Summary Minutes of the
Cardiovascular and Renal Drugs Advisory Committee
March 18, 2009

Location: Marriott Conference Centers, UMUC Inn and Conference Center by Marriott, 3501 University Blvd., East, Adelphi, MD.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information Office.

These summary minutes for the March 18, 2009 Meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration were approved on April 21, 2009.

I certify that I attended the March 18, 2009 meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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Elaine Ferguson M.S.,R.Ph.
Designated Federal Official

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Robert A. Harrington M.D.
Committee Chair

Cardiovascular and Renal Drugs Advisory Committee

March 18, 2009

The following is an internal report which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac

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The Cardiovascular and Renal Drugs Advisory Committee, Center for Drug Evaluation and Research met on March 18, 2009 at the Marriott Conference Centers, UMUC Inn and Conference Center by Marriott, 3501 University Blvd., East, Adelphi, MD. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. There were approximately one hundred and nintey (190) persons in attendance.

Issue: The committee discussed new drug application (NDA) 22-425, dronedarone 400 milligrams oral tablets, Sanofi Aventis, for the proposed indication in patients with a history of, or current atrial fibrillation or atrial flutter, for the reduction of the risk of cardiovascular hospitalization or death.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):

Robert A. Harrington, M.D., F.A.C.C. (Chair), Henry R. Black, M.D. , Sanjay Kaul, M.D., Mori J. Krantz, M.D., F.A.C.C., A. Michael Lincoff, MD, FACC, Darren K. McGuire, M.D., M.H.Sc.,F.A.C.C., James D. Neaton, Ph.D., Emil P. Paganini, M.D., F.A.C.P., F.R.C.P..

Special Government Employee Consultants (Voting):

William Calhoun, M.D., Robert M. Dubbs (Patient Representative), Lewis Nelson, M.D. , Erik R. Swenson, M.D., Sidney M.Wolfe, M.D. (Acting Consumer Representative)

Industry Representative Members Present (Non-Voting):

Jonathan C Fox, MD, PhD, FACC

Guest Speaker (Non-Voting):

None

FDA Participants (Non-Voting):

Robert Temple, M.D., Norman Stockbridge, M.D.

Acting Designated Federal Official:

Elaine Ferguson

Open Public Hearing Speakers: Susan M. Levy, M.D., C.M.D., American Medical Directors Association (AMDA); James Baranski, National Stroke Association; Mellanie True Hills, StopAfib.org & American Foundation for Women's Health

The agenda was as follows:

8:00 a.m.	Call to Order Introduction of Committee	**Robert A. Harrington** Chair, CRDAC
	Conflict of Interest Statement	**Elaine Ferguson, M.S.,R.Ph.** Designated Federal Official, CRDAC
8:05 a.m.	FDA Opening Remarks	**Norman Stockbridge, M.D.** Director, Cardiovascular and Renal Drug Products, CDER
8:15 a.m.	**Sponsor Presentations** Introduction	**Richard Gural, Ph.D.** Sanofi-Aventis
	Unmet Medical need in Patients with Atral Fibrillation/Flutter: Rate and Rhythm Control Studies	**Gerald Naccarelli, M.D.** Hershey Medical Center
	Effect of Dronedarone on Major Cardiovascular Events: The ANDROMEDA and ATHENA Trials	**Milton Packer, M.D.** UT Southwestern Medical Center at Dallas
	Safety of Dronedarone in Atrial Fibrillation/Flutter Trials	**Paul Chew, M.D.** Sanofi-Aventis
	Benefit-Risk of Dronedarone Implications for Patients and Physicians	**John Camm, B.Sc., M.D., F.R.C.P** St. George's, University of London
	Questions to the Sponsor	
10:00 a.m.	**Break**	
10:15 a.m.	**FDA Presentations**	**Abraham Karkowsky, M.D.** Medical Officer, Cardiovascular and Renal Drug Products, CDER
11:00 a.m.	Questions to the FDA	
12:00	**Lunch**	
1:00 p.m.	Open Public Hearing	
2:00 p.m.	Questions to Sponsor and FDA Discussion of questions to committee	
3:30 p.m.	**Break**	
3:15 p.m.	Discussion of questions to committee (continued)	
5:00 p.m.	Adjourn	

Questions to the Committee

The Advisory Committee is asked to opine on the approvability of and appropriate target population for dronedarone for use to decrease the combined risk of cardiovascular hospitalization or death in patients with either a recent history of or current atrial fibrillation or flutter and with "associated risk factors".
Dronedarone was originally submitted as an NDA in 10 June 2005. Based on the results of two placebo-controlled studies ADONIS and EURIDIS, dronedarone delayed the time to the first recurrence of arrhythmia and also decreased symptomatic recurrence of these events in a patient population with a history of either atrial fibrillation or atrial flutter who were in sinus rhythm at the time of randomization.

The application was not approved, largely because of adverse outcomes in ANDROMEDA. ANDROMEDA was a placebo-controlled study of dronedarone 400 mg BID in patients with NYHA Class II-IV and a recent hospitalization for heart failure. Intended to provide reassurance regarding safety in a high-risk population, ANDROMEDA was stopped, with N=627 of a planned enrollment of 1000, for an adverse effect on mortality (25 vs. 12), hospitalization for heart failure (39 vs. 31), and hospitalization for cardiovascular causes (71 vs. 50).

The sponsor then performed ATHENA, placebo-controlled study of dronedarone 400 mg BID in patients who during the last six months had at least one episode of atrial fibrillation or flutter and at least one normal ECG during the same period (in either order). Patients with 'permanent' atrial arrhythmias were precluded from enrollment. Those who were in atrial fibrillation at the time of enrollment were to be converted after a suitable anticoagulation interval. The primary end point was time to first event of cardiovascular hospitalization or death from any cause.

CV hospitalizations or death in ATHENA[*]

	Placebo N=2327	**Dronedarone N=2301**
Any	913	727
Cardiovascular hospitalization	856	669
Death as first event	57	58
Death at any time during study	135	115
[*]As of cut-off date of December 30, 2007.		

There were 25% fewer such events on dronedarone, a difference that was highly statistically significant. The groups separated early and remained separated through 24 months of follow-up. The results were largely homogeneous across a variety of planned subgroups, including US vs. non-US.

1. The sponsor now believes that adverse effects in ANDROMEDA were related to clinical instability of the ANDROMEDA population. Does the Committee find this explanation plausible?

The committee agreed that the explanation was plausible such that it needed to be a treated as a real finding. The committee could not discard the notion that there might be more than one plausible explanation, including the possibility that the finding was chance.

1.1 Causes of death in ANDROMEDA are shown in the table below:

Deaths in ANDROMEDA

	Placebo	Dronedarone
Any	12	25
Cardiovascular	9	24
Heart failure	2	10
Arrhythmia	2	6
(Presumed)	3	5
Myocardial infarction	2	0
Other	0	3
Non-cardiovascular	3	1

Are these differences consistent with the sponsor's hypothesis?

The committee agreed that the differences are consistent with the sponsor's hypothesis.

1.2 In ATHENA, during the pre-specified period of follow-up, there were 135 deaths on placebo (5.8%) and 115 deaths on dronedarone (5.0%; RR=0.86; 95% CI=0.67, 1.11). Are these results compatible with mortality in ANDROMEDA, when you compare …

… confidence limits?
… populations enrolled?
… patient management?

Some committee members expressed that the population's enrolled and patient management were not comparable between the two groups. There was concern that point estimates were in different directions.

Other committee members stated that the results were compatible, that the groups were not dissimilar.

2 ATHENA's planned enrollment was 4300, but the actual enrollment was 4637. Why was that?

The majority of committee members were willing to accept the Sponsors explanation for over enrollment of a trial this size, including additional participants in screening at the sites up to a specified date, once the decision was made to close the study. However it was expressed that the fact that the P value for cardiovascular death changed from being "not significant" at a sample size of 4300 to being "significant" at 4637 warrants additional scrutiny. The sponsor also informed the committee that they didn't have access to the codes, which were held by an outside organization.

3 Some analyses categorized hospitalizations and deaths as cardiovascular or non-cardiovascular. Please comment on …

… the categories of events that were considered cardiovascular or non-cardiovascular.
… the adequacy of the information on the case report form to support categorization.

The committee members agreed that the categorization was flawed and forms were inadequate, resulting in insufficient information.

4 The major categories of cardiovascular hospitalizations are shown in the table below.

Categories of CV hospitalizations in ATHENA

	Placebo N=2327	Dronedarone N=2301
Any	859	675
AF or supraventricular arrhythmia	457	296
Worsened heart failure	92	78
Unstable angina or MI	61	48
Stable angina or atypical chest pain	41	45
TIA or stroke	35	28
ICD or pacemaker	29	32
Arterial procedures	31	27
12 less common categories	113	121

4.1 Is the effect on cardiovascular hospitalizations more than an effect on symptomatic atrial fibrillation?

Two committee members responded yes. No difference in overall numbers, almost entirely accounted for by AF hospitalizations. Hazard ratio's supported the fact that the effect on cardiovascular hospitalizations is mostly driven by atrial fibrillation. Other committee members stated that this is what investigator found to be the primary reason; however, dronedarone has a modest effect on atrial fibrillation recurrence and modest effect on heart rate and they found it hard to believe that these modest effects would impact hospitalizations.

4.2 Are the study results on cardiovascular hospitalization applicable to US practice?

Almost all members agreed that the study results are applicable to US practice. It was noted; however, that there were insufficient numbers of common US minority groups enrolled in the studies including African and Hispanic Americans.

4.3 While heart failure hospitalizations (see above) trended lower on dronedarone (3% vs. 4%), other potential signs of worsening heart failure trended adversely—peripheral edema (6% vs. 5%), fatigue (5% vs. 4%), and dyspnea (5% vs. 4%). How do you reconcile these findings?

These are small absolute variance that can't really be interpreted. The harder endpoint is lower in favor of the drug. Most members agreed that understanding these patients will be more important… knowing the underling reason for their heart failure.

5 Is there an effect of dronedarone on atrial flutter?

Although there was a tick box at baseline for atrial flutter the consensus of the committee seemed to be that clinically you don't want to make a distinction, all moved in the same direction.

6 The secondary end points were arranged to be analyzed sequentially. The first secondary end point was all-cause mortality, which as noted above, trends non-significantly (p=0.25) lower on dronedarone. Thus, one is not entitled to evaluate subsequent end points of cardiovascular hospitalization alone (nominal RR=0.75 and $p << 0.01$) or cardiovascular death (nominal RR=0.70 and p=0.037). However, there was no possibility of getting a claim for all-cause mortality (too broad to be meaningful). Can you ignore all-cause mortality, because it should never have been in the analysis plan, and, if so, is there a reasonable basis for a claim on cardiovascular death?

The committee agreed that they shouldn't get a claim for all-cause mortality and that the quality of the data regarding cardiovascular death is suspect.

7 If you favored a mortality claim in the previous question, are placebo-controlled trials still ethical in this setting?

No one favored a mortality claim.

8 Have dose and regimen been adequately studied? If not, does further study need to be done prior to approval?

Two committee members expressed a strong need for further study prior to approval.

One member suggested more pharmacokinetic and clearance studies in the chronic heart failure population and pharmacokinetic effects when the liver is more or less congested.

9 Who should not receive dronedarone? For each such restriction, please indicate …

… how important it is to restrict use.
… how feasible it is to restrict use.

Dronedarone should not be used if Heart failure class 3 or Low ejection fraction <35%
Restrictions should include clinical instability, limits should reflect severity, and would also restrict due to acuity.

10 How concerned are you about adverse effects of dronedarone on …

… renal function?
… bradycardia?
… QT prolongation?
… heart failure?
… other safety issues?

The following were considered areas of concern by one or more committee members:
Renal function
QT prolongation (less concern was expressed by one member)
Heart failure
Coumadin interactions, better addressed
Digoxin interactions
LFT 2x upper limit of normal (not studied yet)
Most concern about cumulative toxicities, dose and time dependent
Defibrillation thresholds
Lung Function (need for longer term and focused follow-up for pulmonary toxicity by measurement of lung function, particularly diffusing capacity and lung volumes, which are those parameters that are sometimes impaired by amiodarone).

11 VOTE: Should dronedarone be approved to treat patients with non-permanent atrial fibrillation? After the vote, please comment on whether you believe the claim should be any broader or narrower than ATHENA's primary end point.

Vote: 10 yes, 3 no, 0 abstained

Overall the committee members agreed that they would not support a claim for mortality or cardiovascular death.

The committee agreed that the claim should be narrow in scope, prevention of cardiovascular hospitalization driven by atrial fibrillation/flutter.

The committee agreed that there should be a boxed warning for (class III-IV) heart failure patients and one member suggested for severe left ventricular dysfunction.

One member stated that a tolerability claim should not be allowed.