
15	244±40	4417±990	4891±1122	6904±1331
45	313±22	4294±1247	4686±1099	6638±1312

Lymphoblastic transformation test: PHA (cpm) day 359 in females

Dose group mg/kg	Without mitogen	Conc. 1	Conc. 2	Conc. 3
Empty capsule	385±121	10012±1739	13935±4020	14612±5150
5	213±12	6958±1022	8120±1356	8492±2154
15	300±46	7734±1879	10607±2978	13218±4518
45	268±31	8814±1255	12813±1592	11865±1874
PWM: day 184				
Empty capsule	159±18	4655±1448	5266±1671	7526±2329
45	272±31	3736±463	3781±490	5054±1052
PWM: day 359				
Empty capsule	305±39	6826±2544	7164±2377	9809±3359
45	242±24	5070±945	4815±661	6398±613

A 4-week oral immunotoxicity study in the rat (started August 25, 2005)

Table (3.4.4) 1 - IMM0044: anti-KLH IgM- and IgG-producing cells - Mean values

Group	1	2	3	4	5
Dose (mg/kg/day)	0	2	10	50	Cyclophosphamide
No. of animals/group	10	10	10	10	10
Anti-KLH IgM blood levels					
Primary response					
Titer log	3.23	3.05	3.32	2.93	1.90***
Variation	0	– 6%	+ 3%	– 9%	– 41%
Secondary response					
Titer log	3.41	3.11	3.17	3.29	1.96***
Variation	0	– 9%	– 7%	– 4%	– 43%
Anti-KLH IgG blood levels					
Primary response					
Titer log	3.05	3.20	2.96	2.78	1.53***
Variation	0	+ 5%	– 3%	– 9%	– 50%
Secondary response					
Titer log	3.44	3.32	3.29	3.35	2.68***
Variation	0	– 3%	– 4%	– 3%	– 26%

*** = $p < 0.001$ when compared to controls

Table (6.4) 6 - Lymphocyte subpopulations (%) day 28

MALE	CD4+	CD8+	B	NK
Levene	>10% NS	9.3% NS	>10% NS	0.9% **
1-ANOVA	>10% NS	<0.1%***	<0.1%***	---
Group 1 : VEHICLE				
n = 10				
mean	**35.7**	**17.1**	**39.8**	**3.9**
SEM	2.30	1.03	3.69	0.19
Group 2 : SR 33589B 2 mg/kg				
n = 10				
mean	**37.7**	**19.5**	**33.8**	**4.4**
SEM	1.36	0.69	1.84	0.45
Test/group 1		>10% NS	>10% NS	>10% NS
Group 3 : SR 33589B 10 mg/kg				
n = 10				
mean	**34.0**	**18.2**	**42.9**	**4.5**
SEM	1.39	1.60	1.84	0.67
Test/group 1		>10% NS	>10% NS	>10% NS
Group 4 : SR 33589B 50 mg/kg				
n = 10				
mean	**35.8**	**19.2**	**39.0**	**5.9**
SEM	2.32	0.88	1.98	0.81
Test/group 1		>10% NS	>10% NS	4.0% *
Group 5 : CP 4.5 mg/kg				
n = 10				
mean	**39.8**	**34.8**	**19.7**	**4.8**
SEM	1.46	1.33	1.98	0.49
Test/group 1		<0.1%***	<0.1%***	>10% NS

Table (6.4) 7 - Lymphocyte subpopulations (109/L) day 28**

MALE	CD4+	CD8+	B	NK
Levene	6.7% NS	0.2% **	4.7% *	<0.1%***
1-ANOVA	<0.1%***	---	---	---
Group 1 : VEHICLE				
n = 10				
mean	**3.62**	**1.74**	**4.13**	**0.40**
SEM	0.261	0.134	0.549	0.020
Group 2 : SR 33589B 2 mg/kg				
n = 10				
mean	**3.61**	**1.85**	**3.24**	**0.42**
SEM	0.324	0.127	0.337	0.044
Test/group 1	>10% NS	>10% NS	>10% NS	>10% NS
Group 3 : SR 33589B 10 mg/kg				
n = 10				
mean	**3.41**	**1.86**	**4.28**	**0.47**
SEM	0.235	0.222	0.263	0.081
Test/group 1	>10% NS	>10% NS	>10% NS	>10% NS
Group 4 : SR 33589B 50 mg/kg				
n = 10				
mean	**3.27**	**1.79**	**3.64**	**0.53**
SEM	0.260	0.161	0.303	0.067
Test/group 1	>10% NS	>10% NS	>10% NS	9.2% NS
Group 5 : CP 4.5 mg/kg				
n = 10	(9)	(9)	(9)	(9)
mean	**0.82**	**0.71**	**0.43**	**0.10**
SEM	0.078	0.051	0.073	0.009
Test/group 1	<0.1%***	<0.1%***	<0.1%***	<0.1%***

Table (6.4) 9 - Specific immunoglobulins day 20

MALE	IgG titer	IgG titer log(X+1)	IgM titer	IgM titer log(X+1)
Levene	<0.1%***	>10% NS	<0.1%***	>10% NS
1-ANOVA	---	<0.1%***	---	<0.1%***
Group 1 : VEHICLE				
n = 10				
mean	**1376**	**3.05**	**2048**	**3.23**
SEM	278.4	0.098	424.5	0.092
Group 2 : SR 33589B 2 mg/kg				
n = 10				
mean	**1984**	**3.20**	**1344**	**3.05**
SEM	441.9	0.101	277.3	0.087
Test/group 1	>10% NS	>10% NS	>10% NS	>10% NS
Group 3 : SR 33589B 10 mg/kg				
n = 10				
mean	**1200**	**2.96**	**2688**	**3.32**
SEM	262.6	0.121	578.8	0.110
Test/group 1	>10% NS	>10% NS	>10% NS	>10% NS
Group 4 : SR 33589B 50 mg/kg				
n = 10				
mean	**1824**	**2.78**	**1024**	**2.93**
SEM	1049.2	0.193	212.3	0.092
Test/group 1	>10% NS	>10% NS	4.5% *	>10% NS
Group 5 : CP 4.5 mg/kg				
n = 10				
mean	**55**	**1.53**	**107**	**1.90**
SEM	16.8	0.154	27.2	0.117
Test/group 1	<0.1%***	<0.1%***	<0.1%***	<0.1%***

Table (6.4) 10 - Specific immunoglobulins day 2

MALE	IgG titer	IgG titer log(X+1)	IgM titer	IgM titer log(X+1)
Levene	1.8% *	>10% NS	<0.1%***	>10% NS
1-ANOVA	---	<0.1%***	---	<0.1%***
Group 1 : VEHICLE				
n = 10				
mean	**3648**	**3.44**	**2944**	**3.41**
SEM	905.3	0.114	506.6	0.078
Group 2 : SR 33589B 2 mg/kg				
n = 10				
mean	**3136**	**3.32**	**1536**	**3.11**
SEM	951.4	0.135	289.4	0.090
Test/group 1	>10% NS	>10% NS	2.7% *	>10% NS
Group 3 : SR 33589B 10 mg/kg				
n = 10				
mean	**3584**	**3.29**	**2080**	**3.17**
SEM	1199.0	0.175	558.9	0.125
Test/group 1	>10% NS	>10% NS	>10% NS	>10% NS
Group 4 : SR 33589B 50 mg/kg				
n = 10				
mean	**3136**	**3.35**	**2368**	**3.29**
SEM	937.0	0.117	505.3	0.092
Test/group 1	>10% NS	>10% NS	>10% NS	>10% NS
Group 5 : CP 4.5 mg/kg				
n = 10				
mean	**589**	**2.68**	**112**	**1.96**
SEM	121.0	0.094	25.8	0.091
Test/group 1	0.8% **	<0.1%***	<0.1%***	<0.1%***

One mechanism that can explain all observed findings is generally considered to have a greater probability than multiple concurrent or coincident mechanisms. However, it does not seem possible to do that with dronedarone. First, some of the data patterns include changes at the LD and MD but not the HD or there are changes that do not follow a classical dose-response. Possible interpretations are:

1. the changes in numbers are fluctuations within a normal range
2. the changes are real, but not dose dependent
3. a mix up in data?

Second, most of the effects such as the cyclicity, serum and urinary electrolyte changes, changes in thyroid histopathology, some of the ECG changes, seem to fade with increased duration of exposure to the drug. Based upon the available kinetic data it does not appear that there is induction of metabolism. If anything, there seems to be some increase in plasma levels over time. Is there some receptor-based down-regulation or a specific, unidentified metabolite that decreases over time?

Looking for a one-mechanism explanation, the most obvious consideration is the thyroid-mimetic aspect of the drug's structure. Yet neither hypothyroid effects nor hyperthyroid effects fit the data. It is possible that the structure activity relationship of the drug gives mixed effects.

Hyperthyroid vs Hypothyroid effects (Goodman and Gilman 10th edition)

Hyperthyroid effects	**Hypothyroid effects**
Calorigenic effects	Skin changes, Voice changes, poor appetite
Cholesterol lowering	Hypercholesterolemia
Cardiac effects Tachycardia hypertrophy ↑ Stroke volume ↓PVR ↑ cardiac index ↑ pulse pressure angina arrhythmias	Cardiac effects Bradycardia ↓cardiac index ↑ PVR ↑ mean arterial pressure
Insulin resistance	↓insulin secretion, ↓glucose absorption in GI
Exophthalmos	Anemia
	Menstrual irregularities

2.6.6.2 Single-dose toxicity

TXA0224 Single dose oral toxicity study in mice and rats of both sexes(3/31/93 initiated). Five animals/sex/species/group were given single oral doses of 0, 1500 or 2000 mg/kg SR33589B in 10% gum Arabic followed by a 14 day observation period. There was no mortality in either sex of either species. No clinical signs were reported for mice. Rats showed piloerection, prostration and soiled urogenital areas. The 2000 mg/kg group showed ptyalism on the day of treatment. There were moderate effects on body weight gain over the course of the study.

Summary of body weight gain changes in rats and mice

Dose mg/kg	Mice % change from baseline Day1-Day15		Rats % change from baseline Day1-Day15	
	males	females	males	females
0	+41	+19	+95	+59
1500	+35	+16	+69	+44
2000	+30	+17	+70	+50

TXA0232Single dose oral toxicity study in mice and rats of both sexes (June 29, 1993 initiated). Five animals/sex/species/group were given single oral doses of 0 or 2000 mg/kg SR33589B in 0.6% methylcellulose followed by a 14 day observation period. Consistent with the previous study using a different vehicle, no deaths were seen. No clinical signs were reported for the mice. Rats again showed

ptyalism, prostration, piloerection and soiled urogenital area. Moderate body weight gain changes were seen.

Summary of body weight gain changes in rats and mice

Dose mg/kg	Mice % change from baseline Day1-Day15		Rats % change from baseline Day1-Day15	
	males	females	males	females
0	+41	+17	+113	+73
2000	+30	+19	+89	+56

TXA0231 Single dose intravenous toxicity study in mice and rats of both sexes (June 22, 1993 initiated). Five animals/sex/species/group were given single bolus intravenous doses of 0, 10, 15 or 20 mg/kg SR33589B in a vehicle of PEG400, acetic acid, buffer and glucose solution. The administration was followed by 14 days of observation. Death occurred within 5 minutes of dosing and is summarized below.

Summary of premature deaths in mice and rats after IV administration

Dose mg/kg	Mice		Rats	
	males	females	males	females
0	0	0	0	0
10	0	0	0	0
15	1	2	0	0
20	5	4	2	1
LD50	15-20 mg/kg		>20 mg/kg	

Both species showed the same clinical signs of prostration and hematuria (≥15mg/kg in both sexes of mice).

Summary of body weight gain in mice and rats after IV administration

Dose mg/kg	Mice		Rats	
	males	females	males	females
0	+31	+21	+77	+42
10	+28	+11	+76	+43
15	+26	+24	+77	+40
20	----	+23	+70	+54

TXA0290 Single-dose intravenous toxicity study in mice and rats of both sexes (April 13, 1994.) Five animals per species per sex per dose received bolus intravenous doses of 0, 10 or 15 mg/kg followed by a 14 day observation period. A vehicle of mannitol, monosidic anhydrous phosphate, glucose and water for injection. Unscheduled mortality was seen.

Summary of premature deaths in mice and rats after IV administration

Dose mg/kg	Mice		Rats	
	males	females	Males	females
0	0	0	0	0
10	0	0	0	0
15	4	3	5	5
LD50	10-15 mg/kg		10-15 mg/kg	

2.6.6.3 Repeat-dose toxicity

Study title: **Two-week oral toxicity study in the rat**

Key study findings: Target organs of toxicity were the digestive tract, reproductive tract, kidney and liver. Dyslipidosis was also seen.

One HD(160 mg/kg)m and 3 HDf were found dead from D14 to D16. Surviving HD males lost 8% of their starting bodyweight while females lost 7%. LD(30 mg/kg) and MD(70 mg/kg) groups showed the same rate of gain as the controls. The males showed dose-related increases in PCV and RBC. These changes were apparent only in HDf. Both absolute and percentage of reticulocytes were decreased in the HD groups. Lymphocytes, monocytes and neutrophils were increased in the HD groups of both sexes. Serum urea was increased in the drug-treated groups of both sexes. Serum glucose was increased in the MD and HD groups. Albumin was decreased in the HD of both sexes. ALT and AST were increased in the HD groups of both sexes. Serum electrolytes were altered in both sexes with dose-related increases in sodium and potassium (≥30 mg/kg) with decreased calcium at the HD. There were slight increases in renal weight in the HD of both sexes. Significant increases were seen in adrenal, lung, eye and brain weight. In females, uterine weight showed a dose-related decrease. In males, prostate weight showed a dose-related decrease. Drug-treated females showed a predominance of being paused in diestrus. HD males showed testicular changes such as debris, retained spermatids and multinucleated cells. Atrophy of the seminal vesicles was also noted. In the digestive tract, gross changes (≥70 mg/kg) included inflammatory and/or ulcerative lesions in the pancreatic ducts, liver necrosis, erosive/ulcerative lesions in the glandular stomach. Other histologic changes of note included 2 HD m and 2 HD f with necrotic foci in the liver. Other HD changes included fibrous changes in the biliary tract, biliary hyperplasia. Spleen, thymus, lung and mesenteric lymph node primarily at the HD were reported to show infiltration with foamy macrophages. Electron microscopy indicated that dyslipidosis would be an appropriate term for the vacuolation of the Kupffer cells studied. Chronic lymphoid atrophy of the spleen was also reported for the HD (m+f) as was epithelial hyperplasia and hyperkeratosis of the esophagus and stomach. While some changes are probably stress related (splenic lymphoid atrophy, thymic involution, adrenal hyperplasia), other changes may be beyond that, possibly due to weight loss, such as fatty atrophy of the bone marrow and the degenerative change in the male reproductive tract.

Study no.: TXA879
Conducting laboratory and location: Sanofi, Montpelier Cedex, France
Date of study initiation: April 7, 1993
GLP compliance: statement included
QA report: yes (x) no ( )
Drug, lot #, and % purity: SR33589B batch 92.01 in 0.6% methylcellulose.
Doses of 0, 30, 70 and 160 mg/kg/day were given by oral gavage to groups of 10/sex/group. The doses were based on a preliminary 8-day study that used doses of 100, 250 and 600 mg/kg/day

Methods: Test material was given daily for 16-20 days with the last dose given 24 hours before euthanasia and necropsy.
ECGs: days -5, +8 4 rats/sex/group
Ophthalmoscopy: days -6, +10 5/sex/group
Bodyweight: pre treatment then weekly
Food consumption: weekly
Hematology: days -13, +13
Clinical chemistry: days -9, +15
Urinalysis: overnight collection following administration of 10ml/kg tap water 5/sex/group,
Days -1 and +10
TK: 1,2,4,8 and 24 hours post-treatment, the last treatment was administered within 24 hours before necropsy/
Necropsy: D16-D21
Liver samples : 5/sex/group used for assessment of CYP450 effects (reviewed under ADME section).
Statistical significance: * 1.0%<p≤5.0%; **0.1%<p≤1.0%; ***p≤0.1%

Results

Unscheduled mortality: 3 HDf, 1HDm. Prior to death, the animals were thin, with dirty urogenital areas. One female was reported to show prostration and coma. Later findings were decreased thymus volume, white hepatic foci, thinning of the gastric wall with irregular mucosa and erosions. The mesenteric lymph nodes were enlarged with yellowish discoloration. Changes in the stomach and lymph nodes were seen in the LD and MD groups also. Clinical signs reported for the HD group were:
Ptyalism: all animals week 2
Health deterioration all animals week 2 (soiled muzzle, ↓activity, piloerection, soiled urogenital area (5/10males, 6/10 females), thinness, hypothermia)
Hematuria reported for 1/10 males.

Both HD males and females lost weight over the course of the study.

Summary of body weight gain

Dose Mg/kg	Males			Females		
	Day 1	Day 8	Day 14	Day 1	Day 8	Day 14
0	279±8.4	336±9.0	367±12.7	214±3.6	237±5.0	243±4.4
30	273±6.5	331±7.5	354±9.0	218±3.5	254±4.5*	262±4.9*
70	271±5.7	331±6.7	354±7.8	229±3.0**	262±4.6***	270±4.8***
160	277±4.7	283±7.7***	256±12.4***	223±2.7	214±2.4**	208±5.7***

***<0.1% by ANOVA

Hematology in males showed a dose-related increase in RBC and PCV. Hemoglobin was increased at the HD group. Absolute and percentage of reticulocytes were significantly decreased.

Female data showed increased RBC, hemoglobin and PCV in the HD only. Absolute and percent reticulocytes were also decreased.
Both sexes showed significantly increased neutrophil, monocyte and lymphocyte absolute percents at the HD.

Hematology summary

parameter	Males				Females			
	0	30	70	160	0	30	70	160
Rbc x10^3	7873	8007	8076	8821	8202	7832	8002	8895
Hb	151	157	153	162***	157	155	144*	162
Pcv	46	48	48	50***	47	46	44	50
Retics%	2.8	3.2	2.8	1.0	2.0	2.7	2.4	0.9
Reticx10^3	215	250	228	834	166	209	191	77

Absolute and normalized bone marrow cellularity was also decreased (NS) at the HD. However, a dose-response was not apparent.

Heart rate showed dose-related decreases in both sexes. T-wave amplitude was decreased primarily at the HD of both sexes.

Summary of ECG findings

Dose mg/kg	males		Females	
	hr	T wave	Hr	T wave
0	402.7±34.17	0.257±0.013	422.3±30.46	0.256±0.026
30	402.5±21.11	0.215±0.019	417.7±9.95	0.208±0.036
70	384.3±17.22	0.248±0.013	363.2±49.11	0.175±0.024
160	283.0±21.20*	0.178±0.019*	303.1±34.40	0.188±0.013

Hematology and Clinical Chemistry

Monocytes and neutrophils were increased in the HD males and to a lesser extent in the HD females. The results are suggestive of a subacute process.

Differential Summary

Dose	Males			Females		
mg/kg	lymphocytes	monocytes	Neutrophils	lymphocytes	monocytes	Neutrophils
0	9348±877	166±50	1353±188	6066±392	157±30	825±103
160	10643±1197	435±122***	3624±851***	7436±961**	200±45	4044±690***

***p<0.1%

Serum urea and glucose showed increases at the HD of both sexes. Albumin and triglycerides were decreased at the HD of both sexes. Cholesterol showed a slight decrease in HDf and a very slight increase in males. AST and ALT were increased in HD groups of both sexes.

Summary of Clinical Chemistry findings

Parameter	Males: dose in mg/kg			
	0	30	70	160
Urea (mM)	2.93±0.20	3.17±0.15	3.15±0.21	6.97±0.94**
Glucose (mM)	5.93±0.20	5.66±0.14	5.88±0.17	6.71±0.27*
Albumin g/l	32.1±0.23	33.1±0.46	33.3±0.37	30.8±0.68
Triglycerides(mM)	1.05±0.16	0.78±0.05	0.82±0.02	0.42±0.05**
Cholesterol (mM)	2.14±0.13	2.38±0.08	2.38±0.07	2.33±0.17
ALT (IU/l)	22±1.9	21±0.7	24±1.7	67±13.8**
AST (IU/l)	53±2.8	57±2.6	58±3.9	94±16.8*
Females				
Urea (mM)	4.37±0.31	4.28±0.25	4.05±0.22	7.94±1.45*
Glucose (mM)	5.97±0.17	5.85±0.12	6.07±0.12	6.31±0.58
Albumin g/l	36.4±0.37	34.5±0.48	33.5±0.45	30.8±0.62***
Triglycerides(mM)	0.061±0.05	0.67±0.03	0.82±0.05*	0.39±0.07
Cholesterol (mM)	2.87±0.12	2.78±0.15	2.84±0.13	1.98±0.29
ALT (IU/l)	19±1.2	20±1.4	22±1.2	91±23.9
AST (IU/l)	55±2.7	52±1.1	55±3.3	115±32.9

*p<3% **p<0.2% ***p<0.1

Serum sodium increased in both sexes while serum calcium decreased.

Summary of serum electrolyte changes

	Males: doses (mg/kg)			
	0	30	70	160
Na mM	145.9±0.35	148.0±0.47	147.8±0.44	149.8±0.51***
K mM	4.68±0.10	4.89±0.17	4.84±0.08	4.90±0.07
Ca mM	2.89±0.02	2.89±0.04	2.88±0.03	2.59±0.04***
	Females			
Na mM	145.6±0.43	146.2±0.42	147.0±0.37*	151.3±0.31***
K mM	4.62±0.08	4.78±0.12	5.05±0.16	5.14±0.13*
Ca mM	2.89±0.03	2.87±0.03	2.84±0.02	2.58±0.07**
*p<1.5%, **p<0.6%, ***0.1%				

Organ Weight Summary

In males, liver weight was slightly decreased at the HD. Thymic weight showed a dose-related decrease. Weights of the eyes, brain, lungs, spleen, pituitary and testes showed increases. No explanation as to these changes was given.

Summary of relative organ weight changes: males

	Males: dose (mg/kg)			
	0	30	70	160
Liver g/kg	41.59±1.4			35.18±1.1**
Spleen g/kg	2.51±0.14			2.76±0.15
Kidneys g/kg	7.18±0.23			8.56±0.61
Adrenals mg/kg	158±6.4	172±9.3	165±7.2	330±23***
Thymus mg/kg	1945±113	1767±63	1729±131	910±136***
Lungs g/kg	4.05±0.11	4.25±0.15	4.21±0.12	5.15±0.30**
Eyes g/kg	0.778±0.023	0.845±0.029	0.803±0.04	1.141±0.07***
Brain g/kg	5.96±0.17			8.08±0.41***
Pituitary mg/kg	42.2±2.45			50.6±4.91
Testes g/kg	10.4±0.32			14.0±0.64
Prostate g/kg	1.67±0.06	1.59±0.14	1.43±0.10	1.20±0.16

In females, spleen, adrenal, lung, brain, eye, pituitary and kidney weight increased. Uterine weight decreased.

Summary of relative organ weight changes: females

Liver g/kg	40.76±1.00			40.41±0.87
Spleen g/kg	2.83±0.19	3.01±0.14	3.22±0.13	3.49±0.22
Kidneys g/kg	7.29±0.14			8.39±0.36**
Adrenals mg/kg	313±10			475±23***
Thymus mg/kg	2132±134	2054±129	1958±118	868±144***
Lungs g/kg	5.13±0.15			5.85±0.19*
Eyes g/kg	1.149±0.05			1.443±0.082***
Brain g/kg	8.19±0.16			9.78±0.20***
Pituitary mg/kg	66.2±2.54			74.2±4.31
Uterus g/kg	2.46±0.24	2.26±0.24	1.97±0.15	1.49±0.12*
Ovaries mg/kg	440±30	416±19	449±18	451±34

*p<1.2%, **p<0.2%, ***p<0.1

Histological findings

Foamy macrophages were reported for the spleen, thymus and lung, primarily at the HD. Drug-treated females were paused in diestrus with no NOAEL identified. Testicular degeneration was reported in HD males.

Summary of histological findings

	Dose mg/kg							
	0	0	30	30	70	70	160	160
	m	f	m	f	m	f	m	f
Mammary hyperplasia	6		3	1	2			
Liver: necrotic foci						1	2	2
Bile duct: fibrous foci							3	3
Biliary hyperplasia							1	3
Spleen chronic lymphoid atrophy					1		6	6
Spleen: infiltration w/foamy macrophages							3	7
Thymus: infiltration w/foamy macrophages							7	8
Lung: infiltration w/foamy macrophages	4	3	4	2	2	6	9	9
Mesenteric lymph node: infiltration w/ foamy macrophages	0	0	3	1	3	4	10	10
Endometrial hyperplasia		8		6		9		1
Estrus cycle phase:								
Diestrus		1		5		4		8
Proestrus		2		2		0		0
Estrus		0		0		1		0
Metestrus		7		3		5		0
Muciparous aspect of vaginal epithelium		0		2		2		6
Male genital tract								
Vacuoles in seminiferous tubule epithelium	0		0		0		6	
Decreased # of sperm in epididymides	0		0		0		1	
Debris,spermatids, multinucleated cells in	0		0		0		6	

Seminiferous tubule lumens or epydid. Atrophy of seminal vesicles	0		0		0		3	
Epithelial hyperplasia/hyperkeratosis of esophagus							10	10
Epithelial hyperplasia/hyperkeratosis of stomach							6	4

Study title: Three -month oral toxicity study in the rat

Key study findings: There were no consistent body weight effects. HR was decreased at doses ≥5 mg/kg (both sexes). PR interval was increased at 60 mg/kg (HD) in both sexes. There were no clear effects on lymphocyte subpopulations. There was a mild increase in IgM in HDm and a dose-related increase in IgM in females. T3 was decreased slightly in HDm and significantly decreased in all groups of drug-treated females but with no dose response. Prolactin levels do not show a consistent pattern.The significance of the hormone results is not clear. Clinical chemistry changes were consistent with the previous study. There were changes in triglycerides and cholesterol seen at day 28 that did not persist to day 100. Histologic changes were also consistent with previous studies and included foamy macrophage infiltration, synchronization of the drug-treated females in diestrus and splenic congestion. Thyroid hyperplasia was manifested as columnar follicular epithelium, an effect that was more apparent in males (≥5 mg/kg). Infiltration of several organs by foamy macrophages was reported ≥5 mg/kg for lungs, tracheobronchial lymph nodes, popliteal lymph nodes, mesenteric lymph nodes and ≥17.5 mg/kg for the ileum and the femoral bone marrow. Heart weight was increased 5-11% in females and 4-9% in males.

Study no.: TXC0887
Conducting laboratory and location: Sanofi, Montpellier Cedex, France
Date of study initiation: May 13, 1993
GLP compliance: statement included
QA report: yes (x) no ( )
Drug, lot #, and % purity: SR33589B batch 92.01 purity in 0.6% methylcellulose
Doses of 0, 5, 17.5 and 60 mg/kg/day were used

Methods
Groups consisted of 15/sex/dose for the main study and 5/sex/dose for the tk study.
The main study animals were dosed daily for 90 days.
The toxicokinetic animals were treated for 28 days
Observations:
Clinical signs
ECG: Days -2, +97; 2-4 hours after dosing on 5 conscious rats /sex/dose from main study
Ophthalmoscopy: Days -3 and Day +90 on last 10 animals/sex/main study groups
Hematology: Days +26 and +96
Lymphocytes: Day 96. MAb used for determination of CD4, CD8 and B lymphocytes by FAC analysis

IgG and IgM: radial immunodiffusion assays on blood collected at time of necropsy
Clinical chemistry: days 28 and 100
Hormone levels: T4, T3, TSH, prolactin
Urinalysis: 5/sex/main group on overnight urine samples after water loading
Partly done by reagent strip
Ion and creatinine excretion: day 92
TK: blood collected 1,2,4,6 and 24 hours after last treatment on day 28 from the tk groups and at terminal necropsy from 2 rats/sex from the main study groups.
Necropsy: day 103-110 for surviving main group animals

Statistical analysis: p values included in the tables are associated with the following statistical significance:

*significant difference with 1.0%<p≤5.0%
**significant difference with 0.1%<p≤1.0%
***significant difference with p≤0.1%

One MD was found dead, most likely due to a dosing accident.
The males started the study with body weight differences between the groups.

Summary of body weight effects

	Males: dose groups (mg/kg/day)			
	0	5	17.5	60
Day 1	253±2.7	241±2.6	251±3.6	253±3.4
Day 106	539±13	462±21	525±28	486±24
Females				
Day 1	207±3	209±4	206±3	201±3
Day 106	314±12	332±12	351±15	317±4

Hematology

Both sexes showed slight decreases in RBC, Hb and PCV. The significance, if any, is questionable.

At day 96, there was slight difference in the lymphocyte subpopulations. The significance, if any, is not clear.

Summary of lymphocyte populations: mean %±SEM and (mean absolute ($10^3/mm^3$))

	Males: dose (mg/kg/day)			
	0	5	17.5	60
CD4+	44.7±5.5	52.8±4.2	51.7±4.9	52.9±3.7
CD8+	3.5±0.9 (0.26)	4.6±0.9 (0.28)	6.3±1.1 (0.39)	6.2±1.0 (0.42)
B	27.0±2.8(2.07)	19.8±1.3(1.21)	18.7±1.2*(1.19)	23.5±1.5 (1.54)
Females (mg/kg/day)				
CD4+	62.6±1.9	62±2.7	62.8±2.8	61.3±3.5
CD8+	5.5±0.8	6.8±1.1	7.4±1.1	7.6±1.54
B	18.9±0.7	18.7±1.5	16.3±0.7	19.4±2.6

No changes of apparent significance in bone marrow cellularity.

Electrocardiography

ECG changes of note are summarized below.

Summary of ECG changes (mean±SEM)

	Males: doses (mg/kg/day)			
	0	5	17.5	60
HR	485±5	396±42	363±17*	350±19*
P R(0.01s)	4.8±0.09	5.0±0.34	5.1±0.16	5.3±0.17
Females				
HR	489±17	358±31	385±30	326±45**
P R(0.01s)	4.6±0.13	4.8±0.24	4.7±0.45	6.1±0.52**

Clinical chemistry

The changes in urea, creatinine, cholesterol and triglycerides were consistent with those seen in the previous study.

Males: day 28: urea↓ with no DR relationship, creatinine ↑ very slightly at MD and HD , alk phos ↓ HD, triglycerides ↓, dose related increase in cholesterol.

Males: day 100: dose related increase in urea, creatinine increased at MD + HD, glucose significantly increased at MD, triglycerides and cholesterol were decreased

Females: day 28: dose related increase in glucose and creatinine, urea decreased (no DR), alk phos slightly increased at MD and HD.

Females: day 100: glucose significantly increased at MD and HD, creatinine showed a dose-related increase, urea was inconsistently decreased, cholesterol was slightly decreased.

Total protein, albumin and globulins: No dose-related or consistent patterns were apparent.

In both sexes, the electrolytes measured were inconsistently affected at day 28 and the changes were of questionable significance, if any. By day 100, serum K+ was increased in the drug-treated groups without a dose-response relationship.

Summary of Day 100 serum electrolyte changes

	Males: dose (mg/kg/day)			
	0	5	17.5	60
Na mM	147.7±0.56	148.9±0.31	149.6±0.37	148.9±0.42
K mM	4.83±0.10	5.20±0.13	5.24±0.12	5.11±0.10
Cl mM	100.2±0.57	103.4±0.29***	104.1±0.58***	104.2±0.49***
	Females: Dose (mg/kg/day)			
Na mM	148.4±0.38	148.2±0.46	148.8±0.30	147.7±0.41
K mM	4.64±0.10	4.61±0.10	5.13±0.17*	5.03±0.09**
Cl mM	103.1±0.46	104.6±0.32*	105.3±0.37***	105.3±0.51**

IgM was increased at the HD for males and in females showed a dose-related increase.

Summary of Immunoglobulin findings day 103

	Males: dose (mg/kg/day)			
	0	5	60	160
IgM mg/l	1170±52	1162±34	1166±39	1319±49
	Females			
IgM mg/l	1150±29	1191±49	1268±56	1500±35***

***p<0.1%

Endocrine assessment

There was a mild, dose-related increase in TSH and inconsistent changes in T3 and T4.

Summary of thyroid tests, day 98

	Male: dose mg/kg/day			
	0	5	17.5	60
TSH ng/ml	9.6±0.89	10.1±1.1	10.3±0.92	11.3±1.7
T3 nM	1.02±0.06	0.81±0.09	0.97±0.04	0.78±0.05
T4 nM	34.34±1.79	31.03±1.68	35.72±0.83	31.93±1.54
	Female			
TSH ng/ml	6.7±0.43	5.9±0.20	6.9±0.44	8.4±0.56
T3 nM	1.43±0.05	0.91±0.03***	0.96±0.04***	0.99±0.04***
T4 nM	35.66±2.47	34.15±1.07	31.89±1.37	34.52±1.17

***p<0.1%

There was no effect on male prolactin levels. In females, there were non-significant decreases in prolactin at the LD and MD and a non-significant increase at the HD. What do the results mean? Typically, prolactin levels are increased only on the day of proestrus

(Haschek and Rousseaux, Handbook of Toxicologic Pathology, edition I. p.930). Inclusion of estrogen and progesterone levels as well might have been more informative.

Prolactin levels day 98

	Males: dose mg/kg			
	0	5	17.5	60
Prl ng/ml	19.5±5.8	25.1±5.9	23.3±6.6	17.1±7.6
	Females			
Prl ng/ml	17.6±7.42	4.8±1.03	2.1±0.30	35.6±28.46

Urinalysis

Males showed greater excretion of Na (MD and HD), K(HD) and Cl(HD). Females showed inconsistent changes, with decreased Na excretion at the HD. None of the changes were statistically significant.

Organ weight changes

Absolute organ weight changes: spleen was increased at the HD in both sexes; thymus in both sexes showed dose-related decrease; heart was increased in females; prostate was inconsistently decreased; uterus was decreased at the HD; ovaries were increased at MD, HD.

Normalized organ weight changes: Increased spleen at the HD in both sexes ($p<0.001$), decreased thymus in both sexes, heart weight increased in both sexes, decreased uterus at HD, increased ovary weight(HD). Red blood cell congestion of the spleen was noted as a finding in the HD groups, probably accounting for the increased organ weight.

Organ weight changes are summarized below.

Summary of normalized organ weight changes

	Males : dose (mg/kg)			
	0	5	17.5	60
spleen	1.742±0.05	1.847±0.06	1.794±0.08	2.149±0.08***
Thymus	723±33.4	656±31.3	598±31.5*	600±26.3*
Heart	2.89±0.07	3.20±0.06** (11)	3.03±0.05** (5)	3.15±0.065* (9)
	Females			
Spleen	2.152±0.09	2.241±0.11	2.201±0.06	2.852±0.14***
Thymus	1029±46.4	915±66.2	868±75.1	827±40.4
Heart	3.42±0.08	3.55±0.07 (4)	3.74±0.10*(9)	3.72±0.09 (9)
uterus	2.252±0.17	2.12±0.17	2.397±0.24	1.84 (-18)
ovary	298±19.5	289±16.5	303±11.1	334±12.5 (12)

*<1.3%, **0.3%, ***<0.1% Numbers in parentheses ( ) are percent difference from control value.

Histologic Findings

The histologic changes were consistent with previous studies and included foamy macrophage infiltration, synchronization of the females in diestrus, and a congested spleen. Thyroid changes were also apparent in columnar follicular epithelium, a change associated with hyperplasia of the organ.

Summary of histological findings

	Females: dose (mg/kg)							
	0		5		17.5		60	
Cycle: diestrus	4		10		8		10	
Proestrus	1		1		2		1	
Estrus	1		2		3		1	
Metestrus	9		2		2		3	
	m	f	m	f	m	f	m	f
Thyroid : columnar follicular epithelium	9	1	15	0	14	2	15	7

Mesenteric lymph nodes from 3 HD animals were examined by electron microscopy to determine the macrophage morphology. The heterogenous cytoplasmic inclusions were deemed to be probably of lipid nature.

Summary of microscopic infiltration by foamy macrophages

	Dose (mg/kg)							
	0		5		17.5		60	
	m	f	m	f	m	f	m	f
Lungs	6	5	5	5	5	4	7	11
Tracheobronchial lymph nodes	-	-	1	3	1	2	2	2
Popliteal lymph nodes	-	-	5	2	6	5	8	3
Mesenteric lymph nodes	-	-	4	3	7	7	9	11
Ileum	-	-	-	-	1	0	1	1
Femoral bone marrow	-	-	-	-	-	1	1	-

The TK data was reviewed in the ADME section. However, as a reminder, there was accumulation of material from day 30 to day 90. The sponsor calculated an accumulation factor, R. This is summarized in the table:

$R=AUC_{day90}/AUC_{day\ 30}$

Sex	Dose (mg/kg/day)	SR33589	SR35021
M	17.5	2.1	-
F	17.5	1.7	-
M	60	2.5	1.8
F	60	1.9	3.2

Study title: Six-month oral toxicity study in the rat

Key study findings: As seen in the 3-month study changes in renal function were demonstrated by slightly increased creatinine levels in females (≥10 mg/kg after 6 months) and in males and females at 50 mg/kg (after 3 and 6 months). Serum chloride levels were increased in both sexes at all doses. There were no histologic changes reported in association with the renal findings. Foam cell infiltration was seen primarily in lungs at 50 mg/kg (HD), in some lymph nodes of animals of both sexes at the end of treatment and only in males at the end of the recovery phase. Foam cell infiltration was associated with an increase in perivascular lymphoid hyperplasia. There was an alteration in thyroid function in males manifested by a slight decrease in T3 levels and increased incidence of thyroid columnar follicular epithelium. Heart rate was decreased in males after 3 months and in females after 3 and 6 months of treatment. Increased QTa was also seen. Adding up the individual animal results does not always give me the same numbers as the sponsors have in their summary tables.

Study no.: TXC0986
Conducting laboratory and location: Sanofi, Montpellier Cedex, France
Date of study initiation: December 5, 1995
GLP compliance: statement included
QA report: yes (x) no ( )
Drug, lot #, and % purity: SR33589B batch 5 SNP505 purity in 0.6% methylcellulose

Methods
Rats received daily oral gavage doses of 0, 2,10 and 50 mg/kg/day for 191-198 days for the main study or for 30 days for the toxicokinetic study. The reviewer's summary of group numbers is shown below:

Summary of numbers of animals assigned to groups

Dose group(s)	Number of rats
Control , 50 mg/kg/day	30 /sex/group
2 mg/kg/day and 10 mg/kg/day	20/sex/group
Satellite groups for TK study	5/sex/group

Reversibility: 6 weeks (48-49 days) for 10 animals/sex in the control and HD groups

Doses were based on TCX887 where the LD of 5 mg/kg/day caused slight dyslipidosis, some hormonal changes, occasional increases in AST activity with no histologic changes. The HD of 60 mg/kg caused the same changes to a greater degree and in addition, some digestive effects, renal function changes and splenic congestion.

Main Study
ECG: days -4, 98 and 186, 2-4 hours post dose for 5rats/sex/group; day 242 on the other 10 animals/group
Ophthalmoscopy: day-1, 86, 177 on 10/sex/group from main study
Bodyweight: pretreatment then weekly
Food intake: weekly

Hematology: day -12, 91, 182 males // day -11, 92, 183 for females//day 238 in both sexes in recovery groups
Lymphocyte subpopulation: day 185 from 5 rats/sex/group (not the animals used for hormone level detection) CD4 and CD8 cells by FAC analysis
Clinical Chemistry: Day -8, 94, 189 males//day -7, 95, 190 females//day 241 recovery grp
Hormones: T4, T3, TSH, prolactin measured on day 185 and from the recovery animals day 245
IgG and IgM: radial immunodiffusion assay used on blood collected at necropsy
Urinalysis: day -4, 88, 179 overnight collection 5/sex/group after water loading
TK: satellite groups: day 30: 1,2,4,6,24 hours 1/sex/group/time
Main groups: day 191-196: 1,2,4,6,24 hours 2/sex/group/time at necropsy
Necropsy: D191-199. Gross examination, organ weights, collection of tissues for light Microscopy, liver evaluation by EM

Statistical analysis: p values included in the tables are associated with the following statistical significance:
*significant difference with 1.0%<p≤5.0%
**significant difference with 0.1%<p≤1.0%
***significant difference with p≤0.1%

Reversibility Phase
ECG day 242 5/sex/group
Bodyweight and food: weekly
Hematology: Day 238
Clinical chemistry: Day 241
Hormones: Day 245
Necropsies: Day246- D247

Clinical signs seen at the HD include: ptyalism in most animals seen a few minutes after administration, sometimes seen after 71 days of dosing; soiled urogenital area in 6 females; waste of food in 2 males and 10 females.
HD males gained somewhat less than the other groups during the last 80 days of dosing but appeared to regain ground during the recovery phase. The HD females gained more weight than the other dose groups.

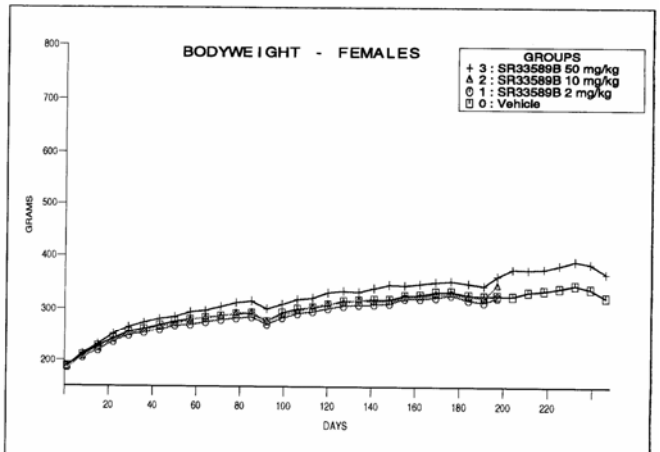


Figure (3.1.5) 2. Body weight - Females

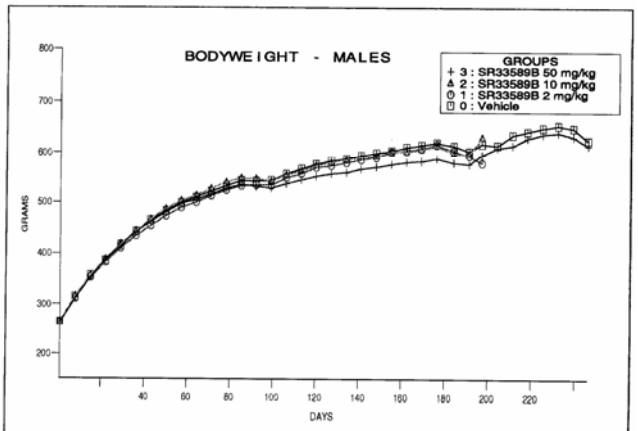


Figure (3.1.5) 1. Body weight - Males

It should be noted that HD females showed markedly increased food consumption for the duration of the study and recovery period.

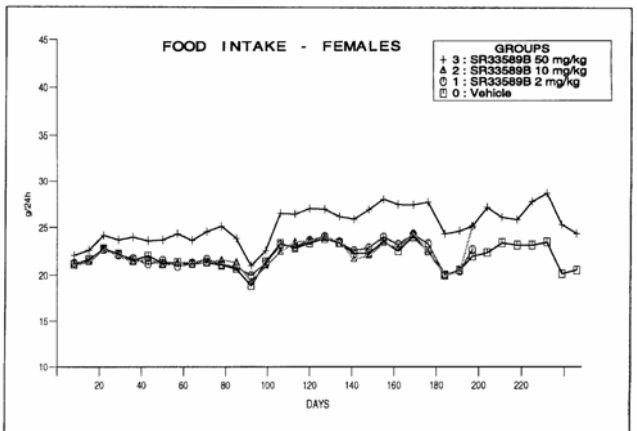


Figure (3.1.5) 4. Food intake - Females

ECG

In males, heart rate was inconsistently decreased in the LD and MD groups. HR changes in the HD group persisted into the recovery period. In females, HR was decreased only at the HD. In the recovery period, HR increased to above control levels. PR interval was increased day 98 in males only. QTc showed an increase only on day 186. T wave

amplitude was markedly increased in females during the recovery period: control 0.0176±0.03 vs HD 0.299±0.015 p<0.02). Some of the ECG changes are summarized on the next page.

Summary of ECG changes

	Males: Dose mg/kg			
	0	2	10	50
HR bpm Day 98 Day 186 Day 242	 472.5±7 407.5±28 406.2±38	 444.7±20 385.4	 462.2±13 412.5±18	 409.0±7 371.3±22 370.4±12
QTa (0.01s) day 186	3.7±0.15	3.8±0.12	4.3±0.44	4.3±0.17
QTc day 186	3.03±0.185	3.03±0.15	3.51±0.356	3.38±0.16
	Females			
HR bpm Day 98 Day 186 Day 242	 483.6±12 417.3±18 351.5±23	 482.6±6 427.8±26	 493.1±7 451.7±12	 395.8±17** 322.2±13** 415.7±26
QTa (0.01s) day 186	3.6±0.08	4.2±0.16**	4.1±0.12*	4.1±0.25
QTc day 186 Day 242	3.02±0.06 2.85±0.20	3.51±0.12**	3.55±0.15*	2.98±0.19 3.33±0.21

*<1.4%, **<0.8%

Hematology and Clinical Chemistry

There was a slight but significant decrease (p<0.01) in hemoglobin (156 ± 1.1 vs control value of 161±0.9) in HD males only seen by day 182. There was a slight increase in the HD group by the end of the recovery (158±1.1).
Triglycerides increased in HD females: 0.64±0.040mM vs 0.50±0.020mM Control, (p<0.03).
IgG and IgM showed slight increases in HD males.

There was no apparent effect on TSH and only a minimal effect on T3 levels in males. T3 in females was increased over control levels in the LD and MD groups.

Summary of Thyroid hormone changes

Dose mg/kg	T3 (nM)		T3 (nM)	
	M Day 185	M day 245	F Day 185	F Day 245
0	0.98±0.04	0.72±0.05	0.82±0.04	0.96±0.06
2	0.97±0.04		1.24±0.06***	
10	0.91±0.06		1.12±0.05***	
50	0.80±0.04*	0.62±0.035	0.82±0.06	0.66±0.05**

*<1.8%, **0.2%, ***0.1%

Prolactin levels were decreased in the drug-treated females during the treatment period and increased over control in the recovery period.

Summary of prolactin values (ng/ml)

Dose mg/kg				
	M Day 185	M day 245	F Day 185	F Day 245
0	33.4±7.8	38.9±8.9	68.9±27.5	141.5±25.1
2	36.6±6.3		32.5±6.6	
10	55.8±6.3		27.3±9.5	
50	22.5±5.8	25.0±3.5	26.4±6.4	294.8±77.8

There were no apparent findings of significance in either the lymphocyte subpopulation analysis or the bone marrow cellularity. IgG and IgM were increased in the HD males. IgM was increased in the HD females.

	IgG mg/l		IgM mg/l	
	males	females	Males	females
vehicle	10242±593	11027±645	1199±47	1213±41
10 mg/kg	10211±899	10557±1159	1296±44	1253±41
30 mg/kg	13318±1150*	10196±855	1390±41*	1474±44***

*1.0%<P<5.0%, ***P≤0.01%

Urinalysis: no findings of apparent biological significance.

Organ weights

There was a slight increase in spleen weight in HD females. Difference persisted at the end of the recovery phase. Relative lung weight was minimally increased in the MD and HD males at the end of the main study. No difference was apparent at the end of the recovery period. There were no obvious differences in pituitary weight at day 191. At the end of the recovery period both sexes showed increased pituitary weight.

Relative organ weights

	Females Dose: mg/kg			
	0	2	10	50
Spleen day 191 Day 246	1.985±0.05 2.050±0.8	2.063±0.08	1.938±0.07	2.284±0.09* 2.139±0.05
Lungs day 191	4.14±0.11			4.36±0.16
Pituitary Day 246	53.8±5.37			60.2±5.41
Ovary day 191 Day 246	324±14.7 346±38.2	312±12.2	345±12.1	347±16.4 265±39.1
Uterus day 191 Day 246	2.474±0.16 2.322±0.21	2.686±0.20	2.226±0.21	1.973±0.12 2.25±0.11
	Males			

Spleen day 191 day 246	1.503±0.05 1.558±0.09	1.614±0.04	1.609±0.07	1.721±0.06 1.643±0.15
Lungs day 191	3.14±0.079		3.22±0.09	3.32±0.108
Heart day 191	2.86±0.07	2.99±0.07	2.92±0.06	3.14±0.10
Pituitary day 246	19.6±1.06			25.4±1.32**

Histological findings

Macrophage infiltration was noted for several lymph nodes, but without the designation of "foam filled". There were no apparent differences for the incidence of the finding between treated and control animals.

summary of histological findings

	Dose mg/kg							
	0		2		10		50	
	m	f	M	f	m	f	m	f
Lungs: perivascular lymphoid hyperplasia	4	6	1	1	3	0	15	12
Lungs: foam cell infiltrate	1	2	1	0	0	1	5	3
Lungs: foam cell foci	8	10	3	1	3	2	16	13
Tracheobronchial lymph nodes: macrophage infiltrate	3	6	2	5	1	6	8	4
Thyroid : follicles with columnar epithelium	10	7	8	4	6	3	18	9

Toxicokinetic Parameters

The female rats showed greater plasma levels of parent drug and metabolite than the males. The increases in AUC were greater than proportional.

Dose mg/kg	SR33589 Cmax mg/l		SR33589 AUC_{0-24} mg h/l	
	male	female	Male	female
	Day 30			
2	0.022	0.000	Nc	Nc
10	0.105	0.093	0.173	0.498
50	0.281	0.339	1.671	3.057
	Day 191			
2	Nd	0.012	Nc	Nc
10	0.110	0.077	0.366	0.369
50	0.527	0.537	4.078	6.331
	SR35021 Cmax mg/l		SR35021 AUC_{0-24} mg.h/l	
	Day 30			
2	0.000	0.000	Nc	Nc
10	0.000	0.000	Nc	Nc
50	0.047	0.073	0.158	0.213
	Day 191			
2	0.000	0.000	Nc	Nc
10	0.000	0.000	Nc	Nc
50	0.168	0.154	1.173	2.278

Study title: 4-day intravenous dose-range finding study in the rat

Key study findings: Very poor local tolerability was demonstrated by marked to severe tail edema and necrosis at all doses of drug. No NOAEL was identified in this study for decreased PCV and Hb, increased serum glucose and serum cholesterol. At doses ≥6 mg/kg (MD), ALT and AST were increased. Adhesions and yellowish areas were seen grossly at 12 mg/kg. Albumin was decreased in females at all doses and was decreased in males only at the HD. Red urine was reported for ≥6 mg/kg. There was a slight increase in normalized spleen weight in both sexes, that was dose-related in males. The sponsor identified the target organ of toxicity as the liver.

Study no.:DDO0499
Conducting laboratory and location: Sanofi Recherche, Montpelier Cedex, France
Date of study initiation: January 25,1993
GLP compliance: statement included
QA report: yes ( ) no ( )
Drug, lot #, and % purity: SR33589 batch RKJ21, purity
Vehicle: PEG400, acetic acid/sodium acetate buffer

Methods: Sprague-Dawley rats (CD(SD)BR), 3/sex/group were given intravenous doses of 0,3,6 or 12 mg/kg/day of drug for 4 days. Drug was given via the tail vein.
Observations: Daily clinical examinations, bodyweight (day1 and 3), food intake (day3), Hematology(day 4), clinical chemistry (day 4), necropsy (day 5)

Statistical analysis: p values included in the tables are associated with the following statistical significance:

*significant difference with 1.0%<p≤5.0%
**significant difference with 0.1%<p≤1.0%
***significant difference with p≤0.1%

Results

Clinical Signs:

Clinical signs reported were

6 mg/kg: Red urine on day 3 in 2f/3
12 mg/kg: prostration on Day 1 (1 m/3), "decubitus" lasting several minutes after treatment on day 1 and day 2 in 6/6 HD animals.

The tail showed severe dark discoloration, marked to severe tail edema and necrosis from day 2 (≥3 mg/kg)

Hematology and Clinical Chemistry

PCV and absolute number of reticulocytes decreased in the drug-treated males. While PCV decreased also in the females, there was no apparent change in absolute reticulocyte number. Hemoglobin concentration also decreased.

Summary of hematology changes

Dose mg/kg	PCV	Reticulocytes/mm3 (%)	Hb g/l
	males		
0	48±2.1	674947±24160 (9.3)	138±4.7
3	44±1.0	730514±12936 (10.9)	133±1.5
6	42±1.5	571873±38310 (9.0)	122±8.2
12	40±2.6	565679±46712 (8.5)	126±8.4
	Females		
0	43±1.5	294952±25117 (4.4)	130±2.0
3	38±2.3	478948±66851 (7.4)	126±9.6
6	39±0.7	385447±51880 (6.4)	114±6.1
12	34±1.0	335101±67471 (6.0)	102±1.5

Summary of neutrophils and lymphocytes

Dose mg/kg	Neutrophils %(absoloute/mm3)		Lymphocytes % (absolute/mm3)	
	males	females	males	females
0	12±1.8 (1274±259)	7±4.0 (587±458)	86±2.5 (9404±1350)	87±6.0 (5847±1848)
3	11±5.5 (958±403)	18±4.5 (1447±291)	85±7.5 (8379±1834)	78±2.8 (6299±827)
6	23±5.7 (2627±761)	20±3.1 (1887±83)	71±6.2 (7929±472)	74±1.7 (7237±896)
12	29±8.5 (3509±1291)	19±7.0 (1538±854)	68±9.3 (7622±442)	78±5.0 (5724±993)

Neutrophils (both percentage and absolute) increased in both sexes. In males, the percentage and absolute number of lymphocytes decreased somewhat. In females, the percentage of lymphocytes decreased slightly while the absolute number increased at LD and MD and was unchanged at HD.

Blood glucose increased in both sexes in a dose-related manner. Creatinine and urea were unchanged in males and slightly increased in females. Both sexes showed a decrease in albumin and consequently shifts in the ratio of albumin to globulins. Increases in the globulin levels were consistent with some kind of immune stimulation as suggested by the neutrophil shifts.
Triglycerides and cholesterol were increased in both sexes.
ALT and AST were increased in both sexes.

There was a non-significant increase in potassium in the HD females that was not seen in the males.

Summary of clinical chemistry findings: males

	Dose mg/kg			
	0	3	6	12
Glucose mM	3.40±0.40	3.73±0.20	4.40±0.43	4.81±0.21*
Albumin g/l	32.7±0.67	30.7±0.33	31.0±0.58	29.3±0.33*
Globulins g/l	23.7±0.88	25.3±0.67	29.3±0.88*	32.0±2.08**
Triglycerides mM	0.87±0.151	0.84±0.123	1.29±0.038*	0.93±0.038
Total choles mM	2.25±0.09	2.59±0.06*	2.99±0.13**	3.24±0.45
ALT IU/l	31±2.5	31±1.7	59±16.4	54±15.7
AST IU/l	72±4.7	77±3.5	114±11.0	100±11.2
K+ mM	5.33±0.27	4.73±0.29	5.23±0.27	4.57±0.09

Summary of Clinical Chemistry Findings: females

Glucose mM	4.87±0.44	5.47±0.51	5.64±0.15	5.89±0.05
Urea mM	4.50±0.47	6.60±1.89	5.15±0.72	5.15±0.57
Creatinine mM	31.0±1.00	32.2±1.45	34.3±2.03	33.7±0.88
Albumin g/l	36.3±0.33	31.7±0.88***	31.3±0.33***	31.3±0.33***
Globulins g/l	25.7±1.20	31.3±2.91	33.7±0.33*	32.0±0.58
Triglycerides mM	0.63±0.15	0.70±0.24	0.87±0.06	0.79±0.16
Total choles mM	1.89±0.26	2.42±0.34	2.46±0.14	2.32±0.03
ALT IU/l	19±1.0	26±2.8	52±21.7	57±18.5
AST IU/l	70±7.2	77±5.6	224±135	209±91.3
K+ mM	4.40±0.17	4.40±0.15	4.47±0.03	5.13±0.12

Organ Weights
Absolute and relative spleen weight was increased in males (dose-related)
Absolute kidney weight showed a dose-related decrease in females ($p<0.05$)
Absolute and relative adrenal weight was increased in the MD and HD ($p<0.01$) females

Relative weight of the adrenals was increased ($p<0.01$) in the LD males.
There was no consistent pattern in the reproductive organ weights of either sex.

Organ Weight Summary

Males				
	Dose mg/kg			
	0	3	6	12
Spleen(absol) g	0.56±0.01	0.63±0.06	0.68±0.04	0.79±0.09
Spleen (g/kg)	3.08±0.04	3.57±0.29	3.69±0.08**	4.26±0.46
Adrenals (mg/kg)	278±2.6	325±2.8***	240±25.5	284±51.2
Pituitary (mg/kg)	38.1±2.9	49.0±6.1	41.4	39.9±4.9
Females				
Kidney (absol) g	1.53±0.013	1.49±0.122	1.43±0.04	1.40±0.02**
Adrenals (absol) mg	58±2.4	47±3.1	66±1.5	83±3.9***
Adrenals (mg/kg)	360±26	292±30	415±10	561±32
Spleen (g/kg)	3.14±0.11	3.74±0.14	3.56±0.32	3.84±0.35
Pituitary (mg/kg)	57.4±1.8	49.1±6.6	58.6±7.3	60.5±3.4

***<0.1%

Histopathology was not done.

Study title: Preliminary toxicity study by intravenous infusion to CD rats for seven days

Key study findings: Beyond the effects of the vehicle, PCV and Hb were decreased in 20 mg/kg (HD m and HDf) and (10 mg/kg) MDf. It is not clear if changes in the hematology are entirely due to the irritation and damage to the injection sites and surrounding tissues. A slight decrease was reported in serum albumin in HD f as well as increases in AST and ALT in the same group. Consistent with the previous study there was poor local tolerability.

Study no.: DDO548

Conducting laboratory and location: Pharmaco LSR, Suffolk, England
Date of study initiation: September 15, 1994
GLP compliance: statement included
QA report: yes ( ) no (x)
Drug, lot #, and % purity: SR33589B, batch 92.01, purity >99%
Vehicle: mannitol, monosidic anhydrous phosphate, water for injection

Methods Sprague-Dawley rats (CD), 3/sex/group were given intravenous doses of 0(saline controls), 0(vehicle controls), 5, 10 or 20 mg/kg/day each day for 7 days. Drug was given via the femoral vein using a surgically installed catheter. After a "post-operative recovery period of a minimum of seven days" dosing began.
Observations:
Clinical signs: twice daily
Bodyweight (pre-study, day of surgery, start of treatment, day 3 after surgery, necropsy)

Food consumption: per week
Hematology, clinical chemistry: day 7
Euthanasia: gross observations, organ weights, tissues collected for histopathology

Statistical analysis: p values included in the tables are associated with the following statistical significance:

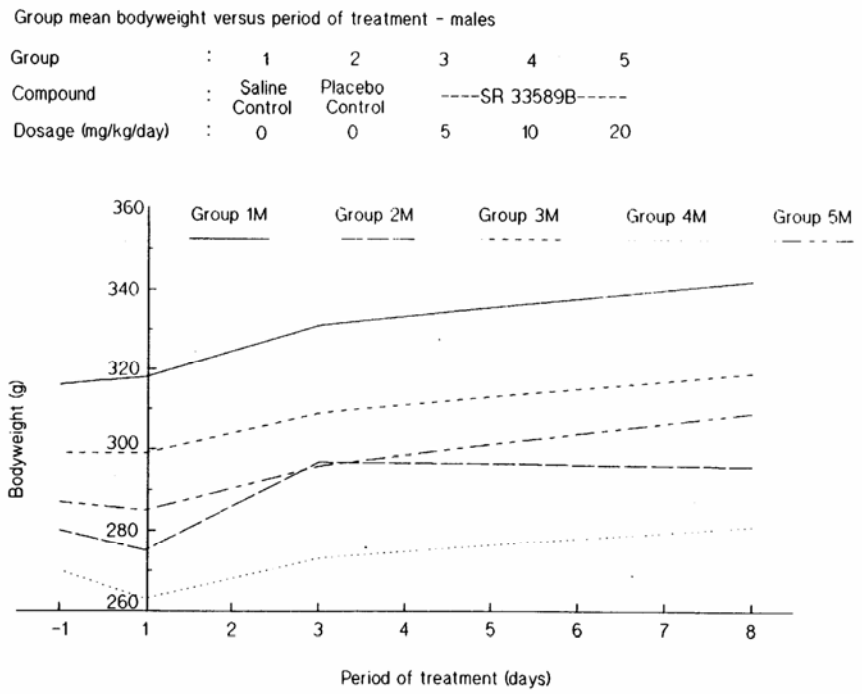
*significant difference with 1.0%<p≤5.0%
**significant difference with 0.1%<p≤1.0%
***significant difference with p≤0.1%

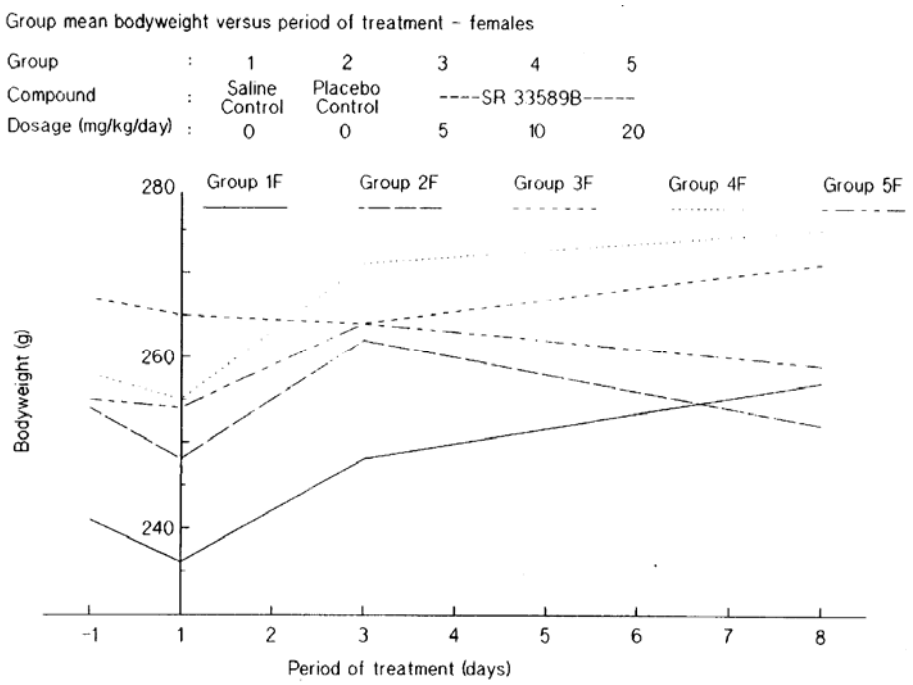
Results
There was no unscheduled mortality. One HD female was euthanized day 2 of treatment for loss of catheter patency and was replaced.
Clinical signs (the sponsor felt that these were associated with the infusion process but not the drug):

Arched back; several treated females, 1 sal control f, 2 HDm
Hunched, low activity; 20 mg/kg animals
Tremors: MD and HD females
Piloerection: HDf
Ptosis: MD and HD animals

Necropsy findings around the catheter tip showed visible damage to the veins and tissues.

Body weight and food consumption
The vehicle control in both sexes showed decreased body weight gain as did the HD females.





There were no consistent effects on food consumption.

Hematology and Clinical Chemistry

Hematology showed a decrease in PCV, Hb and RBC in the HDm and in a dose-related pattern in females. These effects were mild in the vehicle control groups.

Summary of hematology effects (mean ±SD)

Males					
	Dose mg/kg				
	saline	vehicle	5	10	20
PCV %	45±2	43±2	40±3	42±3	38±1
Hb g%	15.3±1.1	14.5±0.8	13.3±1.2	13.9±0.7	12.7±0.4
RBC mil/cm	7.95±0.49	7.35±0.25	6.80±0.91	7.26±0.58	6.54±0.31
Platelets 1000/cm	896±65	921±314	1110±102	928±245	1255±246
PT secs	18.3±4.6	14.1±0.2	14.2±0.4	13.7±1.0	14.1±1.0
Females					
PCV %	43±2	41±4	40±3	38±2	34±4
Hb g%	14.7±0.6	14.1±1.4	13.5±0.5	12.9±0.9	11.7±1.4
RBC mil/cm	7.64±0.74	7.64±0.52	6.68±0.25	6.56±0.47	6.38±0.81
Platelets 1000/cm	920±40	1172±147	1092±200	1174±155	1330±103
PT secs	13.4±0.1	13.4±0.4	14.0±0.6	14.4±0.5	13.5±0.6

There was a dose-related decrease in albumin and the A/G ratio in both sexes. There were mild increases in ALT and AST in females.

Summary of Clinical Chemistry effects (mean ±SD)

Males					
	Dose mg/kg				
	saline	vehicle	5	10	20
Albumin g%	2.8±0.2	2.2±0.6	2.0±0.9	1.9±0.3	1.9±0.2
P mmol/l	2.6±0.1	2.3±0.1	2.5±0.0	2.7±0.1	2.4±0.1
Females					
ALT IU/l	34±9	38±11	37±8	38±2	47±7
AST IU/l	107±20	118±21	122±30	101±16	142±40
Total chol mg%	79±11	64±10	49±11	53±31	49±11
Albumin g%	3.5±0.2	2.9±0.4	2.0±0.1	2.2±0.6	2.0±0.2
K+ mmol/l	2.9±0.3	2.9±0.2	2.9±0.1	2.8±0.3	3.2±0.4

Organ Weights

No trends were apparent in the absolute organ weights.
There were inconsistent increases in normalized lung and kidney weight in treated females.
Normalized spleen weight was also increased in both sexes although a steady dose-related response was not apparent.

Summary of organ weight effects (mean ±SD)

	Dose mg/kg				
	saline	Vehicle	5	10	20
Kidney (rel to body weight)	0.787±0.081	0.800±0.02	0.912±0.06	0.916±0.09	0.864±0.05
Lungs (rel to body weight)	0.498±0.06	0.609±0.05	0.541±0.03	0.692±0.12	0.615±0.04

Histopathology results were not provided.

Study title: Toxicity study by intravenous infusion to CD rats for four weeks

Key study findings: The text of this report notes poor weight gain and marked weight loss in several control animals. The jackets used to protect the catheters were irritating to the animals and the desire to escape from the jackets was so intense that 3 deaths were directly attributed to this. It was also reported that there were corneal opacities and keratopathies due to the period of anesthesia during the catheter implantation. Overall, the reviewer is left with the impression that the animals were stressed, in poor condition, and that the overall value of the study must be questioned.
Intravenous infusion of all doses was associated with a higher incidence of abscesses and/or hematomas than caused by vehicle alone: vehicle 6/20 (no deaths); LD 12/20 (2 deaths), MD 17/20 (3 deaths), HD 18/20 (4 deaths). Hematology also showed dose-related anemia in the males but only in HDf. Increased WBC counts (primarily neutrophilia and monocytosis) as well as decreased total cholesterol and albumin were seen in both sexes. AST and ALT showed dose-related increases in males.

Study no.: TSA0963

Conducting laboratory and location: Pharmaco L.S.R., Suffolk, England
Date of study initiation: November 14, 1994
GLP compliance: statement included
QA report: yes (x) no ( )
Drug, lot #, and % purity: SR33589B (batch 92.01), purity
Vehicle: mannitol, monosidic anhydrous phosphate, water for injections
Methods: Sprague-Dawley rats (10/sex/group) were given either saline (control), vehicle (vehicle control) or intravenous doses of 2,4 or 8 mg/kg/day for 28 -29 days. Injections were made into an indwelling catheter installed in the femoral vein.
Observations:
Body weight: Pretreatment, day 3 after surgery, start of treatment, twice weekly during treatment, at necropsy
Food consumption: Mean consumption per rat calculated for each group per week
Ophthalmoscopy: pretreatment, and after 21 days of treatment the saline, vehicle controls and HD groups were examined
Hematology and clinical chemistry: blood collected day 23
Urinalysis: between days 25-28, urine collected from all rats in individual metabolism cages

Toxicokinetics: day 29, samples collected from 2 rats/sex/group immediately before infusion, immediately after infusion, 2 hrs and 5 hrs after end of infusion

Euthanasia: gross observation, organ weights, tissues preserved for histopath
Electron microscopy: samples of liver and kidney taken from 3 males and 3 females per group

Statistical analysis: p values included in the tables are associated with the following statistical significance:

*significant difference with 1.0%<p≤5.0%
**significant difference with 0.1%<p≤1.0%
***significant difference with p≤0.1%

Results

Unscheduled mortality was seen in the drug-treated animals:

Saline control: 1 female, catheter problem
Vehicle control: 1 female, catheter problem; 1 male
LD: 2 males
MD: 2 males, 2 females Death of the 10 dosed animals was reported to be related to the
HD: 2 males, 2 females irritancy of the infusion.

Clinical signs: were reported for the premature decedents and included swollen abdomen, hunched posture, piloerection. Necropsy of the premature decedents showed:

> Necropsy revealed that all of the above animals had an adhesive mass at the infusion site, often involving the surrounding tissues and associated with inflammation and haemorrhage. The masses were diverse in appearance, and were identified at histopathology as either haematomas, consisting of a cystic space containing gelatinous material and clotted blood, or as abscesses which were paler in appearance and contained purulent material. Other common macroscopic findings included pallor of the internal organs, free and/or clotted blood in the abdomen, swollen spleen and enlarged lymph nodes. Histopathology also indicated changes in the liver, lungs, kidneys, spleen and lymph nodes of most of these animals.

The text states that few behavioral changes were associated with the other animals. These signs, reported almost exclusively for the HD group, included piloerection, decreased activity, hunched, ptosis, ataxia, pallor and slow respiration following dosing during the third week.

Body Weight and Food Consumption

There were no apparent effects on body weight gain and food consumption. However, the text of the report notes that mean weight gain in the HD females was relatively high compared to the saline and vehicle controls. The sponsor attributes this to the poor weight gain of the female control animals and marked weight loss in 2 female saline control animals. It was also noted that the jackets worn to protect the catheters were very irritating to the rats and led to the death of 3 animals. While the HD groups gained more than the control groups, food consumption was decreased in the HD animals.

Changes are summarized below.

Summary of body weight changes (Mean±sd)

Males					
	Dose mg/kg/day				
	saline	Vehicle	2	4	8
Day 0	289±44	318±18	305±27	326±15	310±21
Day 28	370±64	391±29	388±24	399±24	399±36
Change day 0-28	81±39	74±18	75±12	71±33	90±26
Food consumption: week 4	170±39	187±22			159±27
Females					
Day 0	247±23	247±17	253±8	249±10	247±14
Day 28	282±27	279±31	294±17	287±16	297±20
Change day 0-28	34±10	31±19	41±18	40±16	51±25*
Food consumption: week 4	148±32	146±24			139±19

*p<0.05

Ophthalmoscopy: The sponsor states that there were no treatment-related findings. But it was also noted that there were “superficial corneal opacities” and “bands of keratopathy” considered to be associated with the period of anesthesia during the surgery.

Summary of ophthalmic findings post-surgery and pre-treatment

	males			females		
	saline	Vehicle	HD	saline	Vehicle	HD
Corneal opacities	5	5	7	10	7	10
keratopathy±ulcer	4	5	7	2	2	3
Ulcer	0	1	0	1	0	0

Hematology and Clinical Chemistry

A dose-related increase in neutrophils was seen in both sexes. This is consistent with the other intravenous dosing studies and is most likely related to the tissue damage done by the irritancy of the injected material, stress and subsequent health complications.

A decrease in PCV, Hb, RBC was seen in both sexes. In the females, part of the decrease was due to the vehicle. This vehicle effect was not seen in the males.

Summary of hematology mean±SD

Males					
	Dose mg/kg				
	saline	vehicle	2	4	8
PCV%	44±15	44±3	37±10[by]	35±3[cy]	35±3[by]
Hb g%	15.4±0.8	15.3±1.1	12.7±3.8[by]	12.2±1.1[cy]	12.1±1.1[cy]
RBC mil/cm	8.27±0.36	8.24±0.49	6.99±1.96[by]	6.99±0.53[by]	7.06±0.30[ax]
Females					
PCV%	42±3	38±6[a]	38±3[a]	38±3[a]	31±4[cy]
Hb g%	14.8±0.9	13.2±2.2[a]	13.3±1.1[a]	13.0±1.4	10.3±1.3[cz]
RBC mil/cm	7.74±0.48	7.00±1.17[a]	7.01±0.48[a]	6.99±0.64[a]	5.92±0.80[cy]

Significant when compared with saline control: a=p<0.05, b=p<0.01, c= p<0.001
Significant when compared with vehicle control: x=p<0.05, y=p<0.01, z=p<0.001

In males, dose-related increases were seen in AP, ALT and AST. Significant increases were also seen in GGT. A dose-related decrease in total cholesterol was also apparent. Total protein was also significantly decreased as was albumin and the A/G ratio. Potassium was significantly increased at the HD: saline 3.6±0.2 mmol/l; vehicle 3.9±0.4; LD 3.7±0.2; MD 3.9±0.7; HD 4.2±1.0 (p<0.05).

The results in females were very similar to the males. Only the tables of male results will be shown.

Blood chemistry - group mean values after 3 weeks of treatment

Group	:	1	2	3	4	5
Compound	:	Saline Control	Placebo Control	--- SR 33589B ---		
Dosage (mg/kg/day)	:	0	0	2	4	8

Group / sex	AP iu/l	ALT iu/l	AST iu/l	GGT iu/l	Urea mg%	Creat-inine mg%	Glu-cose mg%	Total Bili-rubin mg%	Trig-lyce-rides mg%	Total Chole-sterol mg%
1M	145	44	105	1	31	0.6	87	0.1	55	65
SD	22	10	16	1	4	0.0	8	0.0	12	12
2M	167	42	106	1	30	0.6	88	0.1	53	69
SD	115	7	18	1	7	0.1	13	0.1	20	14
3M	148	89	267	2^{x}	39	0.6	93	0.2^{b}	46	54^{x}
SD	55	146	407	2	20	0.1	12	0.1	16	18
4M	166	139	310	2^{x}	33	0.6^{x}	92	0.2^{b}	49	47^{ay}
SD	31	171	348	1	8	0.1	12	0.0	13	17
5M	176	197^{ax}	480^{ax}	2^{x}	37	0.6	77^{x}	0.2^{cx}	51	46^{by}
SD	37	201	427	1	6	0.1	14	0.1	9	14

SD Standard deviation.
Significant when compared with Group 1: a - p<0.05; b - p<0.01; c - p<0.001.
Significant when compared with Group 2: x - p<0.05; y - p<0.01.

Urinalysis: No trends were obvious in the data presented.

Organ Weight

The same organs affected after oral administration were also affected after intravenous administration.

Summary of organ weight changes

		males			females		
		2mg/kg	4mg/kg	8mg/kg	2mg/kg	4mg/kg	8mg/kg
Brain	Absolute	↑	↑	↑			
Adrenals	Absolute	↑	↑	↑			↑
	normalized	↑	↑	↑			↑
Heart	Absolute		↑	↑			
	normalized				↓	↓	↓
Kidneys	Absolute	↑	↑	↑	↑	↑	↑
	normalized	↑	↑	↑	↑	↑	↑
Liver	Absolute			↑			↑
	normalized			↑			↑
Lungs	Absolute						
	normalized			↑	↓	↓	
Ovaries:	absolute						↑
Uterus+cervix:	absolute						↑
	Normalized						↓
Prostate	absolute	↑	↑	↑			
	normalized	↑	↑	↑			
Seminal	absolute		↓	↓			

Vesicles normalized		↓	↓			
Spleen absolute	↑	↑	↑		↑	↑
normalized	↑	↑	↑		↑	↑

Gross and Histologic Findings

Under macroscopic observations the following items were found for males:

Summary of macroscopic findings

	males				
	sal	veh	LD	MD	HD
Testes appear small	0	0	0	0	1/8
Liver masses	0	0	0	4/8	4/8
Infusion site masses	0/10	2/10	4/10	9/10	9/10
Spleen swollen	1	0	0	4/10	5/10

Under macroscopic observations the following items were found for females:

	females				
	sal	veh	LD	MD	HD
Ovaries markedly enlarged	0	0	0	0	1/8
Liver masses	0	0	0	1/8	4/8
Infusion site masses	1/10	6/10	8/10	8/10	9/10
Spleen swollen	1	1	0	4/10	4/10

Alveolar macrophage accumulations were reported in the lungs of 2 HD males and 1 LD female.
Testicular degeneration (germinal epithelium): 1LD

Histologic findings in the liver

	males					females				
	Sal	veh	LD	MD	HD	Sal	veh	LD	MD	HD
Periacinar necrosis+fibrosis	0	0	0	0	4^{ax}	0	0	0	1	5^{by}
Focal necrosis	0	0	0	0	3	1	1	1	0	0
Necrosis of individual hepatocytes	0	0	0	0	2	0	0	0	0	2

Significant when compared with saline control: a= $p<0.05$, b=$p<0.01$
Significant when compared with vehicle control: x=$p<0.05$, y=$p<0.01$

Discrepancies between text incidences and table incidences were evident.

4-Week intravenous infusion toxicity study in the rat: toxicokinetic data. Complement to the report RS0006950316/01. TSA0963

This report contained the TK data mentioned in the previous study report. Blood samplings were collected day29 immediately before infusion, immediately after infusion, 2 and 5 hours after infusion from 2 rats/sex/sampling time in the treated groups. SR33589 and SR35021 in the plasma were analyzed by HPLC with UV detection.

SR35021 was not detected in either sex. The levels of SR33589 found in the LD group of both sexes was at or below the limit of quantitation and at the final timepoint below the limit of detection. High background levels were reported for the MD and HD groups of both sexes. This is summarized in the reviewer's table below.

Limit of quantitation: 0.020 mg/l
Limit of detection: 0.010 mg/l

Summary of mg/ml SR33589

Relative sampling time (hrs)	males		Females	
	MD	HD	MD	HD
0	0.0455	0.1460	0.0240	0.1275
1.34-1.43	0.0385	0.1690	0.0765	0.0915
3.06-3.13	0.0265	0.1925	0.0325	0.0770

The plasma profiles did not allow assessment of pharmacokinetic parameters.

Study title: Two-week oral toxicity study in the dog

Key study findings: There were indications of alterations in renal (increases in serum creatinine, changes in sodium and potassium excretion, changes in urinary pH) and hepatic function (slight increase in AST, ALT ≥60 mg/kg and histologic findings of inflammatory cell infiltrates in bile ducts). A NOAEL for the renal changes was not identified with serum creatinine increased in both sexes ≥25 mg/kg. Both sexes also showed dose-related decreases in sodium excretion. First degree heart block was seen (≥25 mg/kg) and attributed to the drug as was an increase in QT and QTc (≥60 mg/kg). Prolongation of the PR interval was seen in both sexes (≥25 mg/kg) but was more consistent in the males. Both absolute and normalized prostate weight of all drug-treated males was increased over the control values. Interestingly, the same was true of the uterine weights of the female drug-treated dogs. Ovarian weight was increased in the MD

and HD groups. Due to the seasonally monoestrus cycles of female dogs one would not expect to see any particular pattern in the reproductive tract. Signs of vomiting, diarrhea and ptyalism were seen ≥60 mg/kg. Findings of darkened liver, inflammation of the biliary tract and greenish colic or rectal contents suggest that the GI tract as well as the heart, reproductive tract, liver and kidneys is also a target for drug-associated toxicity.

Study no.: TSA0883

Conducting laboratory and location: Sanofi Recherche, Montpellier Cedex, France
Date of study initiation: March 31, 1993
GLP compliance: statement included
QA report: yes (x) no ( )
Drug, lot #, and % purity: SR33589B, batch 92.01
Given orally in gelatin capsules. Empty capsule used as control.

Methods Beagles, 3/sex/dose approximately 1 yr old, were given daily oral doses of 0, 25, 60 or 140 mg/kg for 15-16 days.
Clinical signs: 2x/day
ECG: days -7 and 10, 2-4 hours after dosing. Leads I, II and III, aVR, aVL, aVF (Bazett's)
Ophthalmoscopy: days -2 and 8
Body weight: pre tx and then weekly
Food intake: daily
Hematology, clinical chemistry: days -9 and 14 from fasting animals
Urinalysis: on overnight samples days -5 and 10, collection method not disclosed
TK: blood collected from all animals day 15 at 1,2,4,8 and 24 hours after dosing
Necropsy: gross observations, organ weights, tissues collected for light microscopy

Statistical analysis: p values included in the tables are associated with the following statistical significance:

*significant difference with 1.0%<p≤5.0%
**significant difference with 0.1%<p≤1.0%
***significant difference with p≤0.1%

Results

No unscheduled mortality was reported.

Clinical signs: reported for ≥60mg/kg/day were vomiting, ptyalism, diarrhea. All described as dose related and related to drug treatment. Vomiting was seen primarily in the first 3 days. Ptyalism was noted from day 4 onwards

ECG The sponsor came to the conclusion that increased QT and AV block were drug-related. This finding may be expected from the pharmacology.
1st degree AV block:

LD: 1m, 1 f
MD: 1m, 1f
HD: 2m, 2f

Increased QT
LD: 1m, 1f
MD: 1m, 2f
HD: 2m, 3f

Heart rate decreased in males but not in a totally consistent or dose-related pattern. PR interval was increased, QTc was increased and T amplitude was increased.

Summary of ECG effects: Males

	Dose mg/kg			
	0	25	60	140
P (0.01s)	4.5±0.20	4.3±0.87	5.0±0.53	5.3±0.24
PR (0.01s)	9.3±1.17	12.5±2.02	12.0±1.16	14.7±1.50
QT(0.01s)	18.8±0.09	23.3±1.15	22.2±0.63*	23.8±1.08*
T amplitude mv	0.166±0.1449	0.135±0.0675	0.466±0.0983	0.241±0.0015
QTc	8.44±0.31	8.11±0.62	9.22±0.27	9.52±0.42

PR interval was increased in a non-dose-related pattern as was T amplitude. QT and QTc were increased also.

Summary of ECG effects: Females

P (0.01s)	4.9±0.39	5.4±0.07	5.0±0.36	5.8±0.12
PR (0.01s)	11.8±0.47	13.5±1.85	12.1±0.50	15.0±0.65
QRS (0.01s)	4.8±0.73	6.2±0.54	5.2±0.41	7.0±0.52
QT(0.01s)	20.4±0.30	21.2±1.10	21.6±1.00	26.4±2.16
T amplitude mv	0.192±0.1058	0.211±0.0491	0.200±0.0333	0.208±0.350
QTc	8.34±0.805	8.77±0.593	9.32±0.241	9.54±0.335

Ophthalmoscopy: 1 HD male showed visible anterior suture lines on the lens and a "slight micropapilla in the tapetal fundus" of both eyes.

Body Weight and Food Intake
All animals seemed to lose some weight during the study with a dose related trend apparent.

Control males lost 4% of baseline while MD males lost 9% and HD males lost 15%.
Control females lost 3% of baseline while LD lost 6%, MD lost 11%, and HD lost 16%.

Food intake also decreased in a dose-related manner.

Hematology and Clinical Chemistry

No consistent trends were apparent in the hematology.

Increased ALT, AST was seen in treated males as well as a decrease in K (HD only). Serum K was decreased in HD females also. Creatinine was increased in both sexes.

Summary of clinical chemistry effects: Males

	Dose mg/kg			
	0	25	60	140
Creatinine mcM	69.7±2.91	72.0±3.51	83.0±3.21	77.0±4.04
Tbili mcM	1.9±0.17	1.7±0.06	1.5±0.43	3.7±1.15
ALT IU/l	20±0.6	42±9.4	68±17.8	56±12.9
AST IU/l	19±1.9	18±2.2	35±15.3	43±22.2
Potassium mM	4.33±0.186			3.87±0.260
P mM	1.37±0.06	1.29±0.094	1.19±0.107	1.13±0.179

Summary of clinical chemistry effects: Females

Dose mg/kg	0	25	60	140
Creatinine mcM	67.7±1.33	68.3±3.71	80.0±5.69	74.00±3.00
Tbili mcM	2.4±0.049	2.0±0.17	2.4±0.09	3.0±0.41
ALT IU/l	31±2.0	25±2.6	62±14.0	36±3.5
AST IU/l	23±6.9	19±5.3	27±5.2	26±6.7
ALP IU/l	167±23.3	126±25.8	68±13.0*	58±0.6**
P mM	1.17±0.026	1.27±0.091	1.21±0.064	1.04±0.027

Urinalysis

Decreased urine pH was seen in both sexes. An apparently dose-related decrease in sodium excretion was seen in both sexes with changes in the ratio of excreted sodium to potassium. The changes persisted when corrected for total volume excretion. In both sexes there were dose-related decreases in creatinine and potassium excretion.

Summary of urinalysis results

Males				
	Dose mg/kg			
	0	25	60	140
pH	6.7±0.17	6.2±0.17	6.0±0.00*	5.3±0.33*
Na mM	136±29.8	108±45.0	40±16.5	32±12.8
Females				
pH	7.2±0.17	6.0±0.29*	5.7±0.17*	5.7±0.44*
Na mM	173±53.1	167±17.3	58±19.2	21±9.7*

*p<2.4%

Organ weight effects

Male organ weight summary

	0	25mg/kg	60mg/kg	140 mg/kg
Liver (absolute + normalized)		↓	↓	↓
Spleen (absolute + normalized)		↓	↑	↑
Heart (absolute and normalized)		↑	↑	↑
Lungs		↓	↓	↓
Prostate absolute	5.34±1.103	8.79±0.98	8.33±0.52	8.26±1.38
Prostate normalized	0.45±0.056	0.72±0.071	0.79±0.062	0.71±0.124

Female organ weight summary

	25mg/kg	60mg/kg	140 mg/kg
spleen (absolute + normalized)	↓	↓	↑
Adrenals (absolute + normalized)	↑	↑	↑
Thymus (absolute + normalized)	↓	↓	↓
Lungs (absolute + normalized)	↓	↓	↓
Pituitary (absolute + normalized)	↑	↓	↓

Data from the female reproductive tract were striking and are shown below. There was no explanation apparent for the increased uterine and ovarian weights.

Summary of female reproductive organ data

Dose group (mg/kg)	Uterus		Ovaries	
	Absolute wght (g)	Normalized wght (g/kg)	Absolute weight (mg)	Normalized wght (mg/kg)
0	4.653±1.7342	0.437±0.1285	1046±144.3	102±8.4
25	5.433±0.9309	0.572±0.0994	1023±154.9	108±16.1
60	15.011±2.592	1.375±0.1402	1746±221.6*	161±9.6*
140	17.019±4.5153*	1.876±0.5504	1486±85.4	161±7.9*

*p<1.6%

Histopathology Findings

Summary of female findings

	0	25mg/kg	60mg/kg	140mg/kg
Mammary hyperplasia	2	2	3	3
Mammary interstitial edema	0	0	3	1
Cystic corpus luteum	0	0	1	1

Summary of findings from both sexes

	0		LD		MD		HD	
	m	f	m	f	m	f	m	f
Chronic inflammatory cell infiltrate of several biliary ducts	0	0	0	0	1	2	1	1
Single necrotic focus (liver)	0	0	0	0	0	1	0	0
Mesenteric lymph nodes: foamy	0	0	0	0	0	0	3	1
Mesenteric lymph nodes+Sudan black inclusions	3	0	2	2	2	2	3	3
EM: lamellar inclusions in hepatocytes	0/6		0/6		3/6		0/6	
EM: myelin-like inclusions in hepatocytes	0		0		0		4/6	

Study title: 3-month oral toxicity study in the dog

Key study findings: Target organs of toxicity were demonstrated to be the digestive tract, heart and thyroid. Heart rate was decreased only in HD males. PR interval showed a dose-related increase in males but was increased only in HDf. T amplitude showed an increase in all drug-treated groups. First degree AV block was seen in 2 males and several times in 1 female. QTc was increased day 93 (≥17.5 mg/kg) in both sexes. There was also a slight prolongation of thrombin time in both sexes (≥5 mg/kg) and liver transaminases (females, 60 mg/kg). Mild decreases in cholesterol levels (HDm only; females: dose-related) possibly indicate some kind of liver involvement. T3 values showed dose-related decreases in both sexes. T4 showed non-dose-related decreases in both sexes.
Urinalysis showed decreased creatinine excretion(males ≥17.5 mg/kg; females: ≥5 mg/kg). Sodium and potassium excretion were decreased in males (≥5 mg/kg). Potassium excretion was decreased in females ≥17.5 mg/kg.

Lung weight showed an increase (50%) in females only. Uterine weight was inconsistently increased in all drug-treated groups. Testes weight was increased in all drug-treated groups.

Study no.: TXC0886

Conducting laboratory and location: Sanofi Recherche, Montpellier Cedex, France
Date of study initiation: June 24, 1993
GLP compliance: statement included
QA report: yes ( ) no ( )
Drug, lot #, and % purity: SR33589B batch 92.01
Administered in gelatin capsule. Empty capsule used as vehicle

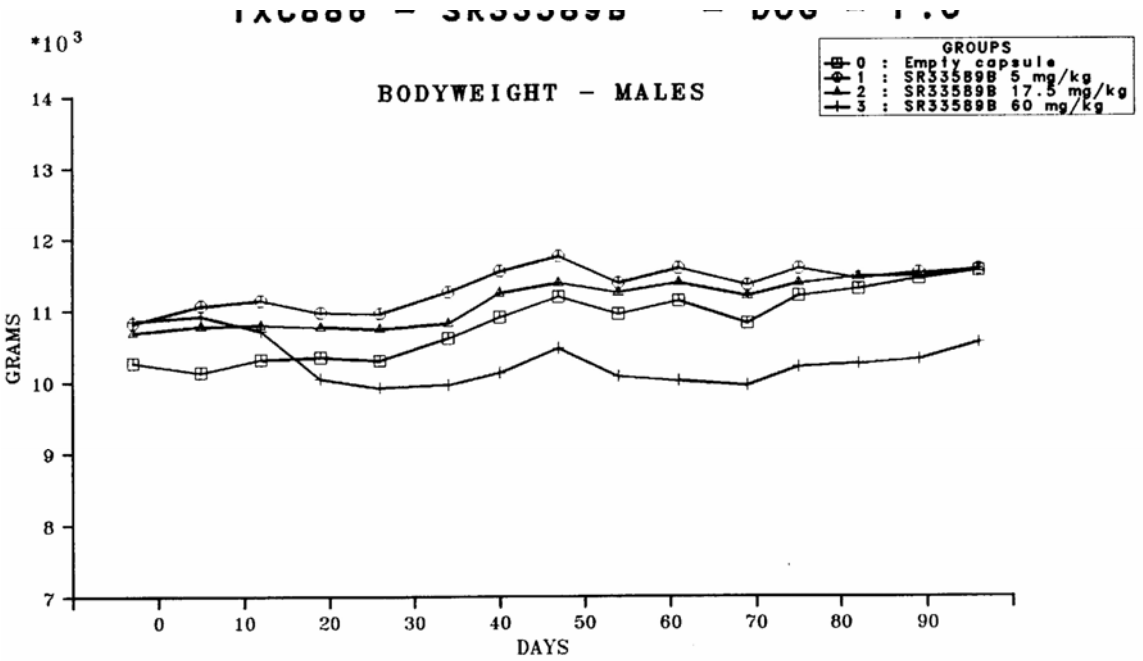
Methods Beagles approximately 1 year old (4/sex/dose) were given doses of 0, 5, 17.5 and 60 mg/kg/day for 97-99 days.
Clinical signs: 2x/day
ECG: days -2, 29, 93 from 2-4 hours after dosing. Leads I, II, III and aVR, aVL, aVF
Ophthalmoscopy: days -2, 85
Body weight: weekly
Food consumption: daily measurement.
Hematology and clinical chemistry: days -7, 30 and 85; day 89 for coagulation
Lymphocyte subpopulations: day 85
Hormone: T4, T3 day 89
Urinalysis: days -2 and 84, overnight samples collected by unknown method
TK: taken days 35 and 97 pre-dose and 1,2,4 and 6 hours after dosing.

Statistical analysis: p values included in the tables are associated with the following statistical significance:

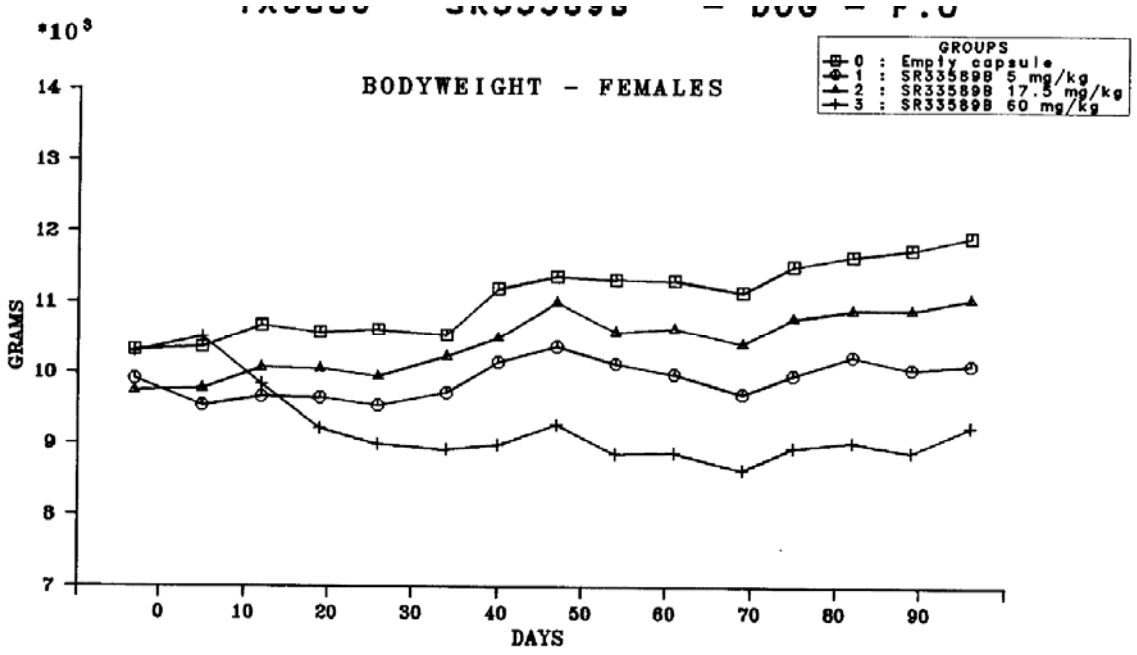
*significant difference with 1.0%<p≤5.0%
**significant difference with 0.1%<p≤1.0%
***significant difference with p≤0.1%

Results
No unscheduled mortality was reported.
Consistent with the 2 week study, reported signs were ptyalism, diarrhea and vomiting. No histologic correlates were reported. Frequency of observations increased with increasing dose.

The HD males showed a decrease in body weight. Food intake was also decreased in this group.



HD females lost weight over the study. The other treated females showed decreased gain. Food consumption was consistently affected only in the HD group.



ECG:
There were inconsistent heart rate effects between males and females.

P duration was increased in females. PR interval was increased in both sexes and in some cases was reported to lead to first degree AV block (2 males on day 29 and 1 female on 2 separate days). QT interval was significantly increased in both sexes. QTc, calculated by Bazett's formula did not show statistically significant differences. RR interval was increased with treatment in both sexes also. T wave amplitude was increased in both sexes.

Summary of ECG effects

Parameter	Dose mg/kg			
	0	5	17.5	60
Males				
HR bpm day 29	111.6±8.9	114.5±11.8	100.0±9.3	95.3±6.8
Day 93	104.9±9.6	102.0±9.3	101.3±8.0	86.4±18.8
PR(0.01s) day 29	9.1±0.9	9.5±0.3	9.3±0.3	13.8±0.4**
Day 93	8.9±0.8	9.5±0.4	9.9±0.7	11.9±0.8
T amplitude mV day 29	0.066±0.05	0.093±0.09	0.228±0.03	0.271±0.08
Day 93	-0.013±0.09	0.141±0.16	0.173±0.04	0.302±0.08
Females				
P (0.01s) Day 93	4.7±0.37	4.8±0.52	4.0±0.13	6.2±0.4*
PR (0.01s) day 29	10.5±0.55	10.4±0.74	9.1±0.69	11.8±0.79
Day 93	10.8±0.66	10.2±0.92	9.5±0.51	12.7±1.22
T amplitude mV day 29	0.090±0.09	0.334±0.09	0.179±0.05	0.183±0.13
Day 93	0.040±0.15	0.140±0.11	0.203±0.07	0.430±0.15

*<4.1%

Summary of QTc effects

Parameter	Dose mg/kg			
	0	5	17.5	60
Males				
QTc day 29	9.04±0.34	8.93±0.27	8.45±0.34	8.71±0.41
Day 93	7.18±0.29	7.55±0.27	8.12±0.31	8.22±0.90
Females				
QTc day 29	7.62±0.39	8.26±0.34	8.76±0.05	8.60±0.37
Day93	7.22±0.23	8.05±0.28	8.39±0.38	8.60±0.38

Hematology and Clinical Chemistry

There were no findings of biological significance in the data as presented. A very unusual finding was the marked increase in basophils seen in the HD males on day 30(27% vs 0% in all other groups). This finding was not repeated on day 85.

There was a slight increase in thrombin time in drug-treated males and females on day 89.

Thrombin time Day 89

	Dose mg/kg			
	0	5	17.5	60
Males Thrombin time (s)	15.7±0.15	20.0±0.65**	20.3±0.08**	19.5±1.06**
Females Thrombin time (s)	16.1±0.68	18.7±0.73*	18.7±0.53*	19.0±0.53*

*p<0.3.4%, **p<0.8%

In both sexes there was a slight shift to greater numbers (%) of T cells and decreased B cell counts. The absolute counts did not change.

There was a slight decrease in total cholesterol in the HD males at 30 and 85 days. The females showed a dose-related decrease in total cholesterol even before dosing started. Likewise phospholipids also showed a decrease in females. HD females showed an increase in ALT at 30 days and 85 . Both sexes showed a decrease in T3 at the HD. T4 was also decreased in HD females (T3/T4 ratio also decreased in this group).

Summary of Clinical Chemistry Findings: Males

	Dose mg/kg			
	0	5	17.5	60
Cholesterol (mg/dl) day 30 day 85	 3.05±0.278 3.10±0.300			 2.86±0.055 2.56±0.127
T3 nM day 89	1.48±0.151	1.21±0.011	1.36±0.084	0.93±0.077**
T4 nM day 89	36.84±3.569	26.64±1.303*	32.11±1.730	27.44±2.609

Summary of Clinical Chemistry Findings: Females

	Dose mg/kg			
	0	5	17.5	60
Cholesterol (mg/dl) Day -7 Day 30 Day 85	 4.45±0.318 4.55±0.327 5.03±0.679	 3.83±0.300 4.23±0.256 3.79±0.251	 3.66±0.400 4.15±0.871 3.60±0.385	 3.54±0.456 3.17±0.307 2.85±0.375
Phospholipids (mM)	5.59±0.42	4.54±0.226	4.33±0.383	3.46±0.465**
ALT (IU/l) day 30 Day 85	24±4.2 22±2.8			33±1.5* 80±51.0
AST (IU/l) day 85	18±3.4			41±19.2
T3 nM day 89	1.60±0.105	1.44±0.192	1.27±0.246	0.64±0.097**
T4 nM day 89	43.18±4.103	37.69±5.273	40.27±4.242	24.47±1.942*

The concentration of creatinine excreted decreased in both sexes. The ratio of sodium to potassium excretion increased in females. The volume of excreted urine showed a decrease in males and an increase in females.

Urinalysis results

Males				
	Dose mg/kg			
	0	5	17.5	60
Creatinine mM day 84	18.7±0.81	18.5±0.67	13.2±1.95*	14.7±1.60
Excreted urine volume ml	137.5±10.31	130.0±17.32	150.0±37.64	96.7±33.33
Sodium µM	31060±4771	29400±2403	25513±1573	23193±8786
Potassium µM	31959±2818	31584±3600	19965±2697	22880±8020
Females				
Creatinine mM day 84	15.7±1.82	11.9±0.46	10.0±1.53	14.8±1.87
Na/K urine concentration	0.95±0.063	1.02±0.171	1.18±0.141	1.32±0.138
Excreted urine volume ml	112.5±13.15	136.7±21.86	190.0±20.82*	140.0±5.77
Potassium µM	30429±2985	33626±6776	24729±6858	21771±6615

Organ weights

Normalized heart weight was slightly increased in the HD groups of both sexes. Normalized testes and prostate weight showed a dose-related increase. A U-shaped effect was seen in the normalized uterine weights.

Organ Weight Summary

Females				
	Dose mg/kg			
	0	5	17.5	60
Uterus g	4.172±0.7004	4.651±0.3927	9.621±4.0399	3.568±0.5642
Uterus g/kg	0.359±0.0413	0.493±0.0540	0.880±0.3553	0.407±0.0661
Lungs g/kg	6.72±0.398			9.06±1.032
Heart g/kg	7.57±0.452			10.76±0.388***
Males				
Testes g/kg	1.387±0.1337	1.466±0.1157	1.529±0.2611	1.535±0.1570

The sponsor provided the following summary of histopathology findings. The reviewer adds no others from the data provided.

Summary of histopathology findings

	0		5		17.5		60	
	m	f	m	f	m	f	m	f
Thymic involution	4	4	4	4	4	4	4	4
Pancreatic serous dedifferentiation							4	3
Decreased subcutaneous adipose tissue								2
Atrophic changes								1

The thymic involution was perceived as most likely physiologic with the exception of the HD group where there was an "increase in the intensity of this change…and its association with other modification might indicate a slight treatment-related stress."

Plasma levels of both compounds were below the limits of detection at the lowest dose. At the MD and HD, the plasma levels of parent compound exceeded those of SR35021.

AUC_{0-24} SR33589 (mg.hr/l)

Dose mg/kg/day	Day 35			Day 97		
	5	17.5	60	5	17.5	60
M	-	2.34	47.7	-	2.57	35.35
F	-	2.59	52.71	-	3.73	44.15
AUC_{0-24} SR35021 (mg.hr/l)						
M	-	0.191	2.991	-	0.408	2.461
F	-	0.347	4.694	-	0.376	3.240

Study title: One-year oral toxicity study in the dog

Key study findings: There were no findings in this study that raised new safety issues . In fact, some of the clinical chemistry changes seen in shorter duration studies were minimal to non-existent here. HR was slightly decreased in the HD groups of both sexes first noted at 93 days and persisting to the end of the study. QTc was increased in males ≥5 mg/kg and females ≥45 mg/kg. Non-significant increases in PR were seen in both sexes, less consistently in the females. Heart weight was increased in the HD animals of both sexes. The sponsor felt that the ECG changes might be related to the change in heart weight, but this is unclear to me as the ECG effects were similar to those of studies with no recorded change in heart weight. Serum and urinary electrolyte changes were still apparent. There were few findings of histological significance.
Changes in thyroid function were manifested by decreased T3 levels (45 mg/kg from 3 months of treatment; ≥15 mg/kg in males at 6 and 12 months; ≥5 mg/kg in females at 12 months). No trend was discernible in the lymphocyte subpopulations. In the lymphoblastic transformation studies, there were decreases in cpm primarily at MD and HD with corresponding decreases in standard error of the mean.

Con A
Females: Day 184: HD caused ~50% decrease in cpm with ~50% decrease in the SEM
Day 359: decrease at HD in 1 mitogen concentration
Males: day 184 no consistent effect
Day 359 decrease in cpm and SEM at MD and HD

PHA
Females: day 184 HD caused decrease in cpm and sem
Day 359 inconsistent decreases across the drug-treated groups

Males: day 184 decrease at MD and HD in cpm and sem
Day 359 decrease at MD and HD
PWM
Females: day 184 decreased at HD
Day 359 decrease at HD
Males :day 184 decreases at MD and HD but not dose-dependent. SEM decreased about 75% from the vehicle values.
Day 359 : decreases at MD and HD

Study no.: TXC0970

Conducting laboratory and location: Sanofi Recherche, Montpellier Cedex, France
Date of study initiation: October 19, 1995
GLP compliance: statement included
QA report: yes (x) no ( )
Drug, lot #, and % purity: SR33589B, batch 5SNP 505 Identity of molecule in capsule checked monthly during study.
Administered in gelatin capsules. Vehicle control was an empty capsule

Methods:
Beagles, approximately 1 year old at the start of the study, 5/sex/group, were given doses of 0, 5, 15, 45 mg/kg/day for 368 to 372 days.
Clinical signs: 2x/day
ECG days -3, 93, 187 and 364 before dosing . Leads I, II, III and aVR, aVL, aVF
Body weight: pre-tx then weekly
Hematology and clinical chemistry: samples collected days -7, 90, 181, 365
Lymphocyte subpopulations: blood collected days -7, 181, 365
IgG, IgM, hormones: performed on frozen samples collected on same days as for clinical chemistry and hematology
Lymphoblast transformation test: days -10, 184, 359 (concanavalin A (conA), phytohemagglutinin (PHA) and pokeweed mitogen (PWM). Cell proliferation measured after 4 days of incubation by measuring ^{3}H-thymidine incorporation.
Urinalysis: days -1, 86, 177, 363 on overnight urine samples, collection method unspecified
Toxicokinetics: samples collected days 30, 188, 366 pre-dose, 1,2,4 and 6 hours after treatment
Necropsy: euthanized days 369-373. gross observations made, organ weights, light microscopy
Statistical results: *1.0%<p≤5.0%; **0.1%<p≤1.0%; ***p≤0.1%

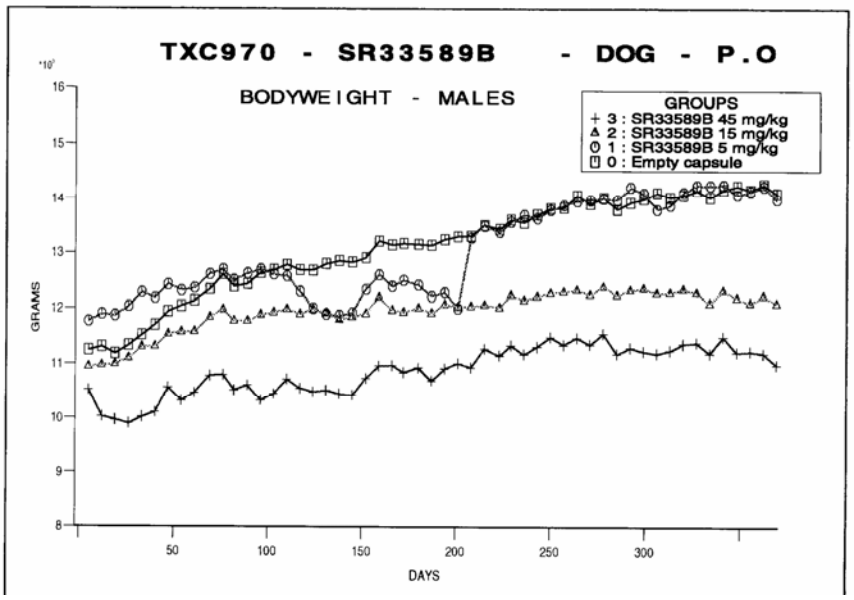
Results
Signs
Ptyalism 1/3 HD females
Vomiting: both sexes, ≥5 mg

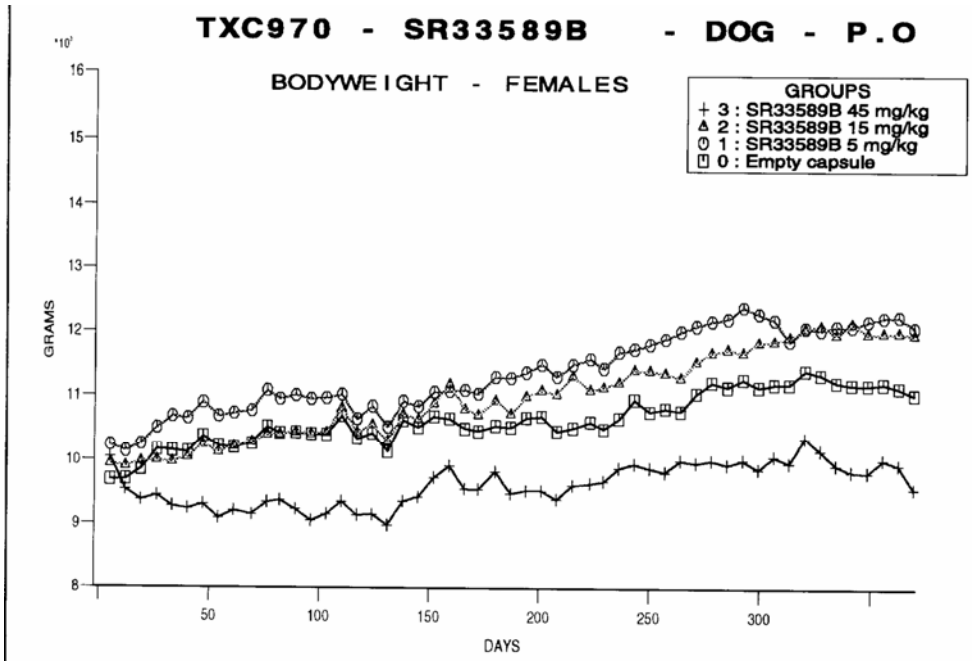
One male from the LD group was euthanized prematurely (day 202) due to declining condition referable to a bacterial enteric infection.

Ophthalmoscopy: no findings were reported

Body Weight

MD and HD males and females gained less than did the controls and LD animals.





There were no apparent effects on food intake.

ECG: There was a slight decrease in HR in the HD groups of both sexes that persisted from 93 days (earliest determination) to the end of the study. There was a great deal of variability in the T wave amplitude data making it difficult to discern any effects. QT and QTc prolongation (Bazett's formula) was seen in both sexes. The data from just day 364 is given as an example. PR prolongation (NS) was also seen in both sexes.

Males				
	Dose mg/kg			
	0	5	15	45
QT (0.01s) Day 364	18.6±0.49	18.8±0.93	19.3±1.17	23.2±0.36**
QTc Day 364	7.71±0.247	7.77±0.281	8.07±0.359	8.67±0.147**
Females				
QT (0.01s) Day 364	19.8±0.20	19.0±0.98	19.3±0.72	25.0±0.98**
QTc Day 364	8.20±0.197	7.74±0.175	7.88±0.291	8.96±0.252

Hematology and Clinical Chemistry

No consistent results in the hematology data as presented. The lymphocyte colony data did not show consistent trends. The lymphoblastic transformation tests also showed a great deal of variability. There may have been a decrease in transformation with increased concentration.

The clinical chemistry data did not indicate any signals not already seen in other studies. Many findings were also minimal and of questionable, if any, significance. Urea in HD males was increased at days 90 and 181 and within the range of the other groups by day 365. Urea was significantly increased in HD females day 365. Total cholesterol was reduced non-significantly in HD females only, at day 365. Phospholipids were decreased at this point also (NS). Total bilirubin was increased in all treated females on day 365 as shown on the next page. However, there is no corroborative data in the hematology so the meaning is unclear. Creatinine which in previous studies has shown relatively consistent increases in this study showed only minor increases in HDm (day 365) and moderate increases in HDf at the same time point.

Blood biochemistry : Total bilirubin (mcM) (Cont'd)

FEMALE	-7	90	181	365
Levene	>10% NS	>10% NS	>10% NS	0.3% **
1-ANOVA	>10% NS	>10% NS	>10% NS	---
Group 0 : EMPTY CAPSULE				
n = 5				
mean	2.2	1.6	2.0	1.9
SEM	0.19	0.08	0.07	0.14
Group 1 : SR 33589B 5 mg/kg				
n = 5				
mean	2.5	1.9	2.2	2.6
SEM	0.29	0.15	0.19	0.42
Test/group 0				>10% NS
Group 2 : SR 33589B 15 mg/kg				
n = 5				
mean	2.4	1.4	2.0	2.3
SEM	0.30	0.13	0.20	0.18
Test/group 0				>10% NS
Group 3 : SR 33589B 45 mg/kg				
n = 5				
mean	2.4	1.7	1.7	2.7
SEM	0.24	0.24	0.20	0.21
Test/group 0				1.0% **

Serum sodium showed consistent decreases in both sexes on days 181 and 365 at MD and HD. Day 365 values are shown below by way of example. Serum potassium was decreased in the drug-treated females. Inorganic phosphate showed variability but appeared to be decreased in the HD females. Blood urea was increased in the HD group of both sexes from day 90 to the end of the study. The LD and MD groups of males showed increased urea day 365. In females, ALT was mildly increased in the HD group at all three determination times but probably of no biological significance. IgG and IgM concentrations showed variability also. No consistent patterns were discernible. T3 showed consistent decreases in males and slightly less consistent decreases in females. The ratio of T3/T4 was more consistently affected (decreased) in the female dogs than the males.

Summary of Clinical Chemistry Effects (Mean ±SEM)

Males				
	Dose mg/kg			
	0	5	15	45
Sodium mM day 365	146±0.32	144.8±0.48	141.4±0.68***	141.6±1.08*
K mM day 365	4.32±0.092	4.28±0.075	4.12±0.066	4.04±0.087
IgG mg/l day 181	4140±90	3955±112	4018±126	8100±653**
IgG mg/l day 365	11822±2994	10418±3014	8298±2470	5612±322
IgM mg/l day 181	1165±156	805±117	840±80	884±119
T3 nM day 365	1.34±0.062	1.35±0.070	1.02±0.075	0.72±0.055***
Females				
Triglycerides mM day 365	0.40±0.062	0.51±0.065	0.38±0.03	0.23±0.022
Choles mM Day 365	3.41±0.413	3.57±0.464	3.97±0.544	2.52±0.125
Sodium mM Day 365	145.0±0.32	143.4±0.75	142.8±0.86	142.8±0.37
K mM day 365	4.16±0.087	4.12±0.124	4.06±0.147	3.76±0.081
IgG mg/l day 181	4342±184	4112±85	4744±666	6392±1614
IgG mg/l day 365	5726±993	6100±1073	5400±1678	4344±245
IgM mg/l day 181	1303±258	885±117	1090±246	1119±260
T3 nM day 365	1.32±0.057	1.12±0.139	1.11±0.086	0.74±0.028***

* 1.0%<p≤5.0%; **0.1%<p≤1.0%; ***p≤0.1%

No apparent effects on the lymphocyte subpopulation percents were noted on either day 181 or day 365. There was a slight decrease in the absolute amount of lymphocytes day 181 in the HD groups. This change was not apparent day 365 and may have been normal variation. It was apparent that the variability inherent in the lymphoblastic transformation analysis may generate data in samples from pre-treatment animals that simulate a dose-response. It is difficult to say that there is any specific drug effect. However, the data generated with PHA and PWM suggests a decrease in transformation day 359 in males. Of note is the decrease in the variance of the drug-treated samples.

Lymphoblastic transformation test: PHA (cpm) day 359 in males

Dose group mg/kg	Without mitogen	Conc. 1	Conc. 2	Conc. 3
Empty capsule	274±54	12834±3308	14479±4869	15634±6456
5	266±16	12077±2375	14071±2897	15614±3172
15	197±13	7793±1700	10161±2810	9963±2887
45	296±44	8001±1936	9340±2289	9858±3397
PWM: day 184				
Empty capsule	239±36	6322±2093	6985±2065	9670±2600
5	217±32	7541±1465	7757±1702	10316±2317
15	259±37	5377±680	5258±700	7648±1100
45	294±44	5263±728	5663±614	8109±492
PWM: day 359				
Empty capsule	330±50	6468±2747	6203±2250	9010±3722
5	363±43	7514±1400	9113±2368	11573±2641
15	244±40	4417±990	4891±1122	6904±1331
45	313±22	4294±1247	4686±1099	6638±1312

Lymphoblastic transformation test: PHA (cpm) day 359 in females

Dose group mg/kg	Without mitogen	Conc. 1	Conc. 2	Conc. 3
Empty capsule	385±121	10012±1739	13935±4020	14612±5150
5	213±12	6958±1022	8120±1356	8492±2154
15	300±46	7734±1879	10607±2978	13218±4518
45	268±31	8814±1255	12813±1592	11865±1874
PWM: day 184				
Empty capsule	159±18	4655±1448	5266±1671	7526±2329
45	272±31	3736±463	3781±490	5054±1052
PWM: day 359				
Empty capsule	305±39	6826±2544	7164±2377	9809±3359
45	242±24	5070±945	4815±661	6398±613

In the urinalysis, creatinine excretion was decreased in HD males days 177(42% vs controls) and 363(54% compared to controls, (1.0%<p≤5.0%). Creatinine excretion was decreased in all groups of drug-treated females without a dose-related pattern.

Urine concentration of creatinine Day 363

Females	0	5 mg/kg	15 mg/kg	45 mg/kg
Creatinine mM	16.1±2.41	7.8±1.59	8.1±1.68	10.8±2.91

A clear dose-related pattern was not seen, but urinary sodium and potassium were decreased in the HD males days 86, 177 and 363. Urinary sodium was increased in the HD females days 86 and 177 and slightly decreased day 363. Urinary potassium was slightly decreased in the HD females day 177 and decreased in a non-dose-related manner all the drug-treated groups.

Bacteria in the urine cytology was variable and showed no consistent pattern. The significance if any is unclear as handling and storage may affect these results.

Organ weights

Weight effects were seen in the same organs as identified in other studies.

Summary of organ weight effects

males				
	Dose mg/kg			
	0	5	15	45
Heart g/kg	7.62±0.272	7.57±0.289	8.51±0.640	10.39±0.282 ***
Lungs g/kg	7.05±0.584	6.30±0.486	8.04±0.767	8.11±0.387
Brain g/kg	5.72±0.485	5.91±0.387	6.22±0.359	7.6±0.449*
Thyroid mg/kg	72±12.1	70±3.7	73±5.5	86±8.6
Testes g/kg	1.210±0.186	1.303±0.119	1.492±0.103	1.511±0.100
Females				
Heart g/kg	8.15±0.460	7.05±0.512	7.67±0.529	9.63±0.384
Lungs g/kg	6.99±0.244	6.32±0.370	6.76±0.716	7.20±0.436
Brain g/kg	6.44±0.349	6.35±0.442	6.46 ±0.428	7.69±0.413
Thyroid mg/kg	87±4.7	81±8.2	78±6.0	97±13.3

```
                                  ----------------------------------------
                                  : Gr.  0  : Gr.  1  : Gr.  2  : Gr.  3  :
                                  :  M   F  :  M   F  :  M   F  :  M   F  :
                                  ----------------------------------------
```

Kidneys (cont'd)

```
    Slight congestion
                                  :         :         :         :  31     :
    Very slight to moderate, focal or multifocal chronic inflammatory cell
    infiltration
                                  :      10":         : 23" 29' :  31"    :
                                  :         :         : 24" 28"*:  32'    :
                                  :         :         :         :  33"    :
                                  * fibrosing  " cortical ' medullary
    Few papillary mineralizations
                                  :   1   7 :  12  16 :  21  27 :  32  36 :
                                  :   3   9 :  13  17 :  22  28 :  35  37 :
                                  :   5     :  14s 18 :  23  29 :      38 :
                                  :         :      19 :      30 :      39 :
```

Lungs (cont'd)

```
Slight or moderate, focal, zonal or multizonal emphysema
                              :   2"  6":  11" 17":  21  26":  33" 36":
                              :   3"  7 :  13  18":  22  27":  34" 37":
                              :   4"  8":  15" 19 :  23  29":      38 :
                              :   5   9 :      20":         :      40 :
                              "subpleural
A few areas of atelectasia
                              :         :         :      27 :         :
Foci or infiltration by foamy cells
                              :   2   6 :      18 :  21  26":  32" 36 :
                              :   5   7 :         :         :      38 :
                              :         :         :         :      39 :
                              :         :         :         :      40 :
                              "subpleural
```

	Gr. 0		Gr. 1		Gr. 2		Gr. 3	
	M	F	M	F	M	F	M	F

Female genital tract

```
Pseudocyesis
                              :       8 :      16 :         :      36 :
                              :         :      17 :         :         :
                              :         :      20 :         :         :
```

Prostate

```
Chronic and/or fibrous inflammatory cell area(s) in the prostate
                              :         :  11     :  22     :  31
                              :         :  15     :  24     :  34
                              :         :         :  25     :
```

Toxicokinetics

Increases in AUC exposure to parent drug were greater than proportional all three sampling days. Exposure did not change over the course of the study, suggesting that there was no apparent saturation phenomenon, no induction of metabolism and no accumulation of compound.

Toxicokinetic Summary

Dose Mg/kg/day	Cmax (mg/l)		AUC_{0-24h} (mg.h/l)	
	males	females	males	females
Day 30				
5	0.007±0.007	0.041±0.011	Nc	0.147±0.035
15	0.331±0.019	0.244±0.091	3.140±0.126	2.053±1.350
45	1.465±0.360	2.242±0.458	20.863±4.229	38.026±8.095
Day 188				
5	0.000±0.000	0.000±0.000	Nc	Nc
15	0.202±0.029	0.204±0.158	2.423±0.161	1.696±1.280
45	1.540±0.147	1.653±0.365	21.232±3.515	25.274±5.611
Day 366				
5	0.015±0.008	0.045±0.010	Nc	0.139(nc)
15	0.254±0.025	0.181±0.107	2.687±0.187	2.359±0.811
45	1.437±0.206	1.289±0.272	22.407±3.780	22.007±3.716

Exposure to the major metabolite was determined for the HD group only. There was no apparent difference (no accumulation or induced metabolism) in exposure at the 3 different sampling times.

Summary of Toxicokinetics for SR35021

Sampling day	Cmax (mg/l)		AUC0-24(mg.h/l)	
	males	females	males	females
30	6.086±0.019	0.175±0.034	1.006±0.274	2.549±0.557
188	0.092±0.009	0.161±0.033	1.281±0.186	2.524±0.219
366	0.080(NC)	0.137±0.013	0.896(NC)	2.152±0.009

Study title: Two-week intravenous toxicity study in the dog

Key study findings: Consistent with other studies, first degree AV block was seen in a HD female. QT prolongation was also seen. Control animals did not show any local signs, therefore, the sponsor ascribed poor tolerance to the infusion process rather than the drug. The sponsor reported that there was slight to marked edema and induration. The dose 1mg/kg was associated with moderate intolerance and 2.5 mg/kg was associated with marked intolerance. Local intolerance made it difficult to impossible to administer drug, resulting in an increased number of injection sites. This resulted in 1/3 animals in the HD group being euthanized and 1 MD male receiving only half of the final dose. Venous thrombosis and phlebitis were also reported. Serum electrolytes and excreted electrolytes, primarily sodium, showed some alterations with drug treatment. The primary organ weight changes were in the liver and the reproductive tracts. The sponsor describes the changes in the female reproductive tract as being physiological. However, this is not clear from the data presented.

Study no.: TSA0885
Conducting laboratory and location: Sanofi Recherche, Montpellier Cedex, France
Date of study initiation: May 26, 1993
GLP compliance: statement included
QA report: yes (x) no ( )
Drug, lot #, and % purity: SR33589B, lot 92.01, purity
Formulation: PEG400, acetic acid, sodium acetate buffer
Vehicle: 5% glucose solution
Injection given over 30seconds

Methods Beagles, approximately 1 year old, 3/sex/group were given intravenous doses of 0, 1, 2.5, 6 mg/kg/day once daily for 13 to 19 days. The last treatment day was the day before necropsy.

Clinical signs: 2x/day
ECG: days-7, 13, 2-4 hours after dosing. Leads I, II, III, aVR, aVL, aVF. QTc was calculated by Bazett's formula.

Ophthalmoscopy: days -1, 10
Body weight: pre treatment and weekly
Food intake: daily per animal and group means calculated weekly
Hematology and clinical chemistry: days-9, 14
Urinalysis: performed on overnight samples collected by unspecified means days-1, 10
Toxicokinetics: day 15 collected blood at 3 and 24 hours from:
Low dose: 6 animals
Mid dose: 4 animals
High dose: 3animals
Necropsy: performed from day 16-20. gross observations made, tissues collected for light microscopy, EM samples unclear from chart

Results
P values included in the tables have the following statistical significance:
* $1.0\% < p \leq 5.0\%$
** $0.1\% < p \geq 1.0\%$
*** $p \leq 0.1\%$

The sponsor's summary of observations is reproduced here.

Observations/group-dose mg/kg/day	0(0)	1(1)	2(2.5)	3(6)
# of injection sites	16	25	36	32
# of animals in which injection could not be done	0	0	1(day15, ½ the dose)	1(day 14, euthanized)
# of animals w/lesions	0	3	5	5
# of sites with lesions	0	5	16	15
#of observations/# of days x# of animals				
total	0/114	18/99	87/92	92/96
slight edema	0	16	31	48
marked edema	0	0	0	5
slight induration	0	2	53	35
limb or area(*)	0	0	3	4

* limb or area = increased limb or area (neck, thigh) volume with a firm consistency

Local intolerance to the vehicle was distinguished from a drug effect by the addition of thrombosis in the drug-treated groups.

Sponsor's summary of macroscopic injection site findings

Dose mg/kg/day	0	1	2.5	6
# of animals	6	6	6	6
# of sites sampled	13	27	46	40
Edema: slight			1	
Moderate		1	3	5
Marked				4
Whitish induration in the subcutaneous tissues				
Slight	8	7	7	2
Moderate	1	9	13	10
Marked		2	4	9
Hematoma: small – moderate	3	9	24	19
Large				3

Summary of injection site microscopy (Sponsor's table)

	Dose mg/kg			
	0	1	2.5	6
# of animals	6	6	6	6
# of sites examined	13	27	46	40
Vascular changes				
Principal vein thrombosis	-	9	16	14
Collateral vein thrombosis	-	3	8	6
Phlebitis	-	5	11	16
Perivascular changes				
Infiltration of hemodynamic origin				
Very slight or slight	5	3	11	1
Moderate or marked	2	2	5	13
Very slight to marked inflammatory cell infiltration	6	10	17	13
Hypodermic changes or changes of the fatty tissue adjacent to the vein				
Infiltration of hemodynamic origin				
Very slight to slight				
Moderate to marked	3	6	7	6
Very slight to marked inflammatory cell infiltration	3	8	15	19
	4	15	24	20

The sponsor noted on page 40 that thrombosis and phlebitis were seen only in animals receiving SR33589B. The hemodynamic and inflammatory perivascular changes already present with vehicle were exacerbated by the addition of drug.

Diarrhea was reported in 1 male from the 6 mg/kg group. Male #21 was euthanized on day 14 as the intravenous injection could not be performed on him that day (reason unspecified). Drug-treated animals ate less and gained less weight than did the control groups.

ECG: 1st degree AV block was seen in 1/3 HD f. This is consistent with other studies. PR duration was increased in both sexes at the HD: male control 10.2±0.71 vs 12.0±0.57 (0.01s) for the HD males and 10.0±0.71 female controls vs 12.0±1.37 for HD females. Not statistically significant for either sex.

QT interval was increased for all drug-treated groups but not in a dose-related fashion. QTc was increased for all male drug-treated groups and the HD females.

Ophthalmoscopy: no treatment-related changes were reported.

Hematology and Clinical Chemistry

PCV and hemoglobin showed slight apparently dose-related decreases in both sexes. Day 14 hematology showed an increased number and percent of neutrophils and slightly increased monocytes in the drug-treated animals. This is consistent with the tissue irritation and damage from the injections. Fibrinogen was increased in all groups compared to baseline. The levels in the HD groups were elevated compared to the control groups. This is again consistent with an inflammatory process and a difference in levels of inflammation between the vehicle and the drug.

Day 14, serum creatinine decreased somewhat in the drug-treated groups in a relatively dose-related way. Globulins increased slightly in the MD and HD females. Serum sodium decreased in a dose-related manner in the males and non-dose-related in the females. Serum potassium was lower in drug-treated animals than control but without a discernible pattern.

Summary of serum biochemistry

Males				
	Dose mg/kg			
	0	1	2.5	6
Sodium mM	150.3±1.20	148.7±0.33	145.7±0.67*	143.5±2.50
K mM	4.47±0.088	4.07±0.033	4.10±0.058	4.10±0.200
Females				
Sodium mM	150.0±0.58	147.7±1.20	148.0±0.58	146.7±1.20
K mM	4.17±0.067	4.30±0.000	4.00±0.115	4.17±0.120

There were mild differences in electrolyte excretion in the drug-treated groups.

Summary of Urinalysis Results

Males				
	Dose mg/kg			
	0	1	2.5	6
Na mM	84±18.8	66±19.1	77±5.7	71±11.3
K mM	31.9±0.99	22.9±6.39	19.8±1.62	26.2±8.30
Females				
Na mM	121±63.7	45±6.1	71±0.6	60±6.6
K mM	18.3±2.11	28.1±10.28	22.7±2.71	30.7±6.45

Liver weight was increased primarily at the HD. Absolute testes weight showed a dose-related decrease. Absolute and normalized uterine weight was increased as was ovarian weight.

Summary of Organ Weight Effects

Males				
	Dose mg/kg			
	0	1	2.5	6
Liver (g) Liver g/kg	295±22 26±1.5	277±23 27±3.0	313±18 30±1.0	328±30 30±4.1
Testes (g)	17±1.4	16±1.2	15±1.3	12±1.0
Testes (g/kg)	1.49±0.14	1.55±0.15	1.41±0.11	1.14±0.08
Females				
Liver (g) Liver (g/kg)	294±11 27±0.5	275±9 28±1.0	290±20 28±0.5	330±37 36±4.4
Adrenals mg/kg	112±4.0	112±3.0	109±5.4	160±30
Eyes (g/kg)	0.996±0.055	1.127±0.016	1.077±0.095	1.181±0.030
Brain (g/kg)	6.76±0.54	7.71±0.12	8.08±1.17	8.50±0.33
Pituitary (mg/kg)	5.6±0.55	6.6±0.49	6.6±0.53	6.3±1.28
Uterus (g) Uterus g/kg	5.2±2.4 0.46±0.19	9.4±5.2 0.971±0.54	13.0±5.3 1.29±0.53	12.0±5.5 1.26±0.56
Ovaries (mg) Ovaries (mg/kg)	729±110 66±12	1106±357 114±37	1250±350 121±32	1483±556 156±54

Toxicokinetics: SR35021 was not detected in the plasma of the animals sampled in the three treated groups. Three hours after dosing SR33589 was present in quantifiable amounts in the plasma of the sampled animals with the exception of 1 LD male. By 24 hours after dosing SR33589 was found only in 1 HD female. Neither Cmax nor AUC_{0-24} were assessed.

Study title: Preliminary toxicity study by intravenous infusion to beagle dogs

Key study findings: As a dose-ranging study for the longer intravenous studies, first degree block was again reported as was thrombosis and phlebitis. I could not find a numerical summary of thrombi and vascular changes. One incident of second degree heart block was also reported.

Study no.: DDO0549
Conducting laboratory and location: Pharmaco L.S.R., LTD, Eye, Suffolk, England
Date of study initiation: September 14, 1994
GLP compliance:

QA report: yes ( ) no ( )
Drug, lot #, and % purity: SR33589B lot L119E, vehicle of mannitol

Methods Eight month old Beagles, 1/sex/group, were given intravenous doses of 5, 10 or 20 mg/kg day. The duration varied with the treatment. The study design is summarized in the sponsor's table reproduced below:

Sponsor's Summary of Study Design

Group 1	Saline solution	20 ml/kg	D1- D5	1 hr infusion
Group2	vehicle	20 ml/kg	D1- D2 D3- D5	1 hr infusion 2 hr infusion (dilution)*
Group3	5 mg/kg/day	D1-D2 D3- D4	5 ml/kg 10 ml/kg	1 hr infusion 2 hr infusion (dilution)*
Group 4 Male only	10 mg/kg/day	D1-D2 D3-D5	10 ml/kg 20 ml/kg	1 hr infusion 2 hr infusion(dilution)*
Group 5	20 mg/kg/day 10 mg/kg/day	D1 D3	20 ml/kg 20 ml/kg	1 hr infusion 2 hr infusion (dilution)*
Group 6	10 mg/kg/day	D8-D21	10 ml/kg	1 hr infusion
	Animals 4M and 1F reassigned as radiographs showed that their cannula were lying beyond the jugular vein in the vena cava.			
Treatment duration	5 days: groups 1-5 (Day 1-Day 5) 14 days: group 6 (Day 8 to day 21)			

*dilution= dilution in 5% dextrose

Animals were monitored for signs, body weight, food intake, ECG, blood pressure, hematology, clinical chemistry

Statistical analysis: p values included in the tables are associated with the following statistical significance:

*significant difference with 1.0%<p≤5.0%
**significant difference with 0.1%<p≤1.0%
***significant difference with p≤0.1%

Results

Two males and 1 female showed no treatment-related changes.
1 male, 1female: severe hypotensive episode on day 1
Those two animals who experienced severe hypotension and 1 other male and 2 other females were euthanized early due to severe reaction such as: decreased activity, tremors, rapid heart beat, pyrexia, swelling around the surgery site and limited use of the forelimb.

1male and 1 female, both from group 6, showed a first degree AV block immediately after dosing. The male also showed second degree heart block prior to dosing on day 14. The animals euthanized prematurely showed elevated fibrinogen and WBC (neutrophil counts), lower platelet counts, shorter thrombin time and slightly shorter prothrombin

times, consistent with an inflammatory and infectious process. The early decedents also showed higher alkaline phosphatase levels, higher triglycerides and cholesterol levels, low calcium and potassium levels. Albumin was decreased and globulin levels were somewhat elevated.

Four out of 5 animals showed a slight anemia.

The sponsor makes an interesting point in the textual summary: "Apart from the hypotensive episode noted in animals that received 20 mg/kg/day, little relationship to dosage was evident in the extent of toxicity noted in these animals and dilution of test material did not have any noticeable activity in alleviating the symptoms [sic] seen [page 45]." I could not find a numerical summary of thrombi and vascular changes.

Study title: Toxicity study by intravenous infusion to Beagle dogs for four weeks

Key study findings:

Study no.: TSA0962

Conducting laboratory and location: Pharmaco LSR Ltd, Eye, Suffolk, England
Date of study initiation: December 6, 1994
GLP compliance: statement included
QA report: yes (x) no ( )
Drug, lot #, and % purity: SR33589 batch 92.01, vehicle of mannitol

Methods Beagles, 3/sex/group received SR33589 for one hour per day by intravenous infusion at dosages of 0, 1, 2 or 4 mg/kg/day for a 4 week treatment period. Catheters were installed in the jugular veins. Saline and vehicle control groups were included. Animals were monitored for signs, bodyweight, food consumption, ophthalmoscopy, electrocardiography, hematology, clinical chemistry and urinalysis. PK samples were collected during the final week of treatment before and immediately after dosing and 1,3 and 9 hours after the end of infusion. Necropsy examination included gross observations, organ weights and histopathology. Liver and kidney samples were collected from all animals for EM.

Statistical analysis: p values included in the tables are associated with the following statistical significance:

*significant difference with $1.0\% < p \leq 5.0\%$
**significant difference with $0.1\% < p \leq 1.0\%$
***significant difference with $p \leq 0.1\%$

Results

No clinical signs or unscheduled mortality were reported.

There were no apparent effects on body weight or food consumption.

Hematology and Clinical Chemistry

A slight anemia was apparent, characterized by decreased PCV, Hb and RBC count. Total WBC count was increased in the drug-treated males, primarily due to a neutrophilia and secondarily to lymphocytosis and monocytosis, suggesting some chronicity to the infectious/inflammatory stimulus. Females showed an increased neutrophil count and a mild increase in monocytes was apparent in the HD group.

There were no consistent or dose-related ECG findings that occured in both sexes. Females showed increased PR and QRS intervals. QT and QTc were apparently unaffected. Amplitudes of Q,R, and S were altered compared to control. The ratio of R:T was also affected.

Masses were seen at necropsy in all groups of animals at the infusion sites. Some distant changes in the hearts (ventricles) and other veins were reported also but without an apparent dose-response relationship. The masses were described as thickened endocardial and intimal areas after microscopic examination. The thickened areas were cellular and sometimes fibrocellular with cellular elements either fibrocytes or myocytes. Leucocytic cell infiltration was seen in the majority of these cases. Focal areas of necrosis were seen. Thus, pathological reaction at the infusion sites and associated vasculature were seen in all groups including both control groups. A dose-response relationship to the vascular irritation was not found.

Possibly due to the small group size, treatment-related changes could not be discerned in the clinical chemistry data, urinalysis, organ weights and pathology.

Study title: 4-week intravenous infusion toxicity study in the dog: toxicokinetic data

Key study findings: SR35021 was not detected. SR33589 was detected in both sexes at all doses. There were no obvious differences between the sexes. The results were close to dose-proportional.

Study no.: TSA0962

Conducting laboratory and location: TK portion conducted at Sanofi Recherce, Montpellier Cedex, France
Date of study initiation: in life December 1994; analysis February 1995
GLP compliance: yes
QA report: yes ( ) no ( )
Drug, lot #, and % purity: SR33589B batch 92-01

Methods Determination of SR33589 and SR35021 in plasma by HPLC with UV detection. LOQ: 0.020 mg/l LOD: 0.010 mg/l

Results SR35021 was not detected.

SR33589 pharmacokinetic results (mean±SD)

Dose mg/kg/day	Males		Females	
	C1h mg/l	AUC_{0-24}(mg.h/l)	C1h mg/l	AUC_{0-24}(mg.h/l)
1	0.087±0.019	0.287±0.038	0.067±0.019	0.167±0.051
2	0.246±0.059	0.605±0.085	0.190±0.057	0.571±0.057
4	0.420±0.128	1.303±0.139	0.422±0.135	1.400±0.305

Study title: Four-day intravenous dose-ranging study in the macaque

Key study findings: This was a dose-ranging study for a proposed longer IV dosing study in non-human primates. Consistent with other intravenous administration studies, poor local tolerability was seen at the injection sites, attributed primarily to the vehicle but, also consistent with other studies, exacerbated by the drug as shown by thrombosis. Dose-dependency for the thrombotic effects was reported as lacking. Drug-treated animals also showed evidence of anemia. ECG changes were seen at doses ≥4mg/kg consisting of 20-30%decreased heart rate (≥4mg/kg) and increased QT and PR intervals. First degree AV block was reported. A male treated with 16 mg/kg died after showing profoundly altered ECG parameters. A female given the same dose went into tonic seizures also accompanied by ECG changes. Recovery was reported to occur after 15 minutes. It was interesting to note that ECG changes were reported to occur at the lower doses 1 hour after IV administration, suggestive of a metabolite effect. ECG changes at the highest dose were reported to occur after the injection but be resolved 15 minutes after the injection.

Study no.: DDO0503
Conducting laboratory and location: Sanofi Recherche, Montpellier Cedex, France
Date of study initiation: January 18, 1993
GLP compliance: statement included
QA report: yes (x) no ( )
Drug, lot #, and % purity: SR33589B batch DJ.07.51.5, vehicle of PEG400, acetic acid and acetate buffer.

Cynomologous monkeys were used.

Sponsor's summary of experimental design

group	animals		compound	Dosage mg/kg/day	Route
	number	first			
0	1M 1F	1 2	Vehicle	----------	IV
1	1M 1F	3 4	SR33589B	2	IV
2	1M 1F	5 6	SR33589B	4	IV
3	1M 1F	7 8	SR33589B	8	IV
4	1M 1F	9 10	SR33589B	16	IV

Animals were examined for signs, conscious ECG, body weight, food consumption, hematology, bone marrow, coagulation, clinical chemistry, toxicokinetics, gross pathology, organ weights, histopathology. Selected liver and kidney samples were analyzed by EM.

Statistical analysis: p values included in the tables are associated with the following statistical significance:

*significant difference with 1.0%<p≤5.0%
**significant difference with 0.1%<p≤1.0%
***significant difference with p≤0.1%

Results:

Unscheduled mortality was seen. The male treated at 16 mg/kg/day died 5 minutes after the first dose (20 second injection). ECG changes before death included :

notched T-wave with a reversal in polarity
sino-atrial block with intermittent junctional rhythm
complete AV dissociation
ST segment depression
Junctional followed by ventricular escape rhythm

The female treated at 8 mg/kg was prostrate during 10 minutes after the injection on the first day of treatment. The female treated at 16 mg/kg day (5 minute injection) showed tonic convulsions during a few minutes at the end of the injection on the first day of treatment associated with ECG changes. The ECG changes seen in the female were:

Gradual decrease in heart rate with concurrent increase in PR interval
10 minutes later, Transient sino-atrial block with transient junctional rhythm, associated with ST segment depression
followed by sinus rhythm and bradycardia
Changes were reported to resolve by 15 minutes after the injection.

Changes on the second day:

No changes during the injection
After injection, HR decreased in association with a depressed T-wave
No other changes were listed
Changes were again reported to have resolved by 15 minutes after the injection

Other recorded and/or described ECG effects include:

Animals treated at 4 mg/kg and 8 mg/kg at 1 hour after treatment showed a 20-30% decrease in heart rate (with prolonged RR interval), first degree AVB (prolonged PR interval) and somewhat prolonged QT interval.

The male treated at 16 mg/kg/day didn't show any changes during the first administration. Immediately after the injection, the animal showed notched and reversed T-wave polarity associated with decreased heart rate and sino-atrial block with intermittent junctional rhythm. In a few minutes, complete atrio-ventricular dissociation was noted with ST segment depression, junctional followed by idioventricular escape rhythm and eventually death.

The female treated with 16 mg/kg didn't show any changes during the first administration. A few minutes later, the animal had a convulsion, during which, HR decreased while the PR interval increased. Ten minutes later, sino-atrial block with transient junctional rhythm was observed with ST segment depression and sinusoidal rhythm with bradycardia. No further modifications were noted from 15 minutes after the injection.

Local tolerability changes were reported for the last day of treatment. Diffuse redness was reported for the control animals, diffuse edema in the LD m and local edema in the LD f. Diffuse redness was reported for the 4 mg/kg f and diffuse edema for the 8 mg/kg m. At necropsy, poor tolerability was concluded, aggravated by thrombosis in those animals who had received SR33589B, with no dose related effect.

The drug produced degrees of anemia in all treated animals except the LD male. A leucocytosis and neutrophilia was also reported for males from ≥2 mg/kg and in the female treated with 16 mg/kg/day. There was also a slight increase in fibrinogen in the HD f. These changes are consistent with inflammation/infection and poor tolerability.

The following clinical chemistry changes were ascribed to drug treatment: slight decreases in glucose levels, moderate decreases in albumin, decreased potassium, chloride and calcium levels in the female treated at 16 mg/kg/day. Increased LDH activity was seen in all animals including controls. This could be related to irritant properties of the vehicle.

Histopathology of the injection sites showed thrombotic changes and subacute phlebitis. Perivascular changes included hemorrhagic or fibrino-hemorrhagic nature and subacute inflammation.

Sponsor's summary of microscopic changes related to the injection

	Dose mg/kg/day				
	0	2	4	8	16
Number of animals	2	2	2	2	2
Vascular changes					
Thrombosis	-	2	2	1	1
Subacute phlebitis	-	2	2	1	-
Perivascular changes					
Infiltration of hemodynamic nature	1	2	-	1	2
Inflammatory infiltration	-	2	2	2	1
Subcutaneous changes					
Infiltration of hemodynamic nature	2	2	2	2	1
Inflammatory infiltration	1	1	1	2	1

Study title: 2-week intravenous toxicity study in the macaque

Key study findings: Consistent with the other intravenous administration studies, there was a dose-related increase in tissue irritation (≥1 mg/kg) and damage with profound gross and microscopic changes of hemorrhage, inflammation and thrombosis as well as muscle necrosis. The sponsor noted in the text that they summarized only the "maximal changes". Not presented in the summary table but mentioned in the text were changes in veins of the axilla, cases of vascular rupture, segmental venous necrosis and muscular and dermal hemorrhagic infiltration, local opportunistic infections, a few cases of widespread necrosis of the crural muscle, with inflammatory, septic, edematous and hemorrhagic changes sometimes associated. Performing injections became technically difficult after 4 or 5 days for all dose groups. A male HD monkey and a female HD monkey died prior to scheduled termination. The findings in the female included multi-focal acute hemorrhagic endomyocarditis in the left ventricle. While the cause of the endocarditis was undetermined, there are plausible causes not directly related to the drug. E.g., infectious. The male showed increased serum glucose, ALT, AST and LDH and increased urinary potassium excretion. Both animals showed proteinuria. The hematology in all drug-treated animals indicated primarily an inflammatory response. Mild, regenerative anemia was seen in females at doses ≥2.5 mg/kg and at 6 mg/kg in males. Decreased serum albumin, triglyceride levels and slightly increased liver weight suggest the liver as one of the target organs. Both absolute and normalized uterine and ovarian weight were decreased in what appears to be a dose-related manner. Given the other reported changes, the changes in these reproductive organs may have been secondary to chronic sympathetic discharge.

Study no.: TSA0884
Conducting laboratory and location: Sanofi Recherche, Montpellier Cedex, France
Date of study initiation: May 18, 1993
GLP compliance: statement included
QA report: yes (x) no ( )
Drug, lot #, and % purity:SR33589B batch 92.01 vehicle of PEG400, acetic acid

The animals were treated once daily for 14 -16 days. Control animals received the vehicle at a similar volume as the high dose animals. Solutions were administered as a bolus injection over 10-20 seconds. The sponsor's summary of design is reproduced below.

Sponsor's summary of experimental design

group	#of animals	First animal number	compound	Dose mg/kg/day	Route of administration
0	3M 3F	1 4	Vehicle	0	IV
1	3M 3F	7 10	SR33589**B**	1	IV
2	3M	13	SR33589**B**	2.5	IV

	3F	16			
3	3M 3F	19 22	SR33589**B**	6	IV

Observations included clinical signs, body weight and food consumption, ECG, ophthalmoscopy,
Hematology, clinical chemistry, urinalysis, gross necropsy, organ weights,
Statistical significance:
* 1.0%<p≤5.0%; **0.1%<p≤1.0%;***p≤0.1%

Results

The following changes were observed at 6 mg/kg: pallor of mucous membranes from day 9 onwards, weakness in 1m and 1 f, abnormal gait in 2m and 1 f, prostration in 1f. One male and 1 female from this group were found dead days 14 and 12 respectively. The male showed weakness the day before. Acute, multifocal endomyocarditis was found in the left ventricle of the female.

At all doses, the injections became technically difficult after 4 or 5 days. The site of the injections needed to be changed several times during the course of the study. In all drug-treated groups, redness was observed at the injection site as well as induration. From ≥2.5 mg/kg, scabs, oozing or edema were noted more in drug-treated than in control animals. A few animals presented with severe and extensive lesions. Limbs were increased in volume and in some cases more than 1 limb was involved. At the highest dose tested, 3 cases of necrotic lesions were reported in hindlimbs. The sponsor's summary of observations on this point is reproduced below.

Macroscopic observations

	Dose mg/kg			
	0	1	2.5	6
# of animals	6	6	6	6
#of injection sites	12	36	35	38
wound				3
edema	0	3	4	7
hematoma	7	15	12	9
induration	1	15	13	16
abscess	1		2	
Microscopic observations				
Necrosis (perivascular and perimuscular)	0	1	3	8
Exulceration focal	0	1	1	0
Ulceration: focal –very widespread	0	1	1	3

Injection sites and associated organs and tissues were described as having organized or recanalized thrombi. Adjacent muscles shoed slight to marked acute fibrous inflammatory cell infiltration and necrotic tissue. Limbs were also reported to show ulceration.

At doses ≥ 2.5 mg/kg: Health was deteriorating as evidenced by lymphoid atrophy and involution of thymus, spleen and lymph nodes and slight-moderate cortical hyperplasia of the adrenals. Other findings were decreased hepatic glycogen, slight-moderate cortical tubular swellings in the kidneys, serous de-differentiation of the pancreas (1/6 MD and 3/6 HD) and slight atrophy of the intestinal mucosa (1/6 HD, no further details).

ECG: HR decreased in the HD groups of both sexes (16% in males , 13% in females compared to baseline). PR duration was increased in males but showed inconsistent, non-dose-related increases in females. T amplitude was decreased by approximately 50% in HD males and from 36-46% in females.

Body weight: Drug-treated animals either gained less than the controls or actually lost weight. A dose-related pattern was not apparent. No NOAEL was defined.

Hematology and Clinical Chemistry

Hematology showed that the drug-treated animals had a regenerative anemia with a pronounced increase in reticulocyte count. No NOAEL was seen. Mild leucocytosis was seen in both sexes, primarily due to neutrophilia. Platelet counts were increased in the MD and HD groups of both sexes also. APTT and thrombin time were increased in males.

Albumin showed a dose-related decrease in males and was decreased in MD and HD males. Triglycerides were decreased in both sexes of drug-treated animals. Bilirubin was increased in both sexes of drug-treated animals. Total cholesterol was decreased in males.

ALT and AST were increased in the HD of both sexes. LDH activity was increased in the MD and HD of both sexes. Ca and K were decreased in the HD of both sexes.

Organ Weights

Both absolute and relative uterine and ovarian weights were decreased in the MD and HD groups. There is no histopathology or data regarding the cyclicity of these animals, making the weight findings difficult to interpret. In males, the absolute and relative liver, adrenal and spleen weight was increased in the HD. Absolute and relative kidney weight was increased in all drug-treated groups.

In females, absolute and relative kidney weight was slightly increased in the MD and HD groups. Absolute adrenal weight was increased in all drug-treated groups without a dose-response.

Summary of organ weight changes

	Dose mg/kg/day			
	vehicle	1	2.5	6
Males				
Adrenal mg/kg	246±3.5	245±27.5	269±19.5	407±59.1
Eyes g	5.87±6.20	6.20±0.161	6.11±0.145	6.33±0.042
Brain g	62.55±1.965	68.72±1.943	61.82±1.355	74.24±2.658*
Brain mg/kg	25.16±1.156	25.93±1.610	24.68±1.854	29.71±0.244
Females				
Adrenal mg/kg	221±9.1	285±20.7	394±59.2	335±34.5
Uterus (g)	3.96±1.37	4.22±0.98	2.22±0.17	1.57±0.16
Uterus g/kg	1.49±0.48	1.77±0.41	1.08±0.09	0.69±0.04
Ovaries (mg)	252±85.5	192±38.2	113±10.7	123±3.0
Ovaries mg/kg	94±24.0	81±16.3	55±5.8	55±4.2
Brain g/kg	23.72±1.37	27.07±2.33	29.23±0.65	28.43±2.22

Histopathology Findings

The histopathology results provided were primarily concerned with the injection sites and findings related to the irritancy potential of the vehicle/drug combination.

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/s/

Elizabeth Hausner
3/3/2006 03:10:35 PM
PHARMACOLOGIST
Elizabeth Hausner

Albert Defelice
3/6/2006 08:10:04 AM
PHARMACOLOGIST

2.6.6.4 Genetic toxicology These studies were previously reviewed by the first reviewer for the IND. They were given a secondary review here for the sake of completeness.

Study title: Ames test-reverse mutation assay on Salmonella typhimurium

Key findings: Toxicity was seen ≥50 µg/plate (-S9) and ≥250 µg/plate (+S9). Under the conditions of the study an increase in revertants was not seen. A decrease in revertants was apparent both ±S9.
Study no.: CEL0593
Conducting laboratory and location: Sanofi Dept of Toxicology , Montpelier Cedex, France
Date of study initiation: May 14, 1991
GLP compliance: statement included
QA reports: yes (x) no ( )
Drug, lot #, and % purity: SR335898 batch MR 13-171-1 dissolved in DMSO, purity by LC 99.6%

Methods Salmonella typhimurium strains TA1535, TA1537, TA98, TA100, TA102 were used ±S9 activation. A pre-incubation method was used in this study: test tubes were incubated for 20 minutes at 37ºC before addition of the top agar.

A preliminary bacterial toxicity test was performed with and without metabolic activation, on tester strain TA98, with a top concentration of 5000 µg/plate. According to these results, the genotoxicity test (CEL593) was carried out at 5 decreasing concentrations of SR 33589B on 5 Salmonella typhimurium tester strains.

Test	Concentrations used µg/plate(conversion factor of 1.066 for salified)
Toxicity test (TA98 only)	
Non-salified	94, 469, 938, 2345, 4690
Salified	100, 500, 1000, 2500, 5000
Genotoxicity test	
Non-salified	4.7, 9.4, 47, 94, 235
salified	5,10, 50, 100, 250
Positive controls –S9	Na azide, 2-nitrofluorene, 9-aminoacridine, mitomycin C
Positive controls+S9	2-aminoanthracene, danthron

Results
Toxic ≥50 µg/plate -S9
≥250 µg/plate +S9
A reverse dose response was apparent. That is, a decrease in the number of revertants was seen.

Study title: Ames Test-Reverse mutation assay on Salmonella typhimurium

Key findings: TA98 +S9 showed a repeatable increase in revertants. A full dose response was not shown due to the level of toxicity at the concentrations tested. Under the conditions of the assay, it appears that the test article in the presence of S9 activation caused an increase in revertants in the TA98 strain.

Study no.: Cel0709

Conducting laboratory and location: Sanofi Toxicology, Montpelier Cedex, France
Date of study initiation: March 23, 1993
GLP compliance: statement included
QA reports: yes (x) no ( )
Drug, lot #, and % purity: SR33589B batch 92-01, vehicle of DMSO

Methods Salmonella typhimurium tester strains TA1535, TA1537, TA102, TA98, TA100 were used ±S9 in the plate incorporation method.

Test	Concentrations used µg/plate(conversion factor of 1.066 for salified)
Toxicity test (TA98 only)	
Non-salified	4.7, 9.4, 47, 94, 235, 469
Salified	5,10, 50, 100, 250, 500
Genotoxicity test	
Non-salified	9.4, 23, 47, 94, 164
salified	10, 25, 50, 100, 175
Complementary study: TA98+S9	
Non-salified	9.4, 23, 47, 94, 164
salified	10, 25, 50, 100, 175
Positive controls –S9	Na azide, 2-nitrofluorene, 9-aminoacridine, mitomycin C
Positive controls+S9	2-aminoanthracene, danthron

Results

-S9: toxicity ≥100 µg/plate except for TA100 (toxicity from ≥175µg/plate)
Residual toxicity at 25 and 50µg/plate in all other strains.

+S9: toxicity from ≥100 µg/plate in all strains

An increase in revertants was seen –S9 at the 50 µg concentration of TA98.

Table (3.1) 1.
Bacterial toxicity on TA98 and TA100

		Without S-9 mix		With S-9 mix	
Tester strain	Concentration (µg/plate)	Bacterial (1) background lawn	Revertant (2) colonies/plate	Bacterial (1) background lawn	Revertant (2) colonies/plate
TA98	0	-	18	-	20
	5	-	19	-	14
	10	-	23	-	12
	50	-	21	-	42
	100	+	14	-	25
	250	++	5	++	0
	500	++	1	++	0
TA100	0	-	122	-	123
	5	-	123	-	120
	10	-	133	-	116
	50	-	114	-	121
	100	-	93	-	85
	250	-	48	-	105
	500	+	4	+	60

(1) Background lawn aspect
- Normal aspect
+ Partial sparsity
++ Sparsity
(2) Mean of 3 plates for solvent control

Table (3.2.2) 1.
AMES TEST : Group results (with S-9 mix)
No. His+ revertant colonies/plate

```
--------------------------
:                Strain  :
:                 TA98   :
--------------------------

      Group 0 :   DMSO

:  n = 5                 :
:  mean            28.4  :
:  SEM             1.50  :

 Group 1 : POSITIVE CONTROL

:  n = 2                 :
:  mean          1540.0  :
:  SEM           10.00   :

Group 2 :   SR33589B   10  microg/plate

:  n = 5                 :
:  mean            34.4  :
:  SEM             2.79  :

Group 3 :   SR33589B   25  microg/plate

:  n = 5                 :
:  mean            37.2  :
:  SEM             2.97  :
--------------------------
```

Table (3.2.2) 1
AMES TEST : Group results (with S-9 mix) (Cont'd)
No. His+ revertant colonies/plate

	Strain TA98
Group 4 : SR33589B 50 microg/plate	
n = 5	
mean	42.2
SEM	4.18
Group 5 : SR33589B 75 microg/plate	
n = 5	
mean	28.6
SEM	4.13
Group 6 : SR33589B 100 microg/plate	
n = 5	
mean	14.8
SEM	2.06
Group 7 : SR33589B 175 microg/plate	
n = 3	
mean	4.0
SEM	0.58

Study title: In vitro gene mutation assay at the locus TK +/- in mouse lymphoma L5178Y cells

Key findings: There was no indication of increased mutation frequency in the data as presented. The positive controls produced appropriate responses.

Study no.: FSRFU-LYM0125-EN-E01

Conducting laboratory and location: Sanofi-Synthelabo, Porcheville, France
Date of study initiation: June 25, 2002
GLP compliance: statement included
QA reports: yes (x) no ( )
Drug, lot #, and % purity: SR33589B, batch NFI 5659038, vehicle of DMSO

Methods

Summary of concentrations used.

Conditions	concentrations
3 hour exposure±S9	9.37, 18.75, 37.5, 75, 150, 300 µg/ml
24 hour exposure –S9	0.1, 0.25, 0.5, 1,2,4 and 5
1st study: 3 hour exposure –S9	2.5,5,7.5,10, 12.5, 15
1st study: 3 hour exposure +S9	10, 15,20, 25, 30 and 35
2nd study: 24 hour exposure -S9	0.5, 1,1.5, 2, 2.5, and 3
2nd study: 3 hour exposure +S9	17.5, 20, 22.5, 25, 27.5, 30
Positive control –S9	Methylmethane sulfonate (MMS)
Positive control +S9	cyclophosphamide

Results

In the preliminary test, relative survival fell from 28% at 9.37µg/ml(-S9, 3 hours) to 0% at 18.75µg/ml under the same incubation conditions. With metabolic activation, relative survival decreased to ~5% at 37.5µg/ml with 3 hours incubation. In the 24 hour, -S9 preliminary test, relative survival at 2µg/ml was 8% and dropped to 0 at the next concentration of 4µg/ml.

There was no indication of increased mutation frequency in the data as presented. The positive controls produced appropriate responses.

Study title: In vitro gene mutation assay at the locus HPRT in Chinese Hamster V79 fibroblasts.

Key findings: With S9 activation, statistically significant increases in mutants were seen in three repeats of the assay.

Study no.:685-3-008
Conducting laboratory and location: Sanofi, Montpellier Cedex, France
Date of study initiation: March 19, 1993
GLP compliance: statement included
QA reports: yes (x) no ( )
Drug, lot #, and % purity:SR33589B, batch 92.01, DMSO as vehicle

Methods

V79 fibroblastic Chinese hamster cells were used ±S9. The concentrations used are summarized below:

Summary of concentrations used

First study	±S9	2.5,10,25, 50, 100 µg/ml
Second study	-S9	1, 2.5, 5, 10, 17.5
	+S9	5, 10, 17.5, 25, 37.5

The highest concentration was based on the limit of solubility.

The positive controls used were

-S9: ethyl methane sulfonate (EMS)

+S9: benzo(a)pyrene [B(a)P].

Results

Without S-9 mix, no gene mutation was induced at the 1ocus HPRT in cultures treated with 2.5, 5 and 10 µg/ml SR 33589B. At 25 µg/ml, a statistically significant increase was recorded but since it was noted at a toxic concentration (only 27 % cell survival), it was not considered biologically relevant.

With S-9 mix, the mutation frequency values in cultures treated with 2.5, 5, 10 and 25 µg/ml were in the same range as solvent control cultures whereas at 50 µg/ml (corresponding to marked toxicity) no mutant colonies were seen.

HPRT/V79 test without metabolic activation

	cfeI	cfeII	Viable Cells $X10^{-6}$	Nb 6TG mutants	MF $x\ 10^{-6}$	Statistic p value
Untreated cells	1.18	1.21	4.37	13	2.98	0.73 ns
DMSO	0.97	1.14	4.11	14	3.41	
SR33589B 2.5 µg/ml	0.91	1.23	4.42	0	0.00	<0.001***
SR33589B 5 µg/ml	1.16	1.13	4.06	29	7.14	0.02*
SR33589B 10 µg/ml	0.76	1.13	4.53	1	0.22	<0.001***
SR33589B 25 µg/ml	0.26	1.07	4.29	71	16.54	<0.001***
EMS 3 mM	1.11	1.11	4.45	1093	245.43	<0.001***
EMS 6 mM	1.01	1.25	4.98	1932	387.95	<0.001***

*p<0.05, **p<0.01, ***p<0.001

Second test: HPRT/V79 test without metabolic activation

	cfeI	cfeII	Viable Cells $X10^{-6}$	Nb 6TG mutants	MF x 10^{-6}	Statistic p value
Untreated cells	1.04	0.85	3.38	8	2.37	0.10 ns
DMSO	1.02	0.90	3.59	17	4.73	
SR33589B 1 µg/ml	1.07	0.88	3.53	4	1.13	0.005**
SR33589B 2.5 µg/ml	1.04	1.01	4.03	17	4.21	0.74 ns
SR33589B 5 µg/ml	1.03	0.98	3.91	46	11.77	0.001***
SR33589B 10 µg/ml	0.89	1.11	4.45	38	8.53	0.04
SR33589B 17.5 µg/ml	0.66	1.02	3.68	0	0.00	0.001***
EMS 3 mM	1.04	0.90	3.23	858	265.80	<0.001***
EMS 6 mM	1.00	1.00	3.98	1797	451.51	<0.001***

*p<0.05, **p<0.01, ***p<0.001

According to the sponsor:

With the S-9 mix

The mutation frequency was heterogeneous, with a statistically significant increase at 10-17.5 and 25 µg/ml, but concentration-unrelated and within historical control values. Therefore these responses have no biological relevance.

The high mutation frequency values obtained simultaneously for the positive controls (EMS and B(a)P proved that the cell system was potentially active.

Second test: HPRT/V79 test with S9 activation

	cfeI	cfeII	Viable Cells $X10^{-6}$	Nb 6TG mutants	MF x 10^{-6}	Statistic p value
Untreated cells	1.02	1.01	4.03	5	1.24	0.31ns
DMSO	1.00	0.92	3.66	8	2.19	
SR33589B 5 µg/ml	0.96	0.98	3.90	16	4.10	0.14ns
SR33589B 10 µg/ml	0.96	0.97	3.87	35	9.05	<0.001***
SR33589B 17.5 µg/ml	0.89	0.98	3.93	41	10.44	<0.001***
SR33589B 25 µg/ml	0.90	1.03	4.10	33	8.05	<0.001***
SR33589B 37.5 µg/ml	0.34	0.94	3.77	4	1.06	0.23ns
BaP 10 µg/ml	0.81	1.02	3.65	197	53.91	<0.001***
BaP 20 µg/ml	1.15	1.00	4.01	255	63.54	<0.001***

*p<0.05, **p<0.01, ***p<0.001

Although a dose response was observed, the sponsor dismissed the results for falling within the range of historical controls.

Study title: In vitro DNA repair assay on rat hepatocytes in primary culture

Key findings: SR33589B was cytotoxic at concentrations of 10 and 25 µg/ml. 5µg/ml had less toxicity but also killed cells. The cells treated with test compound showed results very similar to those of the cell and vehicle controls with respect to net nuclear count and % cells in repair. In this in vitro study there was no evidence of unscheduled DNA synthesis.

Study no.: DNA001

Conducting laboratory and location:
Date of study initiation: April 19, 1993
GLP compliance: statement included
QA reports: yes (x) no ( )
Drug, lot #, and % purity: SR33589B(batch92-01), vehicle of DMSO, purity 99.5%

Methods

Primary culture hepatocytes were prepared from male Fischer rats. The concentrations used were 1, 2.5, 5, 10 and 25 µg/ml. Only the slides for 1, 2.5 and 5 µg/ml were read. DMSO was used as the vehicle.

Results: SR33589B was cytotoxic at concentrations of 10 and 25 µg/ml. 5µg/ml had less toxicity but also killed cells. The cells treated with test compound showed results very similar to those of the cell and vehicle controls with respect to net nuclear count and % cells in repair. In this in vitro study there was no evidence of unscheduled DNA synthesis. The positive control produced appropriate responses.

Study title: In vitro DNA repair assay on rat hepatocytes in primary culture

Key findings: SR33589B killed cells at 10 µg/ml with similar cell development as the controls. Substantial toxicity was seen at 25 µg/ml and precipitation ≥50µg/ml. Positive controls produced appropriate responses. Under the conditions of the assay unscheduled DNA synthesis was not seen following treatment with the test article.

Study no.: CEL0536

Conducting laboratory and location: Sanofi Research, Montpelier Cedex, France
Date of study initiation: May 15, 1991
GLP compliance: statement included
QA reports: yes ( ) no ( )
Drug, lot #, and % purity: SR33589B batch 13-171-11, purity; DMSO was used as the vehicle.

Methods
Primary hepatocyte cultures were prepared from male Fischer rats. The concentrations of test article used are summarized below.

Concentrations µg/ml

Cytotoxicity study	1,5,10,100,250
DNA repair study	1,5,10,25
Slides for 5 and 10 µg/ml were read	

Cells were washed after 2 hours of incubation. Immediately following washing, the cells were exposed to test compound or controls in the presence of 10µC/ml for 18-20 hours.

Results
SR33589B killed cells at 10 µg/ml with similar cell development as the controls. Substantial toxicity was seen at 25 µg/ml and precipitation ≥50µg/ml. Positive controls produced appropriate responses. Under the conditions of the assay unscheduled DNA synthesis was not seen following treatment with the test article.

Study title: Lymphocyte cytogenetic study

Key findings: An equivocal assay. There were some mild increases in aberrations that it would be easy to dismiss if the positive controls had given consistently robust responses.

Study no.: MAF0018

Conducting laboratory and location: Pharmaco L.S.R., Eye, Suffolk, England
Date of study initiation: March 14, 1994
GLP compliance: statement included
QA reports: yes (x) no ( )
Drug, lot #, and % purity: SR33589B batch 92.011-11, purity, DMSO as vehicle

Methods
Human peripheral blood lymphocytes were incubated with test compound to examine the effect on chromosomal structure. Tests were conducted ±S9. Without the S9 mix cells were exposed continuously to test article for 24 to 48 hours. With S9, exposure was limited to 3 hours and cells were harvested 21 or 45 hours later. Colcemid was added to the preparations 3 hours prior to harvest. Mitotic indices were based on the number of metaphases observed per 1000 cells scored. Chromosome aberrations were scored by examination of 100 metaphases per culture.

Summary of concentrations used

Concentrations used µg/ml	Preliminary dose-range finding assay Main cytogenetic assay	±S9 24 and 48 hr sampling times: 25, 50, 100, 200, 600 -S9: 24 and 48 hrs:1.25, 2.5, 5,10,15 and20 +S9: 24hr sampling6.25, 12.5, 25,40 +S9: 48 hr 6.25, 12.5, 25, 35, 45
Doses used fro cytogenetic analysis :duration of Tx +recovery in hours	-S9	24±0: 1.25, 2.5, 5 µg/ml 48±0: 1.25, 2.5, 5 µg/ml
	+S9	3+21: 6.25, 12.5, 25µg/ml 3+45:12.5, 25, 35 µg/ml
Metabolic activation	S9 from arochlor-induced rat liver	

Positive controls (duration of Treatment +recovery in hours
-S9: 24+0 and 48+0: Chlorambucil 2µg/ml
+S9: 3+21 and 3+45: cyclophosphamide 6µg/ml

In the absence of S-9 mix, slides from all cultures treated with SR 335898 at 10, l5 or 20 ug/ml were seen to contain few cells, and no metaphases. At the 24 hour sampling time, no toxicity (i.e. reduction in mitotic activity, compared to concurrent solvent controls) was apparent at l.25 ug/ml: reductions in mitotic activity of 29 and 65% were seen at 2.5 and 5.0 ug/ml respectively. At the 48 hour sampling time, no real toxicity was seen at 1.25 ug/m1: reductions in mitotic activity of 23 and 82% were seen at 2.5 and 5.D ug/ml. Thus dose-related toxicity was apparent at both sampling times.
In the presence of S-9 mix, at the 24 hour sampling time dose-related toxicity was apparent, with reductions in mitotic activity of l4, 17, 48 and 81% at concentrations of 6.25, l2.5, 25.0 and 40.0 ug/ml respectively. During scoring, a reduction in the quantity of cells present was noted on slides from cultures treated at 40.0 ug/ml. At the 48 hour sampling time, no toxicity was seen in cultures treated at 6.25, l2.5 or 25.0 ug/ml: reductions in mitotic activity of 40 and 8l% were seen at 35.0 and 45.0 ug/ml. During scoring, a reduction in the quantity of cells present was noted on slides from cultures treated at 45.0 ug/ml.

Main cytogenetic test - group totals

Compound (ug/ml)	Numbers of cells scored	Mean mitotic index	Cells with aberrations			Cells with aberrations other than gaps		
			Total	Indiv. values %	+ Mean %	Total	Indiv. values %	+ Mean %
24 hour sampling time								
Non-activated cultures								
DMSO (-)	200	8.6	6	2,4	3.0	4	1,3	2.0
SR 33589 B (1.25)	200	8.7	7	3,4	3.5	3	1,2	1.5
SR 33589 B (2.5)	200	6.1	5	2,3	2.5	2	1,1	1.0
SR 33589 B (5.0)	200	3.0	14	6,8	7.0	10	5,5	5.0
Chlorambucil (2.0)	200	9.2	64	31,33	32.0	55	26,29	27.5
Activated cultures								
DMSO (-)	200	9.3	7	3,4	3.5	4	1,3	2.0
SR 33589 B (6.25)	200	8.0	9	4,5	4.5	6	3,3	3.0
SR 33589 B (12.5)	200	7.7	11	4,7	5.5	5	2,3	2.5
SR 33589 B (25.0)	200	4.8	14	5,9	7.0	7	2,5	3.5
Cyclophosphamide (6.0)	200	9.5	68	33,35	34.0	53	26,27	26.5
48 hour sampling time								
Non-activated cultures								
DMSO (-)	200	8.8	5	2,3	2.5	4	1,3	2.0
SR 33589 B (1.25)	200	7.8	7	3,4	3.5	4	1,3	2.0
SR 33589 B (2.5)	200	6.8	5	1,4	2.5	2	0,2	1.0
SR 33589 B (5.0)	163	1.6	6	3,4.8	3.7	4	1.6,3	2.5
Chlorambucil (2.0)	200	10.1	26	12,14	13.0	18	9,9	9.0
Activated cultures								
DMSO (-)	200	7.8	4	2,2	2.0	2	1,1	1.0
SR 33589 B (12.5)	200	9.2	3	0,3	1.5	0	0,0	0.0
SR 33589 B (25.0)	200	9.3	10	3,7	5.0	5	2,3	2.5
SR 33589 B (35.0)	200	4.7	10	4,6	5.0	6	1,5	3.0
Cyclophosphamide (6.0)	200	10.8	25	11,14	12.5	22	11,11	11.0

$$+ \text{ Mean } \% = \frac{\text{No. aberrant metaphases}}{\text{Total cells scored}} \times 100$$

A slight increase in aberrations was seen both ± S9. The responses from the positive control were not always robust, as shown at the 48 hour time point.

Main cytogenetic test - group totals

Compound (ug/ml)	Numbers of cells scored	Mean mitotic index	Cells with aberrations			Cells with aberrations other than gaps		
			Total	Indiv. values %	+ Mean %	Total	Indiv. values %	+ Mean %
24 hour sampling time								
Non-activated cultures								
DMSO (-)	200	8.6	6	2,4	3.0	4	1,3	2.0
SR 33589 B (1.25)	200	8.7	7	3,4	3.5	3	1,2	1.5
SR 33589 B (2.5)	200	6.1	5	2,3	2.5	2	1,1	1.0
SR 33589 B (5.0)	200	3.0	14	6,8	7.0	10	5,5	5.0
Chlorambucil (2.0)	200	9.2	64	31,33	32.0	55	26,29	27.5
Activated cultures								
DMSO (-)	200	9.3	7	3,4	3.5	4	1,3	2.0
SR 33589 B (6.25)	200	8.0	9	4,5	4.5	6	3,3	3.0
SR 33589 B (12.5)	200	7.7	11	4,7	5.5	5	2,3	2.5
SR 33589 B (25.0)	200	4.8	14	5,9	7.0	7	2,5	3.5
Cyclophosphamide (6.0)	200	9.5	68	33,35	34.0	53	26,27	26.5
48 hour sampling time								
Non-activated cultures								
DMSO (-)	200	8.8	5	2,3	2.5	4	1,3	2.0
SR 33589 B (1.25)	200	7.8	7	3,4	3.5	4	1,3	2.0
SR 33589 B (2.5)	200	6.8	5	1,4	2.5	2	0,2	1.0
SR 33589 B (5.0)	163	1.6	6	3,4.8	3.7	4	1.6,3	2.5
Chlorambucil (2.0)	200	10.1	26	12,14	13.0	18	9,9	9.0
Activated cultures								
DMSO (-)	200	7.8	4	2,2	2.0	2	1,1	1.0
SR 33589 B (12.5)	200	9.2	3	0,3	1.5	0	0,0	0.0
SR 33589 B (25.0)	200	9.3	10	3,7	5.0	5	2,3	2.5
SR 33589 B (35.0)	200	4.7	10	4,6	5.0	6	1,5	3.0
Cyclophosphamide (6.0)	200	10.8	25	11,14	12.5	22	11,11	11.0

$$+ \text{ Mean } \% = \frac{\text{No. aberrant metaphases}}{\text{Total cells scored}} \times 100$$

TABLE 5

Main cytogenetic test - group totals of specific aberrations

Compound (ug/ml)	CTG	CSG	CTB	CTF	CSF	CTE	CSE	P	End	Cells with >1 aberration +g	Cells with >1 aberration -g
24 hour sampling time											
Non-activated cultures											
DMSO (-)	2	0	2	1	2	0	0	0	0	1	1
SR 33589 B (1.25)	4	0	2	0	1	0	0	2	0	0	0
SR 33589 B (2.5)	2	1	2	0	0	0	0	0	0	0	0
SR 33589 B (5.0)	4	1	8	1	3	0	0	2	0	2	2
Chlorambucil (2.0)	14	2	44	0	10	6	0	0	0	12	5
Activated cultures											
DMSO (-)	3	0	3	0	1	0	0	2	0	0	0
SR 33589 B (6.25)	3	0	6	0	0	0	0	3	0	0	0
SR 33589 B (12.5)	6	0	4	0	1	0	0	2	0	0	0
SR 33589 B (25.0)	8	0	3	0	4	0	0	2	0	1	0
Cyclophosphamide (6.0)	19	2	45	2	8	10	0	2	0	12	8
48 hour sampling time											
Non-activated cultures											
DMSO (-)	1	0	7	0	0	0	0	3	0	1	1
SR 33589 B (1.25)	3	0	3	0	1	0	0	0	0	0	0
SR 33589 B (2.5)	3	0	0	0	2	0	0	4	0	0	0
SR 33589 B (5.0)	3	0	2	1	1	0	0	3	0	1	0
Chlorambucil (2.0)	9	0	6	1	13	0	0	0	1	3	2
Activated cultures											
DMSO (-)	3	0	1	1	0	0	0	2	0	1	0
SR 33589 B (12.5)	3	0	0	0	0	0	0	3	0	0	0
SR 33589 B (25.0)	5	0	3	0	2	0	0	6	0	0	0
SR 33589 B (35.0)	3	1	4	2	0	0	0	7	0	0	0
Cyclophosphamide (6.0)	3	0	12	1	9	1	1	3	0	2	2

CTG Chromatid gap
CSG Chromosome gap
CTB Chromatid break
CTF Chromatid fragment
CSF Chromosome fragment
CTE Chromatid exchange
CSE Chromosome exchange
P Polyploid cell
End Endoreduplicated cell
+g All aberration types included
-g All aberration types except gaps included

Main cytogenetic test - statistical analysis of the frequency of chromosomal aberrations - comparison between treated and control groups

Compound		SR 33589 B							CBC	CP
Concentration (ug/ml)		1.25	2.5	5.0	6.25	12.5	25.0	35.0	2.0	6.0
S-9 Mix		-	-	-	+	+	+	+	-	+
24 hour sampling time:										
Including gaps (single-sided test)	p-value	0.500	0.729	0.053	0.400	0.235	0.089	-	<0.001	<0.001
	significance	NS	NS	NS	NS	NS	NS	-	***	***
Excluding gaps (single-sided test)	p-value	0.776	0.892	0.086	0.375	0.500	0.272	-	<0.001	<0.001
	significance	NS	NS	NS	NS	NS	NS	-	***	***
48 hour sampling time:										
Including gaps (single-sided test)	p-value	0.386	0.625	0.363	-	0.776	0.086	0.086	<0.001	<0.001
	significance	NS	NS	NS	-	NS	NS	NS	***	***
Excluding gaps (single-sided test)	p-value	0.638	0.892	0.521	-	1.000	0.225	0.142	0.002	<0.001
	significance	NS	NS	NS	-	NS	NS	NS	**	***

CBC Chlorambucil
CP Cyclophosphamide

NS Not significant, p > 0.05
** Highly significant, 0.01 > p > 0.001
*** Very highly significant, p < 0.001

Study title: Micronucleus test in vivo genotoxicity study by the oral route in the mouse.

Key findings: There was no increase in micronucleated nuclei in the data as presented.

Study no.: Mut0046

Conducting laboratory and location: Sanofi Recherche, Montpelier Cedex, France
Date of study initiation: July 7, 1993
GLP compliance: statement included
QA reports: yes (x) no ( )
Drug, lot #, and % purity: SR33589B batch 92.011-11, purity, suspension in 0.6% methylcellulose
Positive control of cyclophosphamide given intraperitoneally in aqueous solution

Methods

Male and females mice OF1 (UIOPS) were used. The treatment groups are summarized below:

Summary of study design

# of animals per group	# of the first animal	compound	route	Dose mg/kg
10 males 10 females	01 11	0.6% methylcellulose	po	0
5 males 5 females	21 26	endoxan	ip	50
12 males 12 females	31 43	SR33589B	po	2000

Animals were euthanized 24 and 48 hours after dosing. One slide per animal was scored. PCEs and NCEs were counted until 2000 PCEs were analyzed.

Results
No clinical signs, toxicity or mortality were reported for any of the animals treated with SR33589B.

2.6.6.5 Carcinogenicity

The Exec CAC minutes of the dose selection process are attached as Appendix A.
The review of the mouse and rat carcinogenicity studies is included as Appendix B.
The Exec CAC minutes of the assessment of the results are attached as Appendix C.

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

Study title: Preliminary Segment I study in the rat

Key study findings: Estrous cycle irregularity or acyclicity was seen in the drug-treated animals. There were decreased numbers of corpora lutea and subsequently decreased implantations and live fetuses. Males were apparently subject only to macroscopic observations. No data was found regarding sperm count, motility or morphology.

Study no.: FER250
Conducting laboratory and location: Huntingdon Life Sciences, Suffolk, England

Date of study initiation: January 17, 1996
GLP compliance: statement included
QA reports: yes ( ) no ( )
Drug, lot #, and % purity: SR33589B batch 5SNP505 in 0.6% methylcellulose

Methods Doses of 0, 10, 30 and 100 mg/kg/day were given by oral gavage to Sprague-Dawley rats, 6/sex/group. Males received the drug from 15 days before pairing to Day 36 of treatment. Females received the drug from 15 days before pairing to day 7 after mating. Males were euthanized after the females on day 36 of treatment (Day 14 of gestation).

Results

Both sexes showed dose related salivation at doses ≥30 mg/kg/day.
Females at 100 mg/kg showed hairloss on one or more regions of the body.

The HD males gained ~10% less than the control group.

Body weight: males (grams)

Dose mg/kg/day	Week 0	Week 5(final)	
0	334± 10	480±45	146(44%)
10	333± 6	469±18	136(41%)
30	329± 8	468 ±18	139(42%)
100	334± 7	442±22	108(32%)

HD females gained less weight than did the control groups in both the pre-mating period and during gestation.

Body weight: females (grams)

Dose mg/kg/day	Week 0	Week 2	Day of gestation			
			Treatment period			Δ from GD0
			GD0	GD7	GD14	
0	228±7	281±13 53	287±21	329±22	374±26	87(30%)
Δ from base		(23%)				
10	227±5	281±7	293±20	335±16	382±16	89(30%)
30	230±9	280±12	285±13	323±17	374±25	89(31%)
100	230±7	262±14	273±11	297±19	345±21	72(26%)
		32(14%)				

Food consumption was decreased in the HD groups of both sexes in the first 2 weeks of the study. Thereafter food consumption was similar across groups.

The overt effects are summarized below. Five out of 6 of the HD females conceived. The mean number of corpora lutea were decreased at the HD and subsequently the number of implantations and liver fetuses. There was some estrous cycle irregularity in the LD and MD groups.

Summary of main reproduction parameters : total number of litters or mean per litter±SD

	Dose mg/kg/day			
	0	10	30	100
Corpora lutea	18.2±2.0	19.2±2.1	19.3±1.9	14.8±2.6
Implantations	16.3±2.8	16.8±1.7	18.3±2.0	12.0±5.5
Pre-implantation loss %	10.1	12.2	5.2	18.9
Live fetuses	15.2±2.8	15.3±1.8	17.0±1.3	11.2±5.1
Dead fetuses	0	0	0	0
Early resorptions	1.17±1.08	1.50±1.22	1.33±1.15	1.00±1.00
Late resorptions	0	0	0	0
Post-implantation loss%	7.1	8.9	7.3	6.7
Estrous Cycles Arithmetic number (percent)				
Regular 4 or 5 day cycle	6(100)	4(67)	5(83)	6(100)
Irregular cycle [a]	0	1(17)	1(17)	0
Acyclic [b]	0	1(17)	0	0

[a] At least one cycle of two, 3, or six-10 days
[b] At least 10 days without estrous

Study title: Study of effects on fertility and early embryonic development in CD rat by oral gavage administration FER0297

This study was previously reviewed (Amendment 062) by this reviewer. A summary will be provided here.
Doses of 10, 30 and 100 mg/kg/day were used. The same study design was used as in the preliminary study. The highest dose again produced some degree of maternal toxicity as the HD females showed body weight gain 8% lower than that of the control group. Water consumption was increased in the MD and HD males by up to 16% compared to controls. Prior to mating water consumption was increased in all the drug-treated female groups by up to 45%. During gestation, HD females consumed up to 20% more water than the controls.

Other significant findings included the tendency to decreased numbers of regular estrus cycles (significant at the MD and HD levels), consistent with the preliminary study. There was also a non-dose dependent tendency to acyclic females in the drug-treated groups. Consistent with the preliminary study was a decreased number of corpora lutea, implantations and live fetuses. Effects such as decreases in live fetuses, increases in early resorptions and increases in post implantation losses were confined to the HD group and may be associated with maternal toxicity. Pre-implantation loss was increased somewhat. Sperm count and motility as well as weight of testes and epididymides were provided. Sperm count estimates were taken from the vaginal smears at mating. Another table was entitled “Sperm analysis” but it is not clear that this was data was obtained through separate analysis.

Summary of reproduction parameters

	Dose mg/kg			
	0	10	30	100
Corpora lutea	17.1±2.3	17.1±1.8	17.8±2.0	15.7±4.1
implantations	16.0±3.1	16.7±1.7	17.0±2.2	13.5±5.3[a]
Pre-implantation loss %	7.6	3.2	4.8	14.6
Live fetuses	15.5±2.8	15.3±2.6	16.1±2.4	11.7±5.1[a]
Early resorptions	0.55±0.74	1.41±1.19	0.77±0.88	1.80±1.34[a]
Post-implantation loss%	3.4	8.4	4.8	13.3[a]
4 day estrous cycle	20(91)	18(82)	10(45)[b]	11(50) [b]
4/5 day estrous cycle	1(5)	2(9)	4(18)	9(41)[b]
5 day estrous cycle	0	0	4(18)	0
Irregular λ	1(5)	0	0	1(5)
Acyclicψ	0	2(9)	4(18)	1(5)

λ at least one cycle of 2,3 or 6-10 days
ψ at least 10 days without estrous

Pre-coital interval summary : mean (%)

Dose mg/kg # animals	Pre-coital interval (days)				
	1-4	5-8	9-12	13-16	17-21
0 n=22	21(95)	1(5)	0	0	0
10 n=22	22(100)	0	0	0	0
30 n=22	17 (77)	2(9)	2(9)	0	1(5)
100 n=22	15 (68)	7(32)	0	0	0

The female NOAEL was 10 mg/kg/day based upon the body weight effects, decrease in regular cycles and alterations in pre-coital interval.

Embryofetal development

The embryofetal studies (Segment II) were previously reviewed and will be summarized here.

TER0242 Preliminary teratology study in the rat

Doses used: 0, 10, 20, 40, 80, 160 mg/kg/day in 0.6% methylcellulose from GD6-GD15
Mortality was seen at the HD (GD14 and GD15). There was a slight decrease in maternal body weight gain at 80 mg/kg from GD6-GD10 and markedly decreased body weight at 160 mg/kg from GD10 onwards. One case of vaginal bleeding was seen between days 15 and 17 in the HD group.

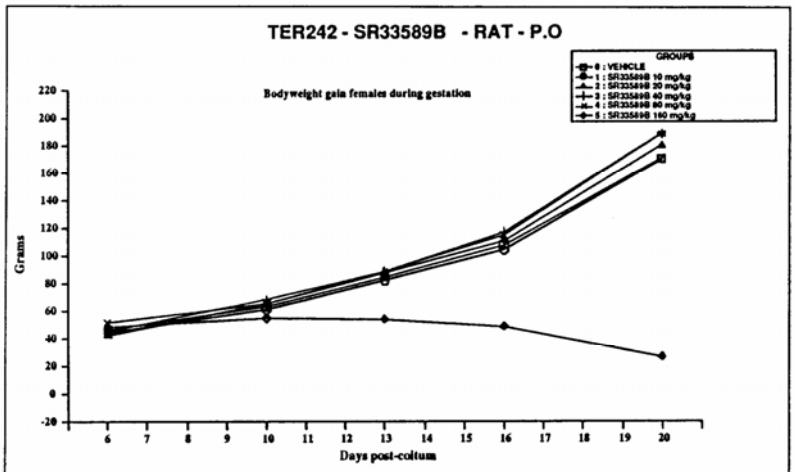

Figure (3.3.1) 1. Body weight gain in females during gestation

The premature decedents in the HD group showed small hemorrhagic thymuses, distended hearts, lungs with grey areas, enlarged hemorrhagic adrenals, meteorism and liquid contents in the GI tract.
The HD group showed slight increases in pre-implantation losses, resorptions and post-implantation loss. Mean fetal weight and placental weight were significantly decreased in this group also.

Fetal malformations were increased at 80 mg/kg/day and at 160 mg/kg/day. In the HD group, 33 fetuses (89%) had at least 1 external abnormality compared to 1 control fetus (1%) and 0 in the 10, 20 40 and 80 mg/kg groups. Several fetuses presented with internal malformations related to sexual differentiation. To quote the sponsor:

> In the control group, 1 fetus out of 92 observed presented a caudal malformation: Anuria, anal imperforation, undifferentiated sexual characteristics (classified as male Fetus).
>
> At 160 mg/kg/d (group 5), 33 of 37 fetuses presented malformations, multiple and often associated together (in 2 of the 3 litters). The main areas concerned were:
>
> - the face (brachygnathia and/or cleft palate)
> - the limbs (anterior and/or posterior clubfeet)
> - the fingers (ectrodactylia and/or syndactylia)
> - the tail (deviations, partial reduction)
> - the anogenital area (undiscernible anogenital space, suspected anogenital fistula, prominent genital papilla). [page 25]

At 160 mg/kg 17 of 18 fetuses examined for skeletal formation showed at least one skeletal malformation: vertebrae, limbs, thoracic cage. The sponsor also noted that fetuses with external malformations also presented with generalized delayed ossification. The internal malformations noted in this group were all related to sexual differentiation and were reported with one particular litter. Three male fetuses showed ectopic testes (gonads in lumbar area). Three female

fetuses had uterine horns around the kidneys, ectopic ovaries (anterior to the kidneys) and 1 fetus had no sexual differentiation and gonads anterior to the kidneys.

At 80 mg/kg malformations were reported for 15 of the 48 fetuses examined. These were primarily of the skeletal system: thoracic cage, limbs and vertebrae. It was also reported that there was an increase in delayed ossification of cervical and thoracic centers and of sternebrae as well. An increased number of asymmetric sternebrae was reported.

The lower doses (≤ 40 mg/kg) did not have malformations. Delayed ossification was observed in cervical and thoracic centers.

Teratologic effects were seen at a maternally toxic dose (160 mg/kg/day) and also with no maternal toxicity(80mg/kg/day).

TER0244 Teratology study in the rat

This study was previously reviewed and is summarized here.
Doses of 0, 10, 30 and 100 mg/kg/day were given in 0.6% methylcellulose from GD6-GD15.
There was a decreased rate of weight gain in the HD group.

Early and late resorptions were increased at the HD as were post-implantation losses.

	Dosage mg/kg/day				Historical control data	
	0	10	30	100	16256 feti	56 studies
# of fetuses (litters examined)	307(22)	324(22)	315(22)	283(22)		
# of male:female fetuses	159:148	149:175	147:168	127:156		
Observations: incidence (# of litters)						
Small fetus <2.80g	1.0(3)	2.5(3)	1.6(3)	33.2(14)	1.45	0.0-4.9
Large fetus <4.10 g	10.1(9)	5.9(9)	10.8(14)	2.5(3)	8.27	0.0-20.8
Shiny fetus	0.3(1)	0.3(1)	0.6(2)	1.8(3)	0.33	0.0-2.7
Mottled fetus syndrome*	0.0(0)	1.5(1)	0.0(0)	0.00(0)	#	#
Severe encephalocele	0.0(0)	0.0(0)	0.0(0)	1.8(2)	0.01	0.0-0.7
Domed head	0.0(0)	0.0(0)	0.0(0)	2.5(2)	0.10	0.0-0.7
Unilateral anophthalmia	0.0(0)	0.3(1)	0.0(0)	1.4(3)	0.01	0.0-0.5
Bilateral anophthalmia	0.0(0)	0.0(0)	0.0(0)	3.2(3)	0.01	0.0-0.4
Unilateral microphthalmia	0.0(0)	0.3(1)	0.0(0)	0.7(2)	0.01	0.0-0.5
Bilateral microphthalmia	0.0(0)	0.0(0)	0.0(0)	1.1(2)	#	#

no record in background control data

	Dosage mg/kg/day				Historical control data	
	0	10	30	100	16256 feti	56 studies
# of fetuses (litters examined)	307(22)	324(22)	315(22)	283(22)		
# of male:female fetuses	159:148	149:175	147:168	127:156		
Observations: incidence (# of litters)						
Pointed/upturned snout	0.0(0)	0.0(0)	0.0(0)	3.2(4)	0.06	0.0-2.2
↓length lower jaw	0.0(0)	0.0(0)	0.0(0)	5.7(5)	#	#
Protruding tongue	0.0(0)	0.0(0)	0.0(0)	0.4(1)	0.02	0.0-1.3
Cleft palate	0.0(0)	0.0(0)	0.0(0)	29.3(10)	#	#
Punctuate dark area/ prom-inent blood vessel on palate	0.3(1)	0.0(0)	0.0(0)	0.4(1)	0.01	0.0-0.3
Edema on body	0.0(0)	0.0(0)	0.0(0)	7.4(6)	0.02	0.0-0.5
Hemorrhage on body	0.0(0)	0.0(0)	0.6(2)	0.7(1)	0.01	0.0-0.3
Umbilical hernia	0.0(0)	0.0(0)	0.0(0)	0.7(1)	0.02	0.0-0.3
Inward curvature of spine at thorax	0.0(0)	0.0(0)	0.0(0)	1.8(1)	#	#

no record in background data

While some of the anomalies listed fall within the range of historical values, all of the defects are found in the same dose group, not distributed amongst all the groups.

	Dosage mg/kg/day				Historical control data	
	0	10	30	100	16256 feti	56 studies
# of fetuses (litters examined)	307(22)	324(22)	315(22)	283(22)		
# of male:female fetuses	159:148	149:175	147:168	127:156		
Observations: incidence (# of litters)						
Unilateral forelimb flexure	0.0(0)	0.0(0)	0.0(0)	1.1(3)	0.02	0.0-3.5
Bilateral forelimb flexure	0.0(0)	0.0(0)	0.0(0)	0.7(2)	0.20	0.0-3.5
forelimbs↓in length/misshapen	0.0(0)	0.0(0)	0.0(0)	1.4(3)	0.01	0.0-3.3
Forepaws misshapen +/or ↓ in size	0.0(0)	0.0(0)	0.0(0)	2.5(2)	#	#
≥2 digits fused	0.0(0)	0.0(0)	0.0(0)	6.7(8)	#	#
Agenesis ≥1 digit	0.0(0)	0.0(0)	0.0(0)	23.7(10)	#	#
↓digital size	0.0(0)	0.0(0)	0.0(0)	0.4(1)	#	#
Hindlimbs ↓ length/misshapen	0.0(0)	0.0(0)	0.0(0)	4.6(5)	#	#
Hindlimbs malrotated	0.0(0)	0.0(0)	0.0(0)	8.5(7)	0.02	0.0-0.6
Tail ↓ in length/kinked/tip curled/rudimentary	0.0(0)	0.0(0)	0.0(0)	37.8(12)	0.01	0.0-0.7

no record in background data

The sponsor's summary of the data indicated that increased fetal effects were reported only in the HD group, associated with maternal toxicity. As noted in the original review:

> …the rats showed maternal toxicity at the HD-100 tested and marked adverse effects on embryo-fetal development. Compared to control, embryo-fetal toxicity induced by the 100 mg/kg/day consisted in statistically significant increase in post-implantation losses ($p<0.05$), reduced fetal/placental

> weights (p<0.001 and p<0.01 respectively), and increased [sic] in the number of rat litters with fetuses showing external, visceral and skeletal malformations (e.g., cranioschisis, cleft palate, incomplete evagination of pineal body, brachygnathia, partially fused carotid arteries, truncus arteriosus, abnormal lobation of the liver, partially duplicated inferior vena cava, brachydactyly, etc.) It should be noted that the structurally related drug amiodarone at 200 mg/kg/day (18X its the [sic] maximum recommended dose) administered to rats during organogenesis was shown to be embryotoxic. This marketed drug is labeled as Pregnancy category D ("… can cause fetal harm when administered to a pregnant woman…").

It was noted in the report for dpn0295, "Study of the effects of SR33589B on pre- and post-natal development" that

> In a preliminary teratology study conducted in the rat [2], females were administered dosages of 0, 10, 20, 40, 80 or 160 mg/kg/d from GD6-15. At a dosage of 160 mg/kg/d, maternal toxicity occurred, including death and decreases in body weight and food consumption. In addition, increases in pre-implantation loss, resorptions, and post-implantation loss were accompanied by decreases in mean fetal body weight, placental weight, and litter size. Upon examination of fetuses, numerous external, skeletal and visceral malformations were observed. At a dosage of 80 mg/kg/d, 30% of the fetuses examined had skeletal malformations, whereas no external malformations were observed. No visceral examinations were performed for the 80 mg/kg/d dosage group.
>
> In the definitive teratology study [3], female rats received dosages of 0, 10, 30 or 100 mg/kg/d from GD6-15. At 100 mg/kg/d, females exhibited decreases in body weight gain and food consumption during the dosing period. A moderate increase in post-implantation loss was noted, as were decreases in litter size, fetal weight, and placental weight. In addition, 198 of 221 fetuses exhibited external, skeletal and/or visceral major malformations. No maternal or fetal effects were seen at dosages of 10 or 30 mg/kg/d.

As terata were seen at a dose of 80 mg/kg with no maternal toxicity, a dose between 30 and 100 might have been useful to define better the NOAEL.

DD0518 13-day oral dose range-finding study in female rabbits

The study is summarized here.

Doses used were 0, 50, 100, 200 mg/kg/day as a suspension in 0.6% methylcellulose given from GD1 to GD13. Rabbits were euthanized GD14. There were no treatment related changes reported for clinical signs, mortality, body weight or food intake. No lesions were reported in the macroscopic examination. Minimal detail was included in this 29 page report.

TER0241Preliminary teratology study in the rabbit

This study was previously reviewed and is summarized here.

Doses of 0, 50, 100, 200 and 400 mg/kg/day were given by oral gavage in 0.6% methylcellulose from GD6 to GD18. Rabbits were euthanized GD28.
Maternal toxicity was seen at the HD. The bodyweight changes for this group were not analyzed. Unscheduled mortality was reported:

0 -
50 1 (day 15), maybe accidental
100 1(day 23) subacute bronchopneumonia
200 1(day 9) subacute bronchopneumonia
400 6 (between day 10 and day 12)

There was a body weight effect at the next lower dose of 200 mg/kg.

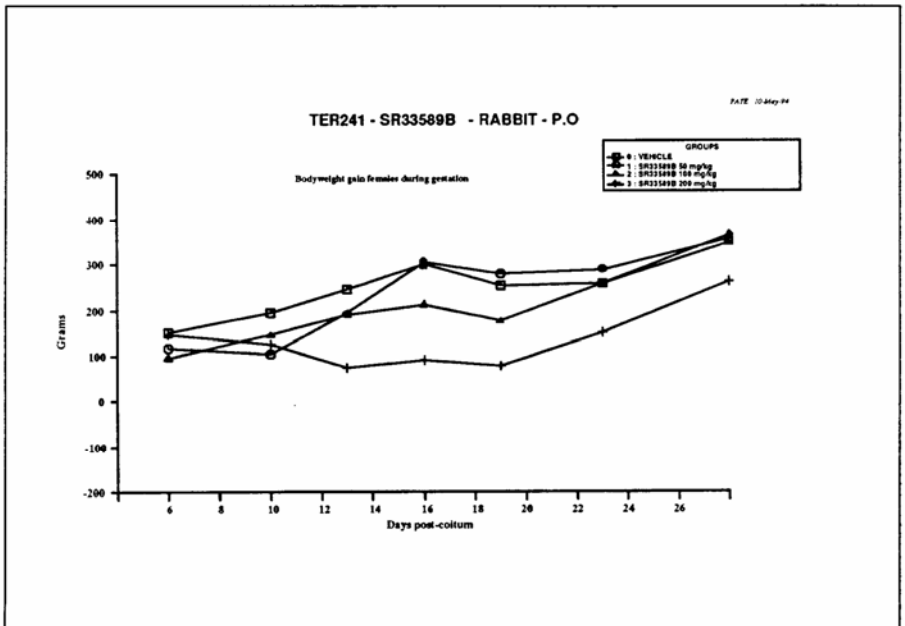

Figure (3.3.1) 1. Bodyweight of females during gestation

Only skeletal and external examinations were performed.
The fetal examinations showed no external or skeletal malformations in the live fetuses. It was reported that no malformations were apparent in the live fetuses. It is not clear from the report how many fetuses were available to make this determination. One dead fetus showed multiple malformations that included abdominal celosomia, absence of caudal formation, fusion of hindlimbs (monopodia) with malformation of digits.

The macroscopic observations on the premature decedent dams included

400 mg/kg: intestinal meteorism, pale heart
≥200 mg/kg lung congestion and hemorrhagic thymus
100 mg/kg vaginal bleeding, pale heart and liver, intestinal meteroism

The study accomplished its goal of determining the HD for the definitive SegII rabbit study.

TER0243 Study of effects on embryo-fetal development in the rabbit.
This study was previously reviewed and is summarized here.

Doses of 0, 20, 60 and 200 mg/kg was given as an oral gavage in 0.6% methocel from GD6 to GD18. Dams were euthanized GD29. Unscheduled mortality was seen in the HD group: 1 HD f was euthanized in extremis and 4 were found dead. Nine out of 18 females in the hd group aborted.

Body weight effects were seen in the MD and HD groups. Food consumption was significantly decreased by 30-73% ($p<0.001$) in the HD group during the treatment period.

A dose related decrease in live fetuses was seen. Post-implantation loss was seen only in the HD group. Pre and post-implantation losses were increased with drug treatment. A non-dose related increase in malformations was reported.

Summary of main reproduction parameters (mean per litter ±SD)

	Dose mg/kg			
	0	20	60	200
Euthanized or found dead before day 29	0	0	1	6[a]
Aborted females	2	0	0	9
Evaluated pregnant females w/ fetuses/mated	18/22	19/22	18/22	5/22
Copora lutea	12.9±2.1	14.1±2.7	12.0±2.5	12.8±2.6
implantations	11.7±2.8	12.1±3.2	10.1±2.7	9.2±1.9
Preimplantation loss %	9.8	14.9	16.6	28.1
Live fetuses	9.4±2.9	9.4±3.2	8.4±3.2	6.0[b]±3.5
Post-implantation loss %	19.9	21.8[c]	16.6	34.8
Weight of fetuses (g)	37.4±2.5	38.6±1.9	40.2±1.9	40.5±2.5
Weight of placenta (g)	4.8±0.3	4.9±0.2	5.3±0.3	5.3±0.3
Main fetal abnormalities				
Multiple malformations of head		3[d]		
Anomalous ribcage + vertebral column		1[e]		1
Anomalous thoracic vertebrae		1[e]		
Brachygnathia and cleft palate			1	

[a] including 2 not-pregnant females; [b] significant compared to the controls $p<0.05$; [c] includes one dead fetus
[d] separate litters; [e] same litter

Two fetuses, both in the 20 mg/kg group but from different litters were grossly abnormal. One fetus showed a proboscis, “reduced” head, both ears pointing forwards, cyclopia, agenesis of the lower jaw and mouth and enlarged and misshapen larynx. The other showed large and misshapen larynx, enlargement and central displacement of both eyes with partially open eyelids, domed head, enlarged snout with agenesis of nares and agenesis of lower jaw with no mouth. The sponsor felt that these animals were affected b y “Froxfield Head Syndrome.”

Both the 20 and 200 mg/kg groups showed an incidence of incomplete ossification of the hyoid body that was elevated compared to current and historical controls. An increased incidence of rib anomalies was also noted in the drug treated groups.

Observations : % fetal incidence (# of litters)	Dose mg/kg				Historical Control data	
	0	20	60	200	1043 feti	11 studies
Incomplete ossification of hyoid body	34.5(14)	42.9 (15)	31.0 (14)	45.0(3)	22.15	6.8-41.9
Asymmetric pelvis	4.7(6)	6.7(9)	6.0 (6)	6.7(1)	5.26	3.6-7.9

There are no clear fetal effects in this study. It is however somewhat troubling that a dose that caused minimal toxicity in the preliminary study caused substantial maternal toxicity in the definitive study.

A maternal NOAEL was 20 mg/kg while the fetal NOAEL is 60 mg/kg/day based upon post-implantation losses. The sponsor felt that 200 mg/kg was a fetal NOAEL but noted that only 5 litters were available to evaluate at this dose.

Prenatal and postnatal development

DPN0295 Study of the effects of SR33589B on pre- and post-natal development (including maternal function) in the rat by oral gavage

This study was previously reviewed and is summarized here.
Doses of 0, 10, 30 and 50 mg/kg/day were given by oral gavage as suspensions in 0.6% methylcellulose. The F0 females were dosed once daily from GD6 to lactation day 20 or day prior to necropsy, whichever was later.
Days of scheduled necropsies:

F1 generation(unselected): PPD4: culled to 5/sex/litter where possible
PPD21-23: males and females not selected for behavioral or Reproductive assessment reduced to 2/sex/litter Where possible.

F1 generation(selected for : Behavioral assessment) PPD67-78 after completion of auditory startle tests

F1 generation(selected for: Reproductive assessment) Females GD20(~20 days after last day of cohabitation) Males PPD118-127 after necropsy of F1 females

Summary of findings in the F0 generation

Observation	Dose mg/kg			
	0	10	30	50
Inseminated females	25	25	25	25
Females delivered (# of litters)	25	24	24	23
Viability index PPD4 (pre-culling)	376/380 (99.1%)	369/378 (97.6%)	388/392 (99.1%)	347/370 (93.8%)
Weight of pups (g) PPD1	6.3±0.1	6.2±0.1	6.1±0.1	5.9±0.1
Weight of pups (g) PPD21	50.9±0.8	48.2±1.1	49.8±1.0	47.6±1.5
F1 generation				
Inseminated females	25	24	23	22
Weight of fetuses (g)	3.26±0.10	3.21±0.05	3.12±0.07	3.12±0.08
Weight of placenta (g)	0.59±0.01	0.55±0.01	0.56±0.01	0.51±0.01*
Observations in F1 pups				
Any variations in the eyes: corneal opacity Litter %	0	0	0	1pup in 1 litter 4%
Malrotated hindlimbs Litter %	0	1 pup in 1 litter 4%	0	0
Small bulgey eyes Litter %	0	0	0	2 pups in 1 litter 4%

*significantly different from control at $p<0.05$

Below is a summary of the times at which the different groups were assessed.

F0 females	
GD0	Day of insemination
GD6-D20 of lactation (or day prior to necropsy)	Tx of F0 females
D21 of lactation (or nearest workday thereafter)	Scheduled necropsy of F0 females that delivered
25 days after presumed GD0	Scheduled necropsy of non-pregnant F0 female
F1 males and Females	
Selected and unselected pups (until weaning)	
PPD1	Day of birth
PPD2	Static righting reflex evaluation begun
PPD4	Litters culled to 5/sex/litter where possible
PPD12	Eye opening evaluation begun
PPD21-23	Weaning. Litter size ↓to 2/sex where possible Scheduled necropsy of unselected pups
Pups selected for behavioral assessment (series 3 and 4)	
PPD28	Vaginal opening evaluation begun
PPD28 (±5 days), PPD35(±5 days)	Passive avoidance test
PPD35	Balanopreputial separation evaluation begun
PPD60 (±5 days)	Auditory startle test
PPD67-78	Scheduled necropsy of males and females
Pups selected for reproductive assessment (series 5 and 6)	
PPD28	Vaginal opening evaluation begun
PPD35	Balanopreputial separation evaluation begun
PPD65(±5days)	Open field motor activity test
≥PPD71	Estrus determination
≥PPD85	Cohabitation
GD0	Day of insemination
GD20	Scheduled necropsy of inseminated females
~20 days after cohabitation	Scheduled necropsy of non-inseminated females
PPD118-127	Scheduled necropsy of males

F1 reproductive performance

There was no apparent effect upon pre-mating estrous cycle and time to insemination data for F1 females, nor upon the course of pregnancy data.

There was a slight increase in resorptions for the mated F1 females

Observations in F1 females Mean±SE (range)

	Dose mg/kg			
	0	10	30	50
resorptions	0.6±0.1 (0-2)	0.8±0.2(0-4)	0.9±0.2(0-4)	1.0±0.3(0-5)
Post-implantation loss%	3.9±0.9 (0-13)	6.1±2.0 (0-33)	5.4±1.5 (0-25)	5.9±1.8 (0-28)
Resorptions %	3.9±0.9 (0-13)	6.1±2.0 (0-33)	5.4±1.5 (0-25)	5.9±1.8 (0-28)

While the F1 offspring of the HD females weighed more than the control group, the ovarian weight was lower.

Body and organ weight data for F1 females (mean±se)

	Dose mg/kg			
	0	10	30	50
Body weight (g)	445.9±8.3	431.6±8.9	441.9±9.4	454.9±8.9
Ovary weight (g)	0.228±0.008	0.204±0.009	0.212±0.009	0.206±0.009

F2 pups weighed (non-significantly) less than the control pups.

Body weight of F2 pups (mean±se)

	Dose mg/kg			
	0	10	30	50
Average male (range)	3.37±0.10 (2.6-5.2)	3.30±0.05 (2.9-3.6)	3.22±0.08 (2.5-3.6)	3.21±0.08 (2.6-3.9)
Average female (range)	3.15±0.10 (2.4-4.9)	3.11±0.05 (2.7-3.5)	3.04±0.07 (2.5-3.4)	3.04±0.08 (2.3-3.6)
Average female placental weight (g)	0.58±0.01	0.55±0.02	0.56±0.02	0.50±0.01*
Average male placental weight (g)	0.60±0.01	0.54±0.01*	0.56±0.01*	0.51±0.01*

*significantly different from control p≤0.05

The gross examination of F2 pups reported only 1 finding in 1 pup in 1 30 mg/kg litter. The one reported finding was encephalocele. The background incidence seems very low.

2.6.6.7 Local tolerance Not reviewed as sponsor is not pursuing an intravenous indication.

2.6.6.8 Special toxicology studies

Study title: A four week oral immunotoxicity study in the rat.

Key study findings:

Study no.: IMM0044/ FSRFU-Imm0044-EN-E01
Conducting laboratory and location: Sanofi-Synthelabo, Montpellier Cedex, France
Date of study initiation: August 25, 2004
GLP compliance: statement included
QA reports: yes (x) no ( )
Drug, lot #, and % purity: SR33589B, batch CL-05754
Formulation/vehicle: 0.6% methylcellulose

Methods
Sprague Dawley rats(10 males/group) were given an oral suspension of dronedarone at doses of 0, 2, 10 and 50 mg/kg. The doses were the same as those used in the 6-month study. Cyclophosphamide was used as a positive control. Animals were treated daily for 28 days, until the day before necropsy. All animals were immunized with keyhole limpet hemocyanin (KLH) on day 15 (primary response) and on day 24 (secondary response). Animals were monitored for signs, mortality, body weight, food consumption, hematology, lymphocyte subpopulations, bone marrow cellularity, IgG and IgM levels.

Results:

There were no effects upon body weight gain. The hematology showed minimal alterations in PCV. The positive control caused a decrease in WBC and marked effects upon the lymphocyte subpopulations. No clinical signs were reported.

Mean log titer values

	Dose mg/kg				
	0	2	10	50	CP
Anti-KLH IgM titer					
Primary response Titer log	3.23	3.05	3.32	2.93	1.90***
Secondary response Titer log	3.41	3.11	3.17	3.29	1.96***
Anti-KLH IgG titer					
Primary response Titer log	3.05	3.20	2.96	2.78	1.53***
Secondary responseTiter log	3.44	3.32	3.29	3.35	2.68***

At the doses used in this study, there were no apparent effects upon the parameters studied. Doses that had caused some kind of clinical signs or alterations in other parameters might have been more informative as to potential immune system effects.

Evaluation of phototoxicity and/or photoallergy in the guinea pig. PHO121-137-141

Three studies were conducted to evaluated the photoxic or photoallergic potential of dronedarone. In the first study, PHO121, a technical problem with the UV lamp made it impossible to complete the experiment. After resolution of the problem the study was started again with the same identified code. The results were presented in this study report. PHO137 was conducted to evaluate the possibility of photosensitization associated with tissue storage. PHO141 was to assess photoxicity and a dose-response if any.

Ten male albino Hartley guinea pigs per group were given oral doses of 10% gum Arabic vehicle or 0.6% methylcellulose, or 30, 100 or 200 mg/kg of dronedarone. The general experimental design for the 3 studies is summarized below.

Veh or control	1st period(photoxicity + induction of photoallergy)			Control of phototoxic disappearance	2nd period photoallergy	
	Dose mg/kg	Days of Treatment	Days UV tx	Days UV irrad w/ no tx	Dose mg/kg	Day tx + irradiation
Lamp contr	-		1,3,7,8,9, 10,11	24, 39, 78	-	92
Gum arabic	100	1,3,7,8,9,10, 11,14	1,3,7,8,9, 10,11	24, 39, 78	30	92
Gum arabic	-				30	92
Lamp contr	-		1,2,28, 29, 30,31, 34,35			58
Gum arabic	-	1,2,3,4,5,6,7 ,8,9,10,13,1 4,15,16,20,2 1,22,23,24,2 7,28,29,30,3 1,34,35			30	58
Gum arabic	30				30	58
Methylcell	-				30	58
methylcell	30				30	58
Lamp contr	-	-	1	15	-	-
Methycell	-	1	1			
methycell	200	1	1			

PHO121

Prior to starting the studies the animals were depilated on the right and left flanks. The UV lamp control group received no treatment.

Other animals received 100 mg/kg in 10% gum Arabic for 7 days (day 1,3,7,8,9,10 and 11) over a period of 11 days. Phototoxic effects were assessed on the first day, the following days corresponding to the period of induction of potential photoallergy. The time interval between drug administration and irradiation was 1 hour. Animals received 1 treatment without irradiation on day 14. The right flank was irradiated. The unirradiated left flank served as a control. This procedure was repeated 7 times on each day of drug administration.

Control of phototoxic effect disappearance

This pertains to persistence of a phototoxic effect. The methods section does not clearly explain what this involved. To quote the report: "…the absence of compound from the animals' organism was controlled after UV irradiation of the skin (without any treatment) on D24, D39 and D78.

Evaluation of photoallergy (second period): The same group of guinea pigs were used for the second period of treatment (day 92) after a treatment free interval of uncertain duration. A group of naïve animals was integrated into the study to serve as control for phototoxicity. Animals were depilated 24 hours prior to irradiation.

Treatments:

UV lamp control with no treatment
Oral treatment (30 mg/kg) 1 hour prior to irradiation (previously treated at 100 mg/kg first period)
Oral treatment (30 mg/kg) 1 hour prior to irradiation (drug naïve, phototoxicity Control)

Left flank received UVB spectrum. Right flank received UVA spectrum.

PHO137(Amiodarone-type protocol)

- Evaluation of phototoxicity and induction of photoallergy (first period)

Animals were depilated.

Treatments (given for 26 days over a period of 35 days):

UV lamp control, no tx
Gum Arabic vehicle
Dosed with 30 mg/kg dronedarone in gum Arabic
Methylcellulose vehicle
Dosed with 30 mg/kg dronedarone in methylcellulose

Phototoxicity assessed the first day, with the following days corresponding to the period of induction of potential photoallergy. There was an interval of 1 hour between dosing and irradiation. The left flank was not irradiated, serving as a control. The procedure was repeated 8 days (D1, D2, D28, D29, D30, D31, D34, D35).

- Evaluation of photoallergy (second period)

The same group of guinea pigs were used for the second treatment period (D58) after a drug-free interval.

Treatments:

UV lamp control, no treatment
2groups got dronedarone in gum Arabic at a dose of 30 mg/kg (1 group served as a phototoxicity control group)
2groups got dronedarone in methylcellulose at a dose of 30 mg/kg (1 group served as a phototoxicity control group)

The left flank received UVB irradiation and the right flank received UVA irradiation.

PH0141 Evaluation of phototoxicity and possible test compound storage at high dose (200 mg)

Treatments:
One group received no treatments
Animals received the oral vehicle
Animals received 200 mg/kg

Animals were exposed to UVA and UVB irradiation on the right flank only. The left flank served as another control. Animals were given 1 treatment on day 1. Animals were "allowed to recover" for approximately 15 days.

Day 15: The animals were exposed to irradiation without treatment. The right flank again received UVA and UVB irradiation while the left flank was unexposed.

The animals used in these 3 protocols were examined for clinical signs, body weight, erythema, cutaneous eruption, edema and hyperkeratosis.

Results

PHO121 at 100 mg/kg: After one administration and one irradiation in the UVA and UVB spectra, a photoxic response was noted in 8/10 animals. During the first period, the phototoxic response was observed during the 6 days of treatment and irradiation. It's not entirely clear how much time without drug the animals were given, but from table (6.2)1 that after a drug clearance phase, several animals were still showing positive reactions to UV irradiation.
Day 25-D40: 0/10 lamp controls had erythema compared to 4/10 drug-treated animals day 25 and 3/10 drug-treated animals day 40.

PHO137 at 30 mg/kg: After 24 days of treatment and 8 days of irradiation, response were not observed which supported a cumulative effect of the drug.

PHO141 at 200 mg/kg: After single treatment and irradiation a phototoxic response was noted in 8/10 animals.

Control of Phototoxic effect disappearance: performed for animals of studies PHO121 and PHO141 as no phototoxic effect was apparent in study PHO137.

PHO121: animals treated at 100 mg/kg during the first period
Day 25: grade 1 reaction in 4/10 guinea pigs
Day 40: grade 1 reaction in 3/10 guinea pigs

Day 79: no reaction reported for any of the guinea pigs

PHO141: animals treated at 200 mg/kg during the first period.
The phototoxic effect was controlled 15 days after cessation of treatment.

The sponsor described the erythematous reactions as being no different between 100 mg/kg and 200 mg/kg doses of dronedarone. The sponsor also makes the comment that the reactions seen in this study cannot be compared to those observed during the study with amiodarone. However, the amiodarone data was not available in the study report and so can't be evaluated. It would have been most helpful to have a side by side comparison of the two drugs, including their UV absorption spectra. The reactions noted were graded 1-2 on a scale of 0-4. Zero was described as no reaction. One was the minimal erythema dose and 2 was well-defined erythema, pale pink.

Study of the hemolytic potential in vitro. HEM0009

Freshly collected baboon blood (Papio ursinus), 0.4ml, was incubated at 37ºC with 0.1 ml test solution for 30 minutes or for 2 hours. Concentrations of drug used were (mg/ml blood): 0.666, 0.333, 0.166, 0.083, 0.041, 0.02 and 0.01. Replicates were not processed. Saline was used as the negative control with saponin as the positive control. The vehicle for the study was 0.01N acetate buffer and 40% PEG400.
Hemolysis % was described as (RBC saline –RBC treated)/(RBC saline). I did not find any description of a standard curve for assessment of how accurate the estimates of hemolysis are.

HEMOLYSIS AFTER 30 MINUTES OF INCUBATION

COMPOUND	mg/ml blood	Hemoglobin (g/l)	Erythrocytes ($10^6/mm^3$)	Hemolysis (%)	Hematocrit (%)	MCV ($micro^3$)
SALINE	0	110	4.63	0	34	73.4
VEHICLE	0	108	4.51	2.6	35	77.6
SAPONIN	0.5	108	2.75	40.6	22	80
	0.2	109	4.29	7.3	36	83.9
SR33589B	0.666	113	0.04	100	0	
	0.333	112	0.44	90.4	Unreadable	
	0.166	107	2.92	36.9	Unreadable	
	0.083	109	4.38	5.3	35	79.9
	0.041	109	4.51	2.6	36	79.8
	0.02	109	4.54	1.9	36	79.3
	0.01	109	4.54	1.9	36	79.3

Results were similar after the 2 hour incubation. Concentrations of drug ≥0.166 mg/ml of blood caused hemolysis equal to or greater than that observed in the presence of 0.2 mg/ml saponin.

RBC compatability:
Two studies were performed using a saponin comparison but not distilled water.

Hemolytic potential in vitro HEM013
Baboon blood (0.4ml) was incubated at 37ºC with 0.1ml test solution for 30 minutes or for 2 hours. The concentrations tested were 0.2, 0.1 and 0.05 mg/ml blood.

Negative control: saline.
Positive control: saponin
Vehicle: acetate/acetic buffer

Summary of hemolysis

Compound	Mg/ml blood	Hemolysis %	
		After 30 minutes	After 2 hours
Saline	0	0	0
vehicle	0	2.6	5
saponin	0.2	2	4
	0.5	44.6	73
SR33589B	0.2	4.6	5
	0.1	0.04	1
	0.05	0	0.7

This study showed that under the conditions used, undiluted formulation of dronedarone induced a hemolytic effect similar to that of the vehicle. This finding did not hold in the in vivo studies.

Study of the hemolytic potential in vitro. HEM0015

In this study, 0.4 ml of human blood was incubated at 37ºC with 0.1 ml test solution for 30minutes or 2 hours. The concentrations of dronedarone tested were 0.2, 0.1 and 0.05 mg/ml blood.
Controls:

Saline
Saponin
Mannitol
Monosidic anhydrous phosphate
Water for injections

Compound	Mg/ml blood	Hemolysis %	
		After 30 minutes	After 2 hours
Saline	0	0	0
Vehicle	0	0.2	3.3
saponin	0.5	57.8	61.1
	0.2	6.1	3.7
SR33589B	0.2	1.4	5.1
	0.1	0.9	1.4
	0.05	0.5	1.2

At 30 minutes of incubation, the hemolysis seen with the drug slightly exceeded that achieved with vehicle alone. After 2 hours of incubation, only the highest dose of drug (undiluted formulation) induced more hemolysis than did the vehicle. The sponsor felt that the hemolysis reported was due only to the excipient.

Study of hemolytic potential in vitro. HEM0026

Human blood, 0.8 ml, was incubated at 37ºC with 0.2 ml test solution for 30 minutes or 2 hours. The concentrations tested were 0.8, 0.4, 0.2, 0.1 and 0.05 mg/ml blood. The vehicle contained hydroxpropyl β-cyclodextrin, D-mannitol, sodium phosphate monobasic and water for injections.

Controls:
Saline
saponin

Summary of hemolytic effects

compound	Mg/ml blood	Diluent	Hemolysis %	
			After 30 minutes	After 2 hours
Isotonic solution	0			
5% glucose serum	0		0	0
Saponin	0.2	EPPI	0	0
	0.5	EPPI	82.7	90.9
Undiluted vehicle	0		0	0
Vehicle dil 1:2	0	Glucose	0	0
SR33589B	0.8		0	1.0
	0.4	glucose	1.0	2.0
	0.2	glucose	0	0
	0.1	glucose	0	0
	0.05	glucose	0	0

Under the conditions of the study, there was slight increase in hemolysis after 2 hours in the 2 highest concentrations of drug. The sponsor attributed this to imprecision in the measurement. In neither of the in vitro hemolysis studies do we see standard curves to assess the range of measurement of the assay. Saponin was included at 2 concentrations but distilled water was not included as the standard positive control.

2.6.6.9 Discussion and Conclusions

2.6.6.10 Tables and Figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

[pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the sponsor]

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: 1) Dronedarone appears to have an undescribed endocrine effect
2) the drug is teratogenic
3)the drug appears to have related carcinogenicity
4) there is a poorly defined effect upon the thyroid gland
5) Target organs of toxicity include the liver, kidneys, gastrointestinal tract and female reproductive tract

Unresolved toxicology issues (if any): 1) Studies are needed for qualification of the impurity SR194090 2) If the sponsor wishes to claim that the mammary tumors are due to a mechanism that is irrelevant to humans, they will need to provide mechanistic data 3)The mechanism by which dronedarone disrupts female cyclicity 4) The receptor binding profile of dronedarone and the major metabolites needs to be investigated. 5) Effect on thyroid hormone turnover.

Recommendations: Approvable based upon clinical considerations and resolution of these issues.

Suggested labeling: See Section I.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

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 /s/
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Elizabeth Hausner
3/3/2006 03:12:55 PM
PHARMACOLOGIST
Elizabeth Hausner


Albert Defelice
3/6/2006 08:05:20 AM
PHARMACOLOGIST
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Memo To The File

NDA number: 21913
Review number: 1
Sequence number/date/type of submission:
Information to sponsor: Yes ( ) No ( )
Sponsor and/or agent: Sanofi-Synthelabo
Manufacturer for drug substance:

Reviewer name: Elizabeth Hausner, DVM
Division name: Division of Cardio-Renal Drug Products
HFD #: 110
Drug:
Trade name: Multac®
Generic name: dronedarone
Relevant INDs/NDAs/DMFs: IND49484

Drug class: antiarrhythmic

Intended clinical population: patients with atrial flutter or atrial fibrillation

In NDA review Part I, the Executive Summary, under Recommendations for nonclinical studies, I listed qualification of impurity SR194090 as something to be done. The review chemist for this NDA advises me that the impurity is not present in the drug product in levels that require qualification. This point is therefore resolved.

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/s/

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3/30/2006 02:39:24 PM
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