

Cardiovascular and Renal Drugs Advisory Committee Meeting
December 9, 2003

FDA Background

NDA 21-526
Proposed tradename Ranexa (ranolazine)
375 mg and 500 mg tablets
CV Therapeutics

Biopharmaceutical Reviews

(Document redacted for Disclosure)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA : 21526

**SUBMISSION DATES: 12/27/02, 2/12/03, 2/28/03, 4/3/03,
4/4/03, 4/15/03, 4/29/03, 6/25/03,
7/01/03, 7/17/03**

IND: 43735

TYPE: 1-S

BRAND NAME: Ranexa™

GENERIC NAME: Ranolazine

DOSAGE STRENGTH: 375 mg and 500 mg Sustained Release Tablets

SPONSOR: CV Therapeutics

DIVISION OF PHARMACEUTICAL EVALUATION: 1

PRIMARY REVIEWER: Peter H. Hinderling, M.D., Joga Gobburu, Ph.D.

**PHARMACOMETRIC REVIEWERS: Nhi Nguyen, Pharm.D.
Atul Bhattaram, Ph.D.**

TEAM LEADER: Patrick J. Marroum, Ph.D.

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RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-526 and finds the clinical pharmacology and biopharmaceutics sections acceptable provided the labeling comments 1-30 are adequately addressed. The requested biowaiver for the 375 mg dosage strength of the SR tablet is granted.

The sponsor is requested to:

1. As a Phase 4 commitment perform a drug interaction study in healthy volunteers of both genders investigating the potential of ranolazine to inhibit the metabolism of a probe substrate mainly metabolized by CYP 2D6.
2. Change the proposed dissolution specifications according to the FDA recommendation as follows:

The table contains three columns of redacted text. The first column has approximately 7 rows of text. The second column has approximately 5 rows of text. The third column has approximately 5 rows of text. The redaction is complete, obscuring all content within the table boundaries.

COMMENTS:

Issues not addressed by the Sponsor include:

1. The sponsor proposed dose range for ranolazine is 500 mg to 1000 mg bid. Mean maximum QTc prolongations in the range of 0-5 msec are not believed to be associated with an increased risk for TdP and sudden death. The estimated mean maximum QTc prolongations at the 500 mg, 750 mg and 1000 mg dose levels of ranolazine are 2.9 msec, 4.9 msec and 6.3 msec, respectively, for patients without additional risk factors (covariates). Fifteen (15)%, 33% and 44% of the patients receiving 500 mg, 750 mg and 1000 mg ranolazine, respectively, are

predicted to experience maximum QTc prolongations > 5msec. Thus, ranolazine is a QTc prolonging drug.

The sponsor has not studied ranolazine in the appropriate target population with refractory angina pectoris and the effective and safe dose range of ranolazine is uncertain. The sponsor has not addressed the benefit-risk relationship issues arising when doses of ranolazine associated with mean maximum QTc prolongations > 5 msec are administered to the target population. It is uncertain what benefit the patients studied in the pivotal trials CVT 3031 and 3033 receive from ranolazine. The potential risk associated with administration of ranolazine doses associated with maximum QTc prolongations >5 msec is TdP with sudden death. There is a need for demonstrating a clinically relevant benefit of ranolazine to counterbalance the risk associated with doses that prolong the mean QTc at peak by more than 5 msec.

2. The sponsor failed to acknowledge the importantly smaller extent and time duration of the exercise improving effect of ranolazine in women that is evident from the analysis of the relationship between the ranolazine plasma concentrations and the effect on exercise duration. Ranolazine in the dose range between 500 mg and 1500 mg has not been shown to exert a statistically significant exercise improving effect in females. Thus, use of ranolazine in females at dose levels between 500 mg and 1500 mg is at best associated with a marginal exercise improving effect. Ranolazine prolongs the QTc interval in females like in males. An increase of the dose of ranolazine in females by a factor of 3.0 to obtain exercise improving effects like in males would be accompanied by mean peak prolongations of the QTc interval exceeding 10 msec. The sponsor failed to perform a separate analysis of the efficacy data in the better "responding" male population that could have possibly resulted in an improved estimate of the least effective dose and concentration of ranolazine. The impact of gender should be addressed carefully when ranolazine is studied in patients with refractory angina pectoris.

3. In trials RAN 1514 and CVT 3031 the results on the exercise improving effect and plasma concentrations of ranolazine are inconsistent. In study RAN1514 with patients receiving 342 mg ranolazine tid (IR formulation) the effect at peak, at a ranolazine concentration of 2131 ng/mL, was not statistically significantly different from placebo. However, in study CVT 3031 with patients receiving 500 mg ranolazine bid (SR formulation), the mean effect of ranolazine at trough, at a much lower concentration of 864 ng mL, was statistically significantly greater than placebo.

4. In the pivotal trials, CVT Studies 3031 and 3033, the measurement of the exercise improving effect of ranolazine at trough may have been affected by uncontrolled factors. Ranolazine is subject to a circadian rhythm resulting on average in 20 % lower concentrations and consequently smaller exercise improving effects at the evening trough than at the morning trough. However, the exercise treadmill tests (ETT) were performed in the morning in both pivotal trials when the ranolazine concentrations were greater.

Because of a drug interaction, the patients in the second pivotal trial, Study CVT 3033, receiving background therapy with diltiazem 180 mg qd had a 41% increase in the plasma concentrations of ranolazine and consequently a greater exercise improving effect at trough at the end of either dose interval than the patients on background therapy with amlodipine or atenolol. De facto the

patients on diltiazem, received doses of ranolazine that were 1.4 times greater than the nominally administered doses of 750 mg and 1000 mg.

These confounding factors should be taken into consideration when ranolazine is studied in patients with refractory angina pectoris.

5. The submission contained little evidence in support of developing racemic ranolazine.
6. The sponsor failed to include the data of the patients with hepatic impairment in the PK-PD population analysis resulting in imprecise estimates of the slope of the ranolazine concentration to QTc relationship and consequently of the risk associated with administration of ranolazine in this subpopulation.
7. The sponsor failed to determine reliably the extent to which co-administered ranolazine in humans increases the exposure to drugs predominantly metabolized by CYP 2D6.

Comments of Dr. Nguyen to the Sponsor:

1. The sponsor used two different compilers for their population analysis of effectiveness, yet the statistical results from different compilers cannot be directly compared. Most of the models were run using the compiler g77 version 2.95 19990728 release from FSF-g77 version 0.5.25 19990728 release. The final model was run using Compaq Digital Fortran compiler version 6.6 (update A). It is recommended that only one compiler be used for all analysis so that the statistical results can be directly compared.

2. The sponsor used Excel for data manipulation. Software programs with manual manipulation, such as Excel, are highly discouraged for data manipulation because changes to the data set cannot be tracked or reproduced. It is highly recommended that software packages that keep a record of changes to the data set, such as SAS or Splus, be used for data manipulation. The NONMEM data set had two notable problems,

- patients assigned to placebo had measurable plasma concentrations, and
- patients assigned to drug had no plasma concentrations.

It is possible that the samples were mishandled, however, it is also possible that during the data manipulation to create the NONMEM data set, the data were mixed up because manual manipulation was used.

3. On a minor note, in the PK PD analysis plan, the sponsor specified that the bias and precision would be calculated and compared against a pre-specified value. Unfortunately, the pre-specified value is expressed as a percentage while the calculations were absolute differences. A more appropriate method of calculating the bias and (im)precision would have been to consider relative (to observed values) deviations.

4. In the future, the sponsor is strongly encouraged to conduct exposure-toxicity analysis such as that performed by the reviewer

Comments by Dr. Bhattaram to the Sponsor:

1. The use of compilers should be consistently stated in the reports. This would help in checking reproducibility of the results. These should be a part of good modeling practices by the sponsor.
2. It is recommended to perform posterior predictive check (PPC) by matching individuals, sampling times and estimating prediction error. PPC as applied by the sponsor is not a sensitive test for the predictive ability of the model because: (a) The proposed model parameters use covariates. Comparison of AQTc without consideration of these covariates might not ensure rejection of poor models (b) The unexplained variability/patient-to-patient variability is high. Hence, the 10th and 90th percentiles would be unacceptably high to reject poor models.
3. The sponsor is recommended to use 'one model' for explaining the concentration- Δ QTc relationship and provide physiological reasoning to use different models. Use of different mathematical models reduces the applicability of the models in various clinical settings.

OCPB briefing held on September 9, 2003. Attendees were Drs. N. Alderson, N. Stockbridge, S. Targum, S.-M. Huang, M. Mehta, P.I. Lee, J. Hunt, C. Sahajwalla, A. Selen, P. Marroum, J. Gobburu, A. Dorantes, K. Reynolds, L. Cantilena, S. Ortiz, A. Bhattaram, N. Nguyen, L. Cana, P. Jadhav, P. Hinderling

Peter H. Hinderling, MD
Division of Pharmaceutical Evaluation I

FT Initialed by Patrick J. Marroum, Ph.D.

CC list: HFD-110; NDA 21256;HFD 860; Hinderling, Marroum, Sahajwalla, Mehta; CDER
Central Document Room

EXECUTIVE SUMMARY

CV Therapeutics, Inc. is seeking approval for Ranexa for the treatment of chronic angina in patients with severe chronic coronary artery disease in whom other antianginals are inadequate or not tolerated. Ranexa contains ranolazine as active drug substance.

Ranolazine is postulated to exert antianginal and antiischemic effects that are believed to be due to a partial inhibition of fatty acid uptake and oxidation, which reciprocally stimulates glucose oxidation. The proposed dose regimen is 500 mg bid, with upward titration through 750 mg bid to 1000 mg bid as needed, based on clinical response. The drug product to be marketed is a methacrylic acid copolymer based SR tablet of 2 strengths, 375 mg and 500 mg.

Item 6 of NDA 21-526 contains 65 study reports including population PK and PK-PD analyses using the combined database of several studies. This review focused on studies involving the SR formulation (22), but also considered studies using different IR formulations that contained relevant information (7). The remaining studies were not reviewed, because they did not provide additional information. In addition, 8 reports in Item 3 of NDA 21-526 were reviewed that reported the results of in vitro studies with ranolazine using human tissues and proteins or characterized the dissolution of the SR tablet. This review summarizes the results of 4 individual review by Dr. Nguyen focused on the relationship between ranolazine concentration and effectiveness and the review by Dr. Bhattaram concentrated on the relationship between ranolazine concentration and effect on QTc. The pharmacometric reviewers evaluated the PK and PK-PD population analyses performed by the sponsor, reanalyzed the data and remodeled the respective PK-PD relationships of ranolazine. Dr. Gobburu reviewed the reports dealing with bioavailability and biopharmaceutic issues including the in vitro dissolution specifications. Dr. Hinderling reviewed the balance of the reports, summarized the findings of the reviews in the Question based Review, the Executive Summary and the Recommendations for the Labeling.

PK

Healthy Volunteers

Ranolazine is a racemic drug. It is a lipophilic base with a pKa of 7.2. The PK of ranolazine after administration of the SR tablets is not linear and not dose proportional, but the surplus increase in C_{max} and AUC(0-12) when the dose is increased from 500 mg bid to 1500 mg bid is only 17.3% and 36.4%, respectively. The peak to trough ratio ranges between 1.6 - 3.0 and the accumulation factor of the drug after multiple dosing ranges between 1.7 to 1.9. The apparent terminal half life of ranolazine varies between 5.9 hours and 8.9 hours. The evening trough concentrations are on average 20% lower than the morning trough concentrations suggesting a circadian rhythm of the PK of ranolazine. The PK of the (+) R- and (-) S enantiomers in males are similar indicating an absence of stereospecificity. Females were not included in the study and

thus it is unknown whether the same conclusion holds for women. Ranolazine is a drug with high intersubject variation of the exposure parameters (CV: 38% to 76%).

Absorption

Peak concentrations of ranolazine after administration of the SR tablets are reached between 2 hours and 5 hours. The extent of absorption of ranolazine from an aqueous solution is 73.1%. The absolute bioavailability of ranolazine from the SR tablet is not known. The mean bioavailability of ranolazine from the SR tablet relative to that from an aqueous solution is 75.8%. Food has no impact on the bioavailability of ranolazine.

Distribution

The apparent plasma protein binding of ranolazine ranges between 60.9% and 63.9% with a slight tendency to decrease with increasing concentrations. The main binding protein is α 1-acid glycoprotein. The apparent red cell to plasma partition coefficient of ranolazine ranges between 0.620 and 0.879. The mean volume of distribution is 82.9 L.

Elimination

The intravenous clearance of ranolazine is estimated to decrease from 557 ml/min to 403 ml/min when the average concentration of ranolazine increases from 1000 ng/ml at the 500 mg dose level to 3600 ng/mL at the 1500 mg dose level. The true elimination half life of ranolazine determined after intravenous dosing ranges between 1.82 hours to 3.17 hours.

Metabolism and Renal Excretion

After administration of 14 C-ranolazine in aqueous solution total radioactivity declines with an apparent half-life of 40.9 hours and the recoveries in urine and feces amount to 73.13% and 24.46% of the dose, respectively. Only 3.13% of a 500 mg dose is recovered in urine as unchanged drug indicating that ranolazine is eliminated mainly by nonrenal routes. The major circulating metabolites in plasma are RS-88390 (CVT-2514) and its conjugate, RS-94287 (CVT-2738), RS-88640 (CVT-2512) and CVT-4786 with respective AUC's relative to ranolazine ranging between 5.0% and 40.0% (Table 1).

Table 1. PK Parameters of Major Circulating Metabolites of Ranolazine

Metabolites	AUC rel	Ae/D	t1/2, hrs
RS-88390	0.21-0.33	0.03	12
RS-88640	0.05-0.12	0.02	22
RS-94287	0.25-0.27	0.14	11
CVT-4786	0.40	0.12	8

Based on information from in vitro and in vivo metabolic and in vivo drug interaction studies, the main enzymes catalyzing the metabolism of ranolazine include CYP 3A4, CYP 2D6 and sulfatases and glucuronidases. The involvement of Phase I enzymes other than CYP 3A4 and CYP 2D6 cannot be excluded. CYP 3A4 metabolizes the largest fraction of administered ranolazine. The fraction metabolized by CYP 2D6 is substantially smaller. The formation of RS-94287 (CVT-2738) is catalyzed by CYP 3A4. CYP 2D6 is involved in the formation of RS-88390 (CVT-2514). The observed small deviation from dose proportionate kinetics after oral administration appears to be due to saturation of the pathways involving the formation of RS-88640 (CVT-2512) and RS-88390 (CVT-2514) whose AUC values increase less than dose proportionately. Alternatively, product inhibition could be responsible for the observed phenomenon. In vitro data indicate that RS-88390 (CVT-2514) can inhibit CYP 3A4 and the metabolism of ranolazine.

Drug-Interactions

In vitro metabolic studies indicate that ranolazine is a substrate of CYP 3A4 and CYP 2D6 and a substrate/inhibitor of P-glycoprotein capable of interfering with the baso-apical transport of digoxin and statins in MDR1 gene transfected canine kidney cells. Additional in vitro results show that ranolazine can also inhibit the metabolism of statins.

The results of the in vivo drug interaction studies testing the possible impact of other drugs on ranolazine are summarized in the Table 2:

Table 2. Results of Interaction Studies Testing the Impact of Co-administered Drugs on the PK of Ranolazine

Drug	Regimen, mg		Ranolazine		DDI ^a	Signific.
	Drug	Ranolazine	dCmax,% ^b	dAUC,% ^b		
Ketoconazole	200 bid	SR 375 bid	157.1	222.5	yes	yes
Ketoconazole	200 bid	SR 1000 bid	216.0	264.2	yes	yes
Diltiazem	180 qd	SR 1000 bid	190 ^c	116 ^c	yes	yes
			50 ^d	52 ^d	yes	yes
	240 qd	SR 1000 bid	240 ^c	138 ^c	yes	yes
			89 ^d	93 ^d	yes	yes
	360 qd	SR 1000 bid	360 ^c	175 ^c	yes	yes
Diltiazem	60 tid	SR 1000 bid	130 ^d	139 ^d	yes	yes
			49.6 ^c	83.1 ^c	yes	yes
Verapamil	120 tid	SR 750 bid	80.1 ^d	89.9 ^d	yes	yes
			92.2	116.6	yes	yes
Paroxetine	20 qd	SR 1000 bid	17.2	19.4	yes	no
Cimetidine	400 tid	IR 171 tid	12.2	25.0	yes	no
Simvastatin	80 qd	SR 1000 bid	16.5	9.7	no	no
Digoxin	0.125 qd	SR 750 bid	22.2	8.7	possible	no

^a Drug-drug interaction ^b Increase in Cmax or AUC in the presence of other drug
^c Respective percent increase in Cmax and AUC of ranolazine in presence of other drug
^d After first dose of ranolazine ^e After multiple doses of ranolazine

The potent 3A4 inhibitors ketoconazole, diltiazem and verapamil, when co-administered, impact the PK of ranolazine clinically significantly. These in vivo results are in agreement with the in vitro findings indicating that a substantial fraction of ranolazine is metabolized by CYP 3A4. In the case of verapamil an inhibition of the P-glycoprotein transport of ranolazine is also possible.

The impact of diltiazem on ranolazine's PK appears to depend on the dose and formulation of diltiazem. Diltiazem's effect on the exposure measures of ranolazine after an initial dose of ranolazine is greater than after repeated doses of ranolazine. The initial effect of slowly released diltiazem on C_{max} is greater than on AUC. A similar time dependency of the effect on C_{max} of ranolazine was not observed with immediately released diltiazem. The same daily dose of slowly and immediately released diltiazem appear to exert similar effects on C_{max} and AUC of ranolazine at steady state.

Co-administered paroxetine, simvastatin, digoxin and cimetidine have no clinically relevant effects on the PK of ranolazine. The small impact on the PK of ranolazine by paroxetine, a potent CYP 2D6 inhibitor, indicates that a minor fraction of ranolazine is metabolized by this enzyme. Thus, a relevant increase in the exposure to ranolazine is not likely in phenotypically or genotypically poor metabolizers of CYP 2D6.

The results of the in vivo drug interaction studies testing the possible impact of ranolazine on other drugs are summarized in the Table 3:

Table 3. Results of Studies Examining the Possible Impact of Ranolazine on the PK of Other Drugs

Regimens, mg		Drug	Drug		DDI ^a	Signific.
Ranolazine	Drug		dCmax,% ^b	dAUC,% ^b		
SR 750 bid	0.125 qd	Digoxin ^c	68.1	88.4	yes	yes
SR 1000 bic	0.125 qd	Digoxin	45.5	59.5	yes	yes
IR 342 tid	0.250 qd	Digoxin	129.7	38.7	yes	yes
SR 1000 bic	60 tid	Diltiazem	5.3	9.2	yes	no
SR 1000 bic	80 qd	Simvastatin	75.3	60.4	yes	yes
		Simvastatin Acid	128.4	44.0		
		HMG CoA Red. Activity	97.3	60.9		
IR 342 tid	5 ^d	Warfarin				
		(+) R	-12.1	9.5	yes	possible
		(-) S	-10.6	7.4	yes	possible
		PT ^e	42.4	20.1	yes	yes
SR 1000 bic	30 ^d	Dextromethorphan	na ^f	na ^f	yes ^g	possible

^a Drug-drug interaction ^b Increase in Cmax and AUC of other drug in presence of ranolazine
^c CHF patients ^d Single dose administration ^e Prothrombin time
^f not applicable ^g Dextromethorphan/dextrorphan ratio significantly increased, Phase 4 study required

Co-administered ranolazine interacts clinically significantly with simvastatin, digoxin and warfarin. Ranolazine affects the PK of digoxin and simvastatin by increasing the exposure measures of these compounds clinically relevantly. In the presence of ranolazine the effect of warfarin on the prothrombin time is clinically relevantly increased. Ranolazine has no impact on the PK of diltiazem. An IR formulation of ranolazine appears to exert a greater effect on Cmax of digoxin than the SR tablet, but this finding has no bearing since only the SR tablet of ranolazine is proposed for marketing. Ranolazine also increases the dextromethorphan/dextrorphan ratio statistically significantly, suggesting a possible inhibition of CYP 2D6. However, this finding requires confirmation by a better-controlled Phase 4 study.

Of the 10 in vivo drug interaction studies conducted, 9 enrolled healthy male volunteers. One of the 3 interaction studies with ranolazine and digoxin was conducted in CHF patients of both sexes. The inclusion of more women in the drug interaction trials would have been desirable.

The impact of inducers of CYP 3A4 or CYP 2D6 has not been studied in vitro or in vivo.

Patients

Patients with Renal Disease

Relative to control subjects patients with mild, moderate and severe renal impairment showed respective increases in C_{max} of 53.5%, 37.0% and 47.2%. The corresponding increases in AUC relative to control subjects were 17.4%, 59.1% and 73.4%, respectively. Because of the impact of increased C_{max} values on QTc renal impairment is a significant covariate for ranolazine. Patients with severe renal impairment experienced an increase of 10 to 15 mmHg following administration of 500 mg ranolazine bid, indicating that 500 mg is the maximum tolerated dose in this population.

Patients with Hepatic Disease

Relative to control subjects the exposure measures of ranolazine in patients with mild hepatic impairment are not importantly altered. However, patients with moderate liver impairment showed a significant increase in C_{max} and AUC of 74.8% and 89.7%, respectively, relative to control subjects. Both the patients with mild and moderate liver impairment displayed an important increase of the slope of the ranolazine plasma concentration to QTc relationship to 0.00710 sec/1000 ng/mL compared to a slope of 0.00256 sec/1000 ng/mL in subjects without liver disease. Liver impairment is a significant covariate for ranolazine.

Patients with the Target Disease

The PK of ranolazine in typical patients with the target disease and in healthy volunteers are comparable with similar mean concentrations and CV about the means.

Exposure-Response Relationships

Concentration/Response Relationships

The exercise improving effect of ranolazine measured by the exercise treadmill test is non-linearly related to the plasma concentrations of the drug. Gender is a significant covariate for the relationship between ranolazine plasma concentration and effect on exercise duration. Compared to males the concentration-effect curve in females is much flatter with females displaying 28% to 42% of the effect in males at identical ranolazine concentrations. The peak effect of ranolazine in females at the 1500 mg dose level is similar to the trough effect in males at the 500 mg level of ranolazine. Consequently, both extent and time duration of the exercise improving effect are importantly smaller in females than in males and the proposed 12 hour dose interval is clearly inadequate. Ranolazine in the dose range between 500 mg and 1500 mg has not been shown to exert a statistically significant exercise improving effect in females. Thus, administration of ranolazine in females at dose levels between 500 mg and 1500 mg is associated with a marginal effect at best.

The QTc prolonging effect of ranolazine is linearly related to the plasma concentration of the drug. Mean QTc prolongations at peak in the range of 0-5 msec are not believed to be associated

with an increased risk for TdP and sudden death. The predicted mean maximum QTc prolongations at the 500 mg, 750 mg and 1000 mg dose levels are 2.9 msec, 4.9 msec and 6.3 msec, respectively, for patients without risk factors (clinically significant PK and PK-PD covariates). Fifteen (15)%, 33% and 44% of the patients receiving 500 mg, 750 mg and 1000 mg ranolazine, respectively, are predicted to experience QTc prolongations > 5msec. Thus, ranolazine prolongs QTc in the dose range proposed by the sponsor.

The sponsor has not studied ranolazine in the target population with refractory angina pectoris, and the effective and safe dose range of ranolazine is uncertain. The sponsor has not addressed the benefit- risk relationship issues arising when doses of ranolazine associated with QTc prolongations > 5 msec are administered to the target population. It is uncertain what benefit the patients studied in the pivotal trials CVT 3031 and 3033 receive from ranolazine. The potential risk of ranolazine treatments associated with maximum QTc prolongations >5 msec is TdP with sudden death. A substantial benefit must be demonstrated for doses of ranolazine associated with a maximum QTc increase > 5msec to outweigh the risk.

The only significant covariate found in the ranolazine plasma to QTc relationship is hepatic impairment. Patients with hepatic impairment showed a 2.8 fold increase in the slope of the ranolazine plasma concentration to QTc relationship indicating that at an identical plasma concentration of ranolazine the QTc interval in patients with liver disease is about 3 times longer than in patients without normal hepatic function. The ranolazine plasma concentration to QTc effect relationship is similar in males and females.

The relationship between ranolazine concentration and the exercise improving effect is slightly nonlinear. The relationship between ranolazine concentration and effect on QTc is strictly linear. Given that the major circulating metabolites have longer half-lives than the parent drug this finding suggests that ranolazine is the main active moiety. However, a contribution by unidentified metabolites with short half-lives cannot be excluded entirely.

The probability for a prospective patient to experience a syncope or dizziness is related to the plasma concentrations of ranolazine. The probability for a patient to experience a syncope at the 500 mg and 1500 mg dose levels is <1% and 1%, respectively. The probability for a patient to experience dizziness at the same dose levels is 5% and 12%, respectively.

Dose Response Relationships

The identified covariates for the PK of ranolazine, renal impairment and moderate hepatic impairment, increase the exposure and the result is a shift of the dose-efficacy and dose-safety curves to the left. The PK-PD covariate hepatic impairment increases the steepness of the dose-QTc relationship for ranolazine in patients with mild or moderate liver impairment. The covariate female gender flattens the dose-exercise duration curve.

Patients with severe renal impairment showed an increase in diastolic blood pressure of 10-15 mmHg after 500 mg ranolazine bid indicating that this dose constitutes possibly the highest safe dose in this population.

Conclusions and Recommendations for the Labeling

Because the effective and safe dose range of ranolazine in the studied population is uncertain and unknown in patients with refractory angina pectoris definitive statements regarding contraindications and dose adjustments for ranolazine cannot be made.

The submission provides evidence that ranolazine can exert a concentration dependent exercise improving effect in the presence and absence of other antianginals. The submitted data indicate also that ranolazine prolongs the QTc interval dose- and concentration dependently. There is uncertainty about the least effective concentration of ranolazine. Doses in excess of 750 mg ranolazine are associated with mean maximum QTc prolongations > 5 msec in the subjects studied who did not have risk factors. Ranolazine is a QTc prolonging drug.

The exercise improving effect of ranolazine in females is importantly reduced. The exercise improving effect of ranolazine in the dose range between 500 mg and 1500 mg in women has not been shown to be statistically significantly different from placebo. Administration of ranolazine in females at dose levels of 500 mg and 750 mg is associated with a marginal effect at best. It is likely that the data from the "better responding male" subpopulation would have permitted to better estimate extent and time duration of the exercise improving effect of ranolazine at the tested dose levels.

Hepatic impairment increases significantly the sensitivity towards the QTc prolonging effect of ranolazine. Administration of ranolazine to patients on ketoconazole (400 mg/day), diltiazem (180-360 mg/day) or verapamil (360 mg/day) or other potent CYP 3A4 inhibitors increases the exposure to ranolazine clinically importantly. As a consequence the QTc prolongation by ranolazine in the presence of potent CYP 3A4 inhibitors is significantly increased relative to when ranolazine is administered alone.

Renal impairment increases the exposure to ranolazine to a smaller extent. In patients with severe renal impairment 500 mg ranolazine increased diastolic blood pressure by about 10 mmHg to 15 mmHg. Thus, blood pressure should be monitored after initiation of treatment and up-titration of the dose of ranolazine.

The increase in QTc in patients presenting with more than one covariate is proportionate to the product of the individual "increase factors" caused by the PK or PK-PD covariates.

Ranolazine is a drug with high intersubject variation in both PK and PK-PD. Monitoring of the QTc interval before and after initiation of a treatment with ranolazine or after uptitrating the dose is required. But, practicing Cardiologists should realize that with ranolazine QTc monitoring is a tool with very limited sensitivity to detect a true drug related increase in QTc.

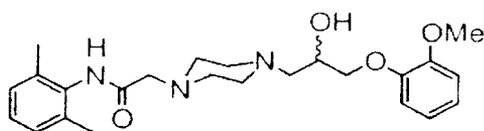
QUESTION BASED REVIEW

1. INTRODUCTION

A. What Are the Highlights of the Chemistry, Formulation and Physical-Chemical Properties of the Drug and Drug Product?

Structure

Ranolazine is (N- (2,6-dimethylphenyl)-2-[4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]piperazinyl]acetamide) or (\pm)-4-[2-hydroxy-3-(O-methoxyphenoxy)propyl]-1-piperazineaceto-2',6'-xylidide and has the structural formula:



The molecular formula of Ranolazine is $C_{24}H_{33}N_3O_4$. Ranolazine has a molecular weight of 427.54.

Formulation and Manufacturing

RanexaTM contains the active ingredient ranolazine (free base). The drug substance is a white to off-white solid. The to be marketed film coated, sustained release (SR) tablets of 375 mg and 500 mg strength are for oral administration.

The composition of the commercial forms of the SR tablets is defined in the following table:

Ingredient	375 mg SR Tablet Quantity (mg/tablet)	500 mg SR Tablet Quantity (mg/tablet)
Core Tablet		
Ranolazine	375.0	500.0
Methacrylic Acid Copolymer (NF)
Microcrystalline Cellulose, NF
Hydroxypropyl Methylcellulose (2910), USP
Sodium Hydroxide, NF
Magnesium Stearate, NF (non-bovine)
Purified Water ^a , USP
Tablet Core Weight (mg)
Film-Coating		
OPADRY YS (Light Blue)
OPADRY (Orange)
Carnauba Wax ^b , NF
Purified Water ^a , USP
Film-Coated Tablet Weight (mg)	515.0	686.7

^a Not a finished product ingredient; removed during processing

^b Trace quantities (0.002 to 0.003% by weight)

The proposed manufacturers for drug substance and drug product for the commercial SR tablets are [REDACTED] respectively. The 375 mg and 500 mg SR tablets will be packaged and labeled by [REDACTED]

Partition Coefficient and Solubility

The pKa values for the monoprotonated and diprotonated forms of ranolazine are 7.2 and 2.2, respectively. Ranolazine is freely soluble in buffered solutions at pH ≤ 4.40. Ranolazine is soluble in dichloromethane and methanol. The apparent octanol/water partition coefficient at pH 7.4 is 117.49.

B. What is the Proposed Mechanism of Action and Therapeutic Indication?

Ranolazine has anti-anginal and anti-ischemic effects that are believed to be due to a partial inhibition of fatty acid uptake and oxidation, which reciprocally stimulates glucose oxidation during periods of ischemic challenge. Ranolazine inhibits enoyl-CoA hydratase and carnitine translocase, enzymes that mediate the beta-oxidation of fatty acids. Ranolazine appears to shift ATP production away from fatty acid oxidation in favor of more oxygen efficient carbohydrate oxidation, thereby reducing oxygen demand without decreasing the ability of the heart to do work. Its antianginal effects appear to be via optimization of myocardial metabolism during ischemia, rather than reduction of work. It is claimed to have minimal effects on blood pressure

and heart rate. CV Therapeutics intends to market ranolazine for the treatment of chronic angina in patients with severe coronary artery disease in whom other anti-anginals are inadequate or not tolerated.

C. What is the Proposed Dosage and Administration?

The proposed dose regimen is 500 mg bid, with upward titration through 750 mg bid to 1000 mg bid as needed, based on clinical response. The mode of administration is oral.

II. CLINICAL PHARMACOLOGY

A. 1. Was there a Reasonable Basis for the Selection of the Clinical Endpoints, Surrogate Endpoints or Biomarkers and were they Measured Properly to Assess Efficacy and Safety in Clinical Pharmacology Studies?

Yes.

The basis for selecting the primary efficacy endpoint, the duration of the symptom limited exercise treadmill test (ETT) at trough, and the biomarker for safety, the QTc interval duration, was reasonable.

Yes.

The primary efficacy and safety endpoints were properly measured.

ETT duration in the angina patients was measured at morning trough (pre-dose, 12 (\pm 0.5) hours after evening dose) and additionally at morning peak (4 (\pm 0.5) hours after the morning dose) in the 2 pivotal trials. The ETT used a modified Bruce protocol. To qualify for participation in the pivotal trials the patients had to be able to exercise between 3 min to 9 min, and the primary reason for stopping had to be moderate severe angina with level 3 pain of the chest pain scale. The 2 baseline ETT values were not to differ by more than 20% or 60 sec.

Twelve Lead ECGs were recorded to measure the QT and RR intervals. The lead with the longest QT interval was selected for determining the interval duration. The QT interval was measured in several studies with healthy volunteers over a 12 hour interval at steady-state with frequent sampling. The QT interval in the target population was recorded at morning trough and peak. The QT intervals at baseline were measured over 24 hours in a few studies in healthy volunteers. In the majority of studies baseline values were only obtained predose. From 1 to 3 complexes were obtained at each time point. The measurements of the QT interval were done manually by blinded Cardiologists of a Core ECG laboratory. Different correction formulae, usually without justification, were applied in the individual studies to correct the QT intervals for heart rate. Precision and accuracy of the QT QTc interval values appeared not to have been a concern in designing the individual studies in healthy volunteers or patients. However, the sponsor conducted a population analysis that investigated the relationship between ranolazine

plasma concentration and the QTc interval using the database from several studies in volunteers and patients. The analysis included an evaluation of the most appropriate heart rate correction procedure.

A.2. Were there Confounding PK Factors that Impacted Potentially the Measurements of the Clinical Endpoints?

Yes.

Ranolazine is subject to a circadian rhythm resulting on average in 20 % lower trough concentrations and consequently smaller exercise improving effects at the evening interval trough than at the morning trough. However, the ETTs were performed in the morning in both pivotal trials. Thus, the extent of the exercise improving effect at the evening trough and consequently the time duration of the effect of ranolazine are unknown.

Because of a drug interaction, the patients in the second pivotal trial receiving background therapy with diltiazem 180 mg qd had a 41% increase in the plasma concentrations of ranolazine and consequently a greater exercise improving effect at trough at the end of either dose interval. De facto the patients on diltiazem, received doses of ranolazine that were 1.4 times greater than the nominally administered doses of 750 mg and 1000 mg. Thus, the extent of the exercise improving effect at the end of either dose interval and consequently the time duration of the effect of ranolazine per se in patients on background therapy with other antianginals are not known.

B. Were the Correct Moieties Identified and Properly Measured to Assess Clinical Pharmacology?

Not entirely.

The 5 major circulating metabolites with AUCs relative to ranolazine of between 5.0% and 40.0% were RS-88390 (CVT-2514) and its conjugate, RS-88390 (CVT-2514), RS-94287 (CVT-2738), CVT-4786 and RS-88640 (CVT-2512). Ranolazine and 3 of the 5 major circulating metabolites RS-88390 (CVT-2514), RS-88640 (CVT-2512) and RS-94287 (CVT-2738), were quantified in plasma and urine in pertinent studies in healthy volunteers and patients with impaired elimination. The conjugate of RS-88390 (CVT-2738) was only determined in the mass balance study. CVT-4786 was measured in the mass balance study (CVT Study 3019) and together with 7 minor metabolites in 5 studies with healthy volunteers and patients with compromised eliminatory capacity using non GLP-assay methods.

The combined evidence accumulating from *in vitro* and *in vivo* studies, suggests that ranolazine is mainly responsible for the exercise improving and QTc prolonging effects.

The (+) R- and (-) S enantiomers of the racemic ranolazine were determined in plasma in a study in male healthy volunteers. The pharmacokinetics of the 2 enantiomers are not stereospecific in

males. Whether the same holds true in females is not known. The pharmacologic and toxic activities of the individual enantiomers in the preclinical database are not well defined. No reports on the pharmacodynamics of the ranolazine enantiomers exist in the clinical database. Assuming that the pharmacokinetics of ranolazine in males and females are not stereospecific a rationale for developing racemic ranolazine is only given if the two enantiomers display identical pharmacodynamics. A difference in pharmacological or toxic activity between the enantiomers results in patients receiving ineffective or toxic drug molecules when the racemate is administered.

Assay Validation

The validation of the assays used in most of the in vitro metabolism studies was incomplete because precision and accuracy estimates from QC samples were not available. However, the results of these reports were accepted because the same, LC/MS/MS method after complete validation was employed to measure ranolazine in the PK samples.

A few early clinical pharmacology studies used a unvalidated HPLC assay with fluorimetric detection to measure ranolazine plasma concentrations. The results of these reports were accepted, because the plasma concentration values reported appeared to agree with those obtained in comparable studies that used a fully validated LC/MS/MS method.

C. What are the Exposure-Response Relationships for Efficacy and Safety?

The population pharmacokinetic model for ranolazine developed by the Sponsor underpredicted the peak plasma concentrations of ranolazine significantly and the parameters were not used to model the PK-PD relationships for ranolazine. Instead, the sponsor conducted a population analysis of the concentration-response relationship with the efficacy and QTc endpoints for ranolazine. The pharmacometric reviewers reanalyzed the data and remodeled the PK-PD relationship for ranolazine and the findings are reported in the following. The individual ETT or Δ QTc data and the corresponding plasma concentrations were used. Δ ETT and Δ QTc values were obtained by subtracting the respective baseline values from ETT or QTc on drug or placebo. $\Delta\Delta$ ETT and $\Delta\Delta$ QTc were obtained by subtracting the placebo value from Δ ETT or Δ QTc.

Additional issues relating to the PK-PD relationship of ranolazine including potential evidence for a carry over effect in pivotal study CVT 3031, potential outlier status of a center in pivotal study CVT 3033 and alternative dosing schedules were brought up by the medical reviewers of the ranolazine team and are also addressed below.

1. Efficacy

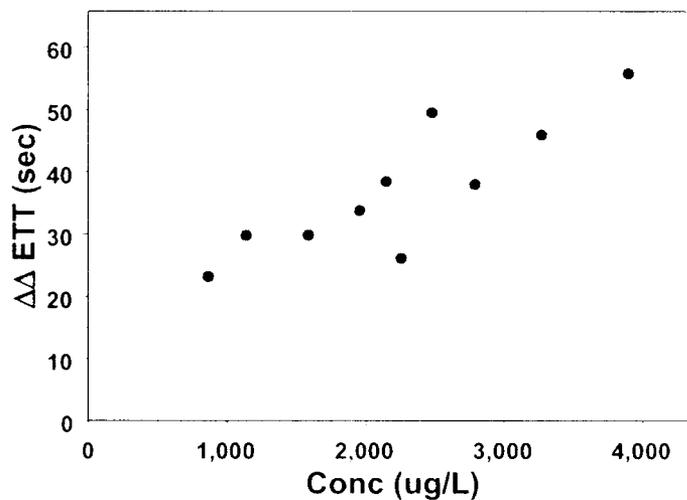
1.1 Ranolazine Plasma Concentration-ETT Relationship

1.1.1 What are the Characteristics of the Relationship between Ranolazine Plasma Concentration and Effect on ETT?

The relationship is slightly nonlinear and gender is a significant covariate.

The observed mean $\Delta\Delta\text{ETT}$ values increase with increasing steady state peak and trough concentrations over the tested dose range of 500 mg to 1500 mg ranolazine bid as shown in Figure 1.

Figure 1. Linear Plot of Observed Mean $\Delta\Delta\text{ETT}$ at Peak and Trough versus the Corresponding Observed Mean Plasma Concentrations of Ranolazine in Pivotal Studies CVT 3031 and 3033



Using a population analysis the reviewer modeled the relationship between ranolazine plasma concentrations and ETT of the individuals using linear and nonlinear models. An empirical nonlinear Emax model predicted the observed data generally more precisely and underestimated the 500 mg ETT data of study 3031 significantly less than a linear model and thus is considered the final model. Gender is a significant covariate as evidenced by the vastly different respective EC50 values of 2400 ng/mL and 10980 ng/mL in males and females. Gender also impacted the baseline value with males walking longer than females. A drug independent learning effect with the subjects walking longer in successive ETTs was apparent from the patients receiving placebo treatment and is considered in the model. Subjects with CHF showed a smaller learning effect than subjects without CHF. The predicted exposure-response relationship and the $\Delta\Delta\text{ETT}$ values for males and females are shown in Figure 2 and Table 1, respectively.

Figure 2. Pharmacometric Reviewers Model Predicted and Observed Mean $\Delta\Delta$ ETT Values

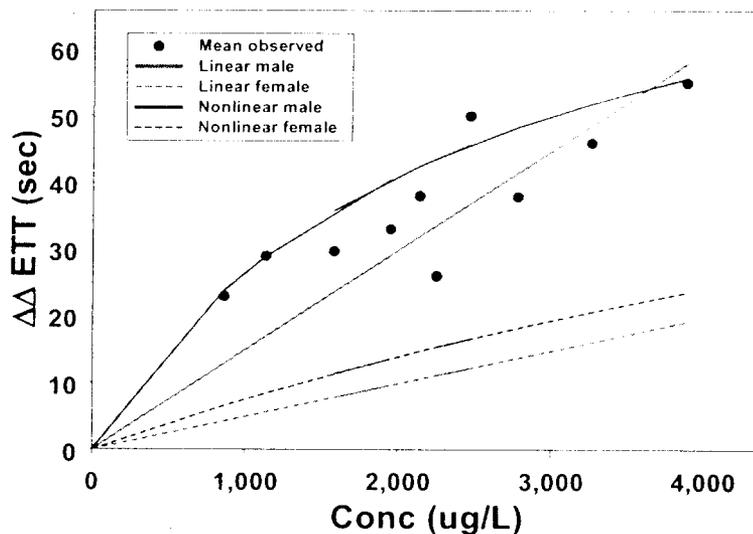


Table 1. Reviewer's Final Model Predicted Peak and Trough Mean $\Delta\Delta$ ETT(seconds)

	Males		Females	
	Trough	Peak	Trough	Peak
500 mg SR q 12h – CVT 3031	23.8	28.9	6.6	8.4
750 mg SR q 12h – CVT 3033	35.8	42.5	11.4	14.7
1000 mg SR q 12h – CVT 3031	40.4	45.7	13.6	16.5
1000 mg SR q 12h – CVT 3033	43.6	48.3	15.3	18.2
1500 mg SR q 12h – CVT 3031	51.9	55.7	20.6	23.5

Table 1 indicates that the $\Delta\Delta$ ETT values in females are significantly smaller than in males. At identical doses and concentrations the effects in females are between 27.7% and 42.2 % of those in males. The peak effect in females at the 1500 mg dose level is similar to the trough effect in males at the 500 mg level. Ranolazine in the dose range between 500 mg and 1500 mg bid is unlikely to exert an effect that is statistically significantly different from placebo. In order to put the exercise improving effect of ranolazine in both genders in perspective it should be noted that the maximum observed drug effect of ranolazine in males and females represents only 29% and 12 %, respectively, of the learning effect.

1.1.2 Do Differences in Baseline Walking Time or Learning Capacity Affect $\Delta\Delta$ ETT Relevantly?

No.

$\Delta\Delta\text{ETT}$ at trough expressed as percent increase in walking time in a typical females increases from 27.7 % to 31.0 % of that in a typical male at the 500 mg dose level when the difference in baseline walking between the genders is considered.

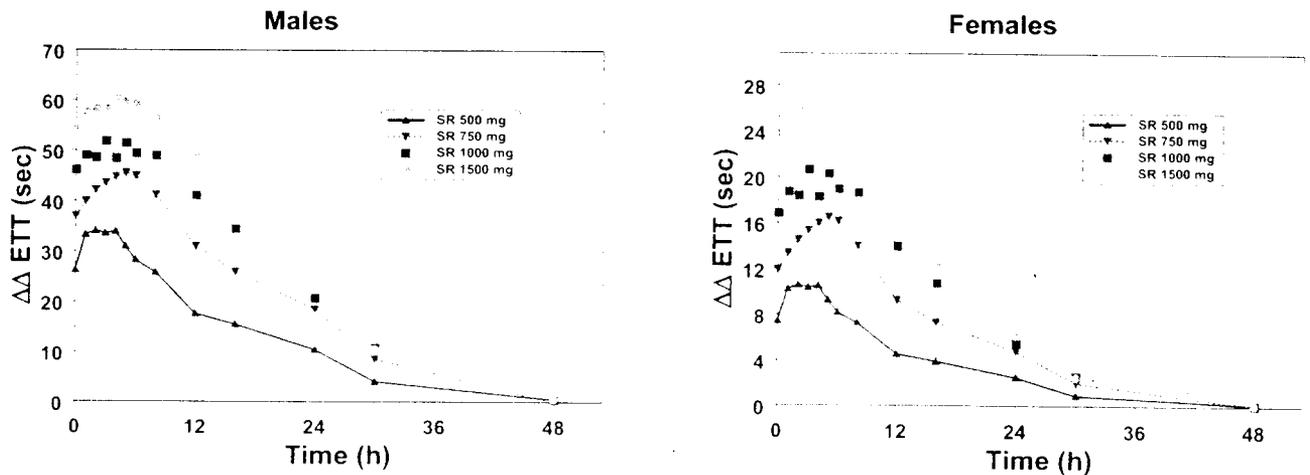
The percent increase in walking time in patients with CHF relative to patients without CHF is only 0.4 %, if the difference in learning is considered.

1.1.3 What are the Factors Impacting Time Course and Time Duration of Ranolazine's Effect on $\Delta\Delta\text{ETT}$?

The factors are gender and ranolazine dose.

The time course of ranolazine's effect on $\Delta\Delta\text{ETT}$ by ranolazine in males and females is shown in Figure 3:

Figure 3. Model Predicted Time Course of $\Delta\Delta\text{ETT}$ at Steady State for Ranolazine Doses Ranging between 500 mg to 1500 mg Administered every 12 Hours (Note the Difference in the Scale of the y-Axes in Males and Females)



The mean time to 50 % reduction of the peak effect is about 8 hours at the 500 mg dose level and increases to about 16 hours at the 750 mg, 1000 mg and 1500 mg dose levels in males. In

females the mean time to 50% reduction of the effect on $\Delta\Delta\text{ETT}$ at all 4 dose levels is about 6 hours to 10 hours. The model predicted effect on $\Delta\Delta\text{ETT}$ at the end of the night trough (0 hour) is greater (up to about 60%) than at the end of day trough (12 hour). This may be caused by a circadian rhythm in the pharmacokinetics of ranolazine with greater concentrations at the end of the night trough in the morning than at the end of the day trough in the evening. It is noteworthy that in the other studies the difference between the two trough concentrations was on average about 20% and thus, the difference in the effect on $\Delta\Delta\text{ETT}$ between morning and evening trough is accordingly smaller.

1.1.4 Is the 12 Hour Dose Interval Optimal For Ranolazine?

Not, if the sensitivity of the typical patient for incurring an angina attack is time dependent and antianginal protection is not required during specified time intervals.

The incidence of angina and other cardiovascular events is reportedly maximal in the morning hours (8 a.m. to 12 a.m.) (1-3). In order to have peak concentrations and antianginal effects of ranolazine occur during the 8 a.m. to 12 a.m. time interval the optimal dose regimen for ranolazine would include a 8 hour dose interval during the night and a 16 hour dose interval during the day. This is demonstrated by the simulations shown in Figures 5 and 6 for the 500 mg dose level:

Figure 5. Simulation Predicted Mean $\Delta\Delta\text{ETT}$ Values for 500 mg bid Regimens with Uneven Dose Intervals for Males (Left) and Females (Right)

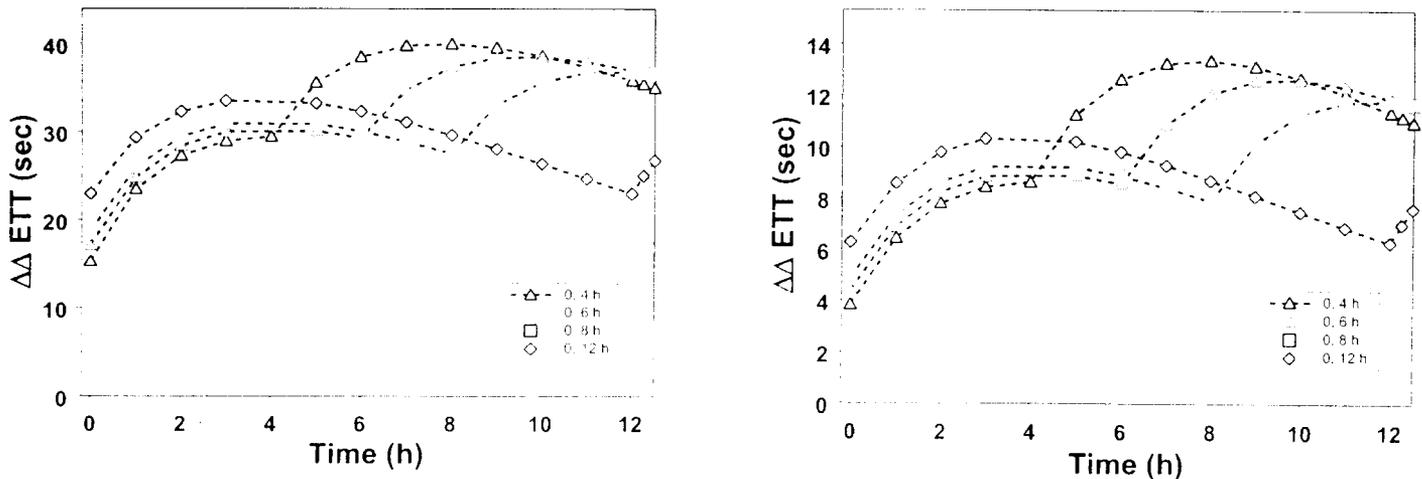
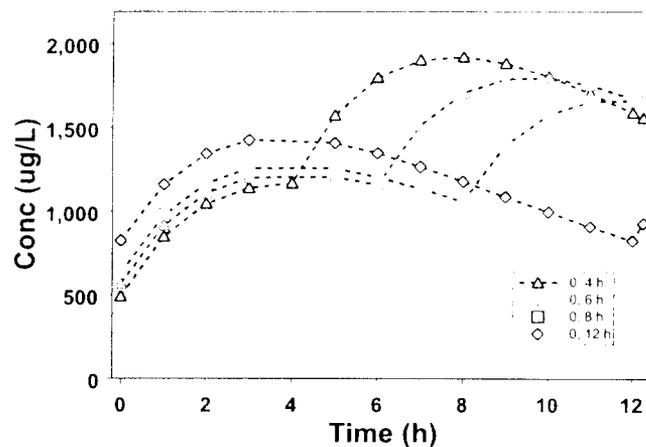


Figure 6. Simulation Predicted Mean Concentrations of Ranolazine for 500 mg bid Regimens with Uneven Dose Intervals



The simulations did not consider the presence of a circadian rhythm. In the optimal uneven dose interval scenario patients would take ranolazine at 10 p.m. and at 6 a.m. The disadvantage of this regimen is that at the 500 mg dose level ineffective trough concentrations are occurring during the time interval between 5 p.m. to 10 p.m. regimen. The regimen with uneven dose intervals at the 750 mg dose level of ranolazine would exert QTc prolongations > 5 msec. Other bid dose regimens with uneven dose intervals (4 and 20 hours or 6 and 18 hours) also shown in Figures 5 and 6 are inferior. They are impractical and associated with exaggerated swings between peak and trough concentrations.

1.1.5 Do Concomitant Medications Significantly Affect the Relationship between Ranolazine Concentration and $\Delta\Delta\text{ETT}$?

No.

Atenolol and other beta-blockers, diltiazem, verapamil, amlodipine and other calcium-channel blockers and nitrates do not have a significant impact.

1.1.6 Is there Evidence for a Carry-Over Effect in the Relationship between Ranolazine Concentration and $\Delta\Delta\text{ETT}$ in Study CVT 3031?

No.

Separate population analyses of the studies with a cross over design without washout periods (Studies CVT 3031, RAN080, RAN1514) or a parallel design (Study CVT 3033) showed that inclusion of a drug effect in the model improved the prediction significantly. This finding signaled a high correlation between ranolazine concentration and effect on ETT that would not be expected in the presence of a carry over effect in cross over studies when the concentration-effect relationship is modeled using a monotonous function. Also, the EC50 values for ranolazine in the studies, independent of their design, were similar. These results did not support the presence of a carryover effect that affected the relationship between ranolazine concentration and effect on ETT.

A possible source for the carry over effect found by the Statistical Reviewer in the analysis of Study CVT 3031 with a cross-over design is the learning effect that enabled patients on placebo to increase the walking time in consecutive ETTs. This learning effect was taken into consideration in the model used by the Pharmacometric Reviewer. The learning capacity was modeled using an Emax model (L50 = 8 to 12 days, Lmax = 3.19 min). Since the learning effect is sizeable and evolves slowly over time it is likely to have impacted the ETT measurements taken at the end of the approximately 7 day long treatment periods in Study CVT 3031.

Other potential causes for a carry-over effect include pharmacokinetic and pharmacodynamic properties of the drug and/or its metabolites. The pharmacokinetics of ranolazine are characterized by a short mean apparent half life of about 7 hours that appears not to change importantly with dose. The pharmacodynamics are characterized by a dose dependent time to 50% of the peak effect, t50. The t50 value at the 1500 mg dose level does not exceed 16 hours. Thus, at the end of a 7-day dosing period little, if any, drug or drug effect remains that could impact subsequent treatment periods importantly in studies CVT 3031, RAN080, RAN1514 with cross-over designs.

1.1.7 Does Russian Center 710 in Study CVT 3033 Impact the Relationship between Ranolazine Plasma Concentration and Δ ETT Significantly?

No.

A significant correlation between drug concentration and Δ ETT remained after removing the data of Russian Center 710 from the database and the EC50 values were similar before (EC50=2400 ng/mL and 10'980 ng/mL in males and females, respectively) and after removal (EC50=2690 ng/mL and 11'000 ng/mL in males and females, respectively) of the data from that center. Thus, the respective concentration- Δ ETT relationships in Russian center 710 and the other centers of Study 3033 combined were similar. This result suggested that other causes must account for the "outlier" status assigned to the center based on consideration of the steeper dose-response curve found. Factors responsible for a shift of the dose-response relationship in Russian center 710 could be higher concentrations of ranolazine. There was evidence for a doubling of the ranolazine concentrations in the lowest quartile of the observed concentration range in patients of the Russian center 710 compared to the patients of the other centers combined.

2. Safety

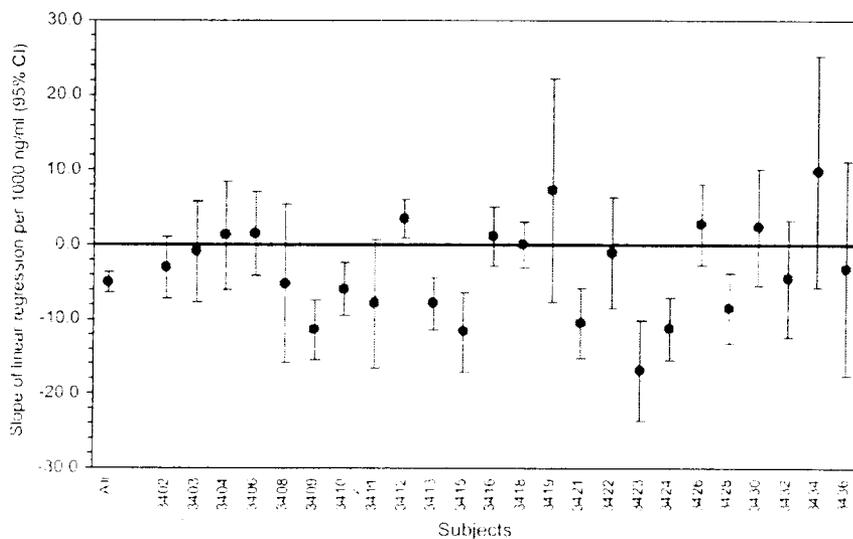
2.1. Plasma Concentration-QTc Effect Relationship

2.1.1 Does Ranolazine have an Effect on Heart Rate?

No.

Figure 7 shows a plot of the individual and average slopes of linear regressions of Δ RR on ranolazine concentrations:

Figure 7. Plot of Averaged and Individual Slopes of the Regressions of Δ RR on Ranolazine Concentration



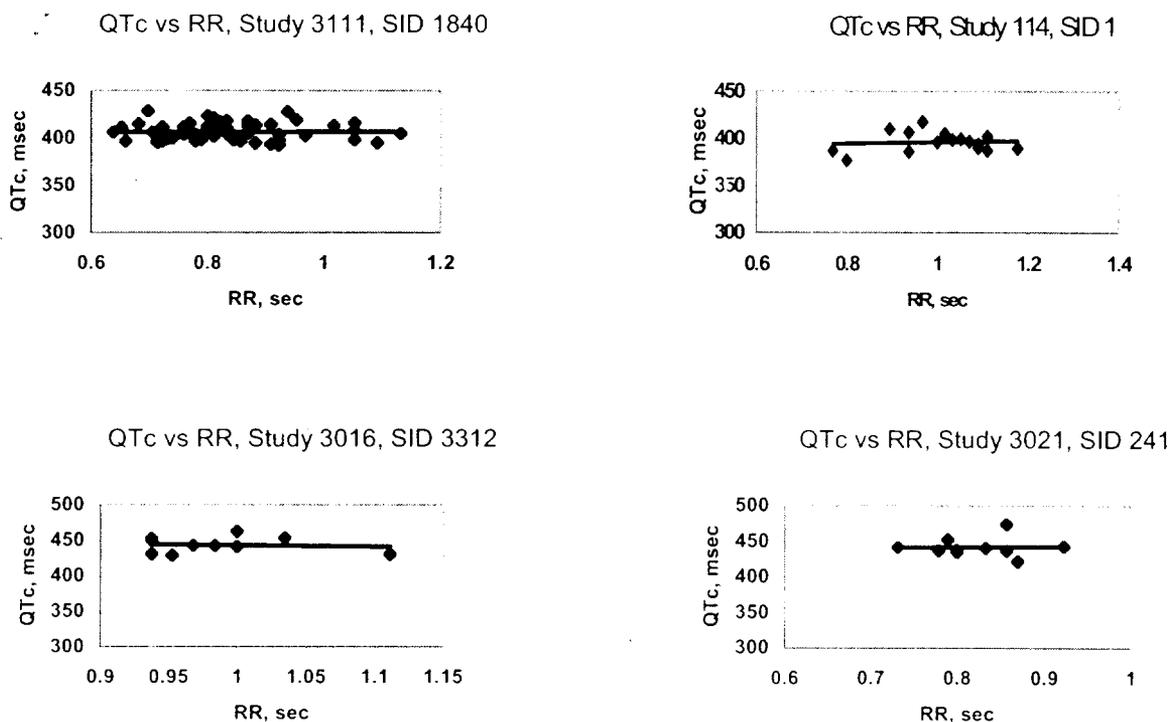
The average slope is -5 msec/1000 ng/mL indicating a negligible effect of ranolazine on heart rate.

2.1.2 What is the Best Procedure to Correct QT for Heart Rate?

Use of individual correction factors.

Use of an individual correction factor β in the formula $QTc = \alpha \cdot QT/RR^\beta$ reduced the intersubject variation best as shown in Figure 8.

Figure 8. Plots of the QTc against RR in Representative Subjects Using An Individual Correction Factor β

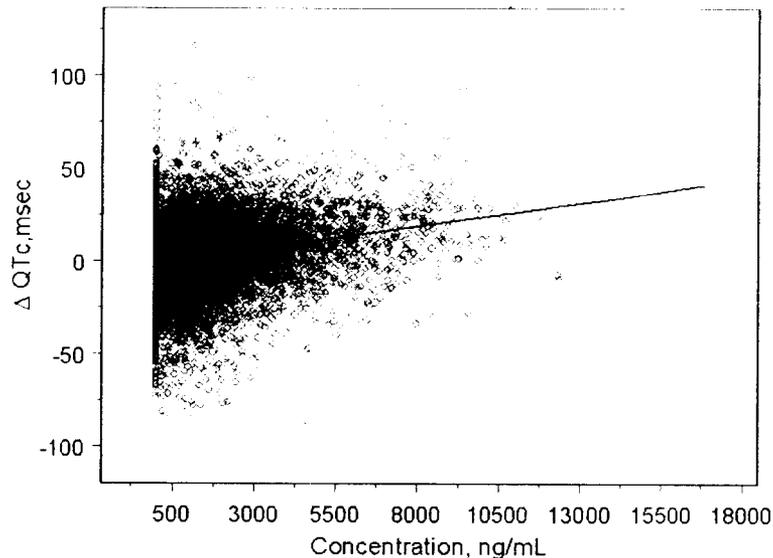


2.1.3. What are the Characteristics of the Relationship between Ranolazine and the Effect on QTc and what are the Factors affecting this Relationship?

The relationship is linear and the only significant covariate is hepatic impairment.

The relationship is linear with a slope of 0.00256 msec/1000 ng/mL as shown in Figure 9:

Figure 9. Linear Plot of ΔQ_Tc against Ranolazine Concentrations



The only significant covariate identified is hepatic disease. The slope is increased to 0.00710 msec/1000 ng/mL in patients with mild or moderate hepatic impairment (Child-Pugh A or B). This corresponds to a 2.8 fold mean increase. Gender, renal disease, CHF or diabetes does not impact the relationship significantly.

Possible causes for the steeper slope of the ranolazine concentration- Q_Tc curve in subjects with hepatic impairment include 1) Hypokalemia and/or hypomagnesemia 2) Increased exposure to a metabolite more potent than the parent drug 3) Pathophysiology associated with hepatic impairment.

Of the possible causes hypokalemia, known to be associated with increased Q_Tc interval duration, can be excluded. All 16 subjects (5 females and 11 males) with hepatic impairment had normal potassium levels. Magnesium levels were not measured.

Among the identified 11 metabolites only RS-89983 showed an increase in exposure, but only in subjects with moderately impaired liver function. The AUC ratio of RS-89983 to ranolazine remained unchanged. The exposure to ranolazine in the subjects with mild hepatic impairment relative to healthy subjects was not importantly increased. Thus, the hypothesis of an increased exposure to a metabolite more potent than ranolazine is not plausible.

Based on the available information pathophysiological changes including hypomagnesemia associated with liver impairment appeared to be most likely responsible for the observed increased sensitivity to ranolazine's QTc prolonging activity in patients with liver impairment.

2.1.4 What is the Time Course of $\Delta\Delta\text{QTc}$?

Because of the linear relationship between effect on $\Delta\Delta\text{QTc}$ and ranolazine concentration the time course of $\Delta\Delta\text{QTc}$ and the plasma concentrations mirror each other. The time to 50% of the peak effect is about 8 hours and dose independent. Figure 10 shows the time course of $\Delta\Delta\text{QTc}$ during a 12 hour dose interval at steady-state and after cessation of treatment for dose levels of 500 mg to 1500 mg of ranolazine administered every 12 hours.

Figure 10. Linear Plot of the Time Course of $\Delta\Delta\text{QTc}$ at Steady State and after Cessation of Treatment at Doses of 500 mg to 1500 mg Ranolazine administered every 12 Hours to Healthy Male Volunteers

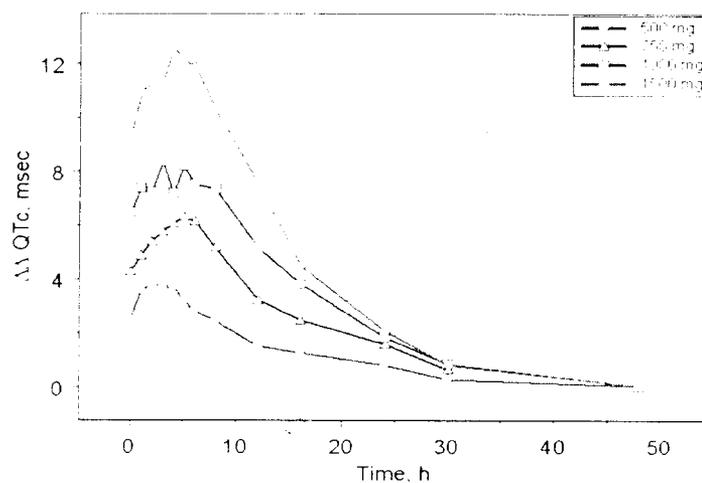


Figure 10 indicates that t50 of ranolazine's effect on QTc is 6 hours to 8 hours and in the range of the apparent terminal half life of ranolazine.

2.1.4. Do Safety Endpoints Other than the QTc Interval show a Dependency on Ranolazine Concentration?

Yes, syncope and dizziness.

The probability of experiencing a syncope or dizziness increases with increasing concentrations of ranolazine as shown in Figures 11 and 12:

Figure 11. Linear Plot of the Probability of a Patient to incur a Syncope against Ranolazine Plasma Concentration

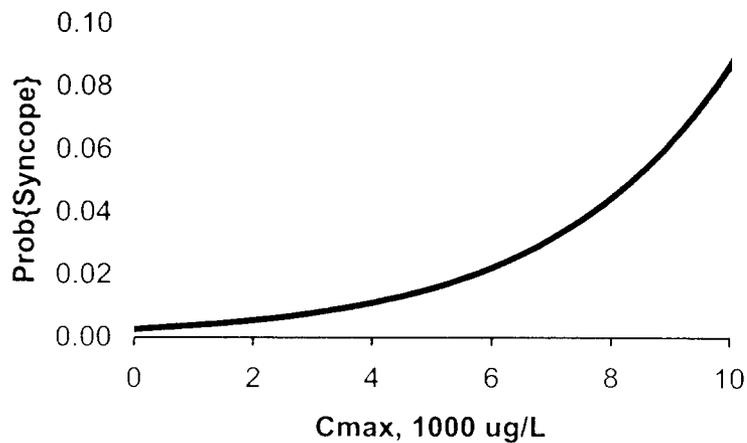
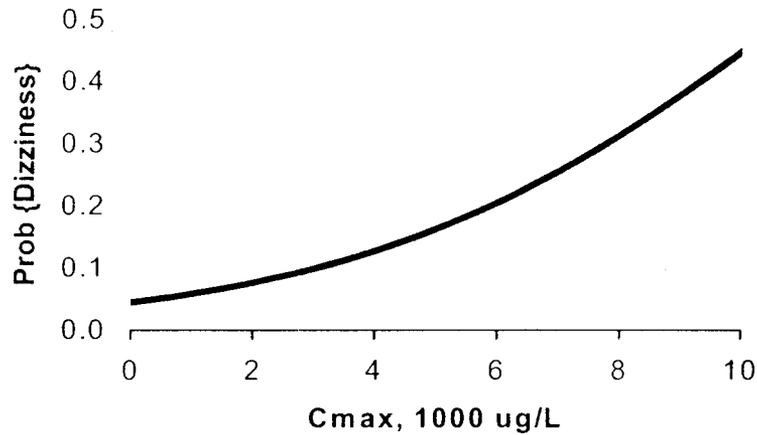


Figure 12. Linear Plot of the Probability of a Patient to incur Dizziness against Ranolazine Plasma Concentration



The mean peak concentrations after administration of 500 mg or 1500 mg ranolazine bid in study 3031 were about 1150 ng/mL and 3900 ng/mL, respectively. The probability of experiencing a syncope at the 500 mg dose level of ranolazine is about 0.5% and increases to about 1% at the 1500 mg dose level.

The probability of experiencing dizziness at the 500 mg dose level of ranolazine is about 5% and increases to about 12% at the 1500 mg dose level.

Asthenia, an AE reported often in subjects receiving ranolazine, was not found to depend significantly on the plasma concentration of ranolazine.

1. Which Intrinsic Factors Affect the Dose-Response Relationship for Both Efficacy and Safety?

Renal and hepatic impairment.

Renal and hepatic impairment impact the PK of ranolazine and increase Cmax and consequently shift the dose-response relationship for $\Delta\Delta\text{ETT}$ and $\Delta\Delta\text{QTc}$ to the left in patients presenting with one of these intrinsic covariates.

3.1 Which Factors Affect the Dose-Response Relationship for Efficacy?

Gender.

The ranolazine concentration- $\Delta\Delta$ ETT curve in females is by 58% to 72% flatter resulting in a significantly decreased extent and time duration of effect compared to males.

3.2 Which Factors Affect the Dose-Response Relationship for Safety?

Hepatic disease.

Relative to subjects without hepatic disease the dose-response curve for the QTc interval in subjects with hepatic disease is steeper. This is the result of the importantly increased slope of the ranolazine concentration-QTc curve in patients with hepatic disease. In subjects with moderate hepatic impairment the increased exposure (C_{max}, AUC) causes additionally a shift to the left in the dose-response curve.

3.3 Which Subpopulations have a Significantly Different Efficacy to Safety Relationships for Ranolazine?

Female patients and patients with hepatic impairment.

At any given dose level of ranolazine and resulting effect on QTc, female patients display a smaller effect on $\Delta\Delta$ ETT than male patients. At any given dose level and resulting effect on ETT, patients with hepatic impairment display a greater effect on QTc than patients without hepatic disease. Thus, the therapeutic range of ranolazine and the risk-benefit relationship in females is worse than in males. The same is true for patients with hepatic impairment when compared to patients without hepatic impairment.

3.3 What Undesirable Effects of Ranolazine are Dose Limiting?

QTc-prolongation primarily and syncope secondarily are dose limiting for ranolazine in the target population at large. Elevation of supine diastolic blood pressure by 10-15 mmHg in patients with severe renal disease receiving 500 mg ranolazine constitutes an additional potential dose limiting factor in this subpopulation.

• Do Pharmacokinetic Parameters Change with Time?

No.

In the patients with the target disease (safety population, Study CVT 3033) the mean ranolazine plasma concentrations measured after 2, 6 and 12 weeks of treatment with ranolazine and

background therapy appeared to be comparable, suggesting no important time dependency as shown in Table 4:

Table 1. Arithmetic Mean Trough Plasma Concentrations of Ranolazine at the End of Treatment Weeks 2, 6 and 12

Dose, mg bid		750	1000
Week 2	N	271	261
	Mean	1683.0	2350.4
	SE	70.5	107.0
Week 6	N	261	246
	Mean	1578.3	2285.2
	SE	63.8	105.1
Week 12	N	256	237
	Mean	1577.6	2164.7
	SE	71.0	89.2

However, in the time interval between 2 weeks and 12 weeks of treatment 9.2% of the patients withdrew from the study at the 750 mg or 1000 mg dose levels. Thus, the possibility cannot be excluded entirely that the non-completing subjects displayed greater concentrations of ranolazine camouflaging a trend for an increase of the true mean ranolazine concentrations over time in the completing subjects.

• Is there Evidence of a Diurnal Rhythm of the Pharmacokinetics?

Yes.

A diurnal variation in the pharmacokinetics of ranolazine with on average 20 % smaller trough plasma concentrations in the evening, i.e. at the end of the day dosing interval, than in the morning, i.e. at the end of the night dosing interval, has been observed in 7 clinical studies with healthy volunteers.

A circadian variation in absorption, distribution or elimination of ranolazine could be the cause for the observed phenomenon. A diurnal variation of the renal elimination of ranolazine as a cause for the circadian rhythm can be ruled out.

D. Are the Pharmacokinetics in Healthy Volunteers and Angina Patients Similar?

Yes.

Table 2. Mean (SD) Peak and Trough Concentrations in CVT 3031 and CVT 3033

	SR 500 mg	SR 750 mg	SR 1000 mg	SR 1000 mg	SR 1500 mg
	CVT 3031	CVT 3033	CVT 3031	CVT 3033	CVT 3031
Trough (ng/mL)	864 ± 720	1585 ± 1076	1954 ± 1425	2255 ± 1550	3264 ± 1917
Peak (ng/mL)	1136 ± 721	2145 ± 1235	2473 ± 1522	2785 ± 1537	3891 ± 2021

The mean C_{max} and C_{min} values in healthy volunteers and in patients with the target disease were comparable in the dosage range between 500 mg to 1500 mg bid. In the healthy volunteers the C_{max} values tended to be greater (+22 %) and the C_{min} values tended to be smaller (-8.2 %) than in the patients with the target disease.

The exposure measures in healthy volunteers indicate that ranolazine's PK are nonlinear and not dose proportionate. The excess in C_{max} and AUC when the dose is increased from 500 mg to 1500 mg is only 17.3% and 36.4%, respectively. The cause for the deviation from linear PK is saturation, self inhibition or product inhibition of ranolazine's disposition. In vitro data indicate that RS-88390 (CVT-2514) and ranolazine are inhibitors of CYP 3A4, the main enzyme involved in the metabolism of ranolazine.

Absorption

Absolute bioavailability of ranolazine from the SR tablets in healthy volunteers and patients with the target disease has not been determined.

Healthy Volunteers

After oral administration of a single dose of 500 mg ¹⁴C ranolazine in solution 73.13% of the dose was recovered in urine as total radioactivity indicating good absorbability. The mean bioavailability of the SR tablet relative to a solution was 75.8%. Food has no impact on extent or rate of bioavailability of ranolazine from the SR tablet. Mean t_{max} for ranolazine ranges from 2 hours to 5 hours after administration of the SR tablet.

Distribution

Protein binding and red cell partitioning have not been determined in patients with the target disease.

Healthy Volunteers

The apparent plasma protein binding of ranolazine measured at room temperature over the clinically relevant concentration range ranged between 60.9% and 63.9% with a tendency to

slightly decrease with increasing concentrations. The major binding protein is α 1-acid glycoprotein. The apparent red cell to plasma coefficient ranged between 0.620 and 0.879. The mean volume of distribution of ranolazine after intravenous administration is 82.9 L.

Metabolism

The exposure measures of the main metabolites and the AUC ratios of the main metabolites to ranolazine have not been determined in the target population.

Healthy Volunteers

Ranolazine is eliminated mainly by nonrenal pathways. The major circulating metabolites are RS-88390 (CVT-2514) and its conjugate, RS-94287 (CVT-2738), RS-88640 (CVT-2512) and CVT-4786 with respective AUCs between 5.0% and 40% relative to ranolazine. The metabolites RS-88390 (CVT-2514), RS-88640 (CVT-2512) and RS-94287 (CVT-2738) have $t_{1/2}$ values in the range of 10 hours to 20 hours, longer than ranolazine. The half-life of CVT-4786, a product of RS-94287 (CVT-2738) was reported to be 8 hours, but this value is likely to be underestimated. Additional metabolites are formed and the percentage of an oral dose of ranolazine that is identified either as ranolazine or a metabolite in urine is 46.46%. The following scheme depicts the known metabolic pathways of ranolazine:

Only 3.13% of a 500 mg oral dose is excreted in urine as ranolazine. RS-88390 (CVT-2514)-conjugate, RS-94287 (CVT-2738) and CVT-4786 are the major metabolites excreted in urine and together they account for 31.51% of the dose. The percentage of an oral dose of ranolazine that was identified as either ranolazine or a metabolite is 46.46%.

The renal clearance values of ranolazine, RS-88390 (CVT-2514), RS-88640 (CVT-2512) and RS-94287 (CVT-2738) are 49.6 mL/min, 30.0 mL/min, 125.6 mL/min, and 205.9 mL/min, respectively, indicating involvement of tubular secretion in addition to glomerular filtration in the renal elimination of the latter two metabolites of ranolazine.

What are the Variabilities of Pharmacokinetic and Pharmacokinetic-Dynamic Parameters in Volunteers and Patients?

1. Pharmacokinetics

Ranolazine is a drug with high intersubject variation.

Healthy Volunteers

The coefficients of variation about the mean ranged between 42.2% and 67.0% for AUC and between 37.8% and 63.9% for C_{max} of ranolazine in a representative study in healthy volunteers with repeat administration of 500 mg, 1000 mg and 1500 mg ranolazine bid (Study CVT 3015). These data indicated that ranolazine is a drug with large intersubject variation. The intra-subject variability (CV, %) in healthy, male volunteers for C_{max} and AUC in the same study was estimated to be 27.7% and 22.3%, respectively.

Patients with the Target Disease

The coefficient of variation about the mean peak and trough concentrations in the pivotal trials ranged between 51.6% and 82.3%. The data in patients with the target disease confirmed the important intersubject variation displayed by the PK of ranolazine.

1.2. Pharmacokinetics-Pharmacodynamics

Ranolazine is a drug with high intersubject variation.

Plasma Concentration/ETT Relationship

The population analysis performed by the Agency estimated that the intersubject variation (CV) of the slope is 113%.

Plasma Concentration QTc Relationship

The population analysis by the Agency estimated that the intersubject variation of the slope (CV) is 61.4%.

E. What Dosage Regimen Adjustments, if any, are Recommended for Each of These Groups?

The effective and safe dose range of ranolazine in the studied patients is uncertain and unknown in patients with refractory angina. Thus, definitive recommendations for dose adjustments and contraindications cannot be made.

- ***Body Weight***

Body weight appears not to be a clinically significant covariate for either the PK or PK-PD of ranolazine.

Body weight has been identified as a covariate for both the linear clearance and volume of distribution of ranolazine in the population PK analysis performed by the sponsor. However, the model predicted peak concentrations were significantly smaller than the observed peak concentrations of ranolazine. It is uncertain whether the model predicted dependence of the parameters on body weight are reliable. Body weight was not found to impact the ranolazine plasma concentration to ETT or QTc relationship in the population PK-PD analysis performed by the Agency.

- ***Gender***

Gender is a significant covariate for the relationship between plasma concentration and exercise improving effect. However, gender is neither a significant covariate for the ranolazine concentration to QTc relationship nor for the PK of ranolazine.

Gender impacts significantly the relationship between ranolazine concentration and effect on ETT. The exercise performance improving effect in females at peak and trough by ranolazine is reduced to 27.5% to 42.2% of that in males within the dose range of 500 mg to 1500 mg bid. The effect on ETT in a female at peak after a dose of 1500 mg ranolazine is similar to that of a male at trough receiving a dose of 500 mg. As a consequence it is unlikely that ranolazine in the dose range between 500 mg and 1500 mg displays a statistically significant effect on ETT in females. The population PK-PD analysis of the ranolazine concentration to QTc relationship performed by the Agency did not indicate a difference between males and females.

A single dose study in healthy young subjects receiving a subtherapeutic single dose of an IR formulation of ranolazine showed a statistically significant 37 % smaller mean oral clearance in males than in females. However, a comparison of the mean concentrations of ranolazine across genders in pivotal Studies CVT 3031 and 3033 shows that females and males have comparable ranolazine plasma concentrations. Gender is not considered an important covariate for the PK of ranolazine.

- ***Race***

An adjustment of the dose based on PK or PK-PD differences by race appears no to be justified.

The database of the sponsor contained overwhelmingly data from Caucasian subjects (98%) and the power for detecting racial differences in the PK or PK-PD of ranolazine was inadequate.

- ***Elderly***

Age appears not to be a clinically relevant covariate for ranolazine.

The sponsor did not conduct a study to specifically evaluate the effect of chronological age on the PK or PD of ranolazine. A comparison of the mean concentrations of ranolazine in pivotal Studies CVT 3031 and 3033 showed that patients ≥ 65 years of age display on average 3% and 19%, respectively, greater concentrations than patients < 65 years old. The observed differences are too small to justify a dose adjustment in subjects ≥ 65 years of age.

- ***Pediatric Patients***

No studies were conducted in pediatric subjects.

- ***CYP 2D6 Poor Metabolizer Phenotype***

A dose adjustment for ranolazine in poor metabolizer subjects of CYP 2D6 appears not to be necessary.

The sponsor did not perform a study in subjects with the CYP 2D6 poor metabolizer phenotype to assess the tolerability of ranolazine. However, a drug interaction study with the strong CYP 2D6 inhibitor paroxetine was performed in subjects with the extensive metabolizer phenotype. Paroxetine transformed the extensive metabolizers into poor metabolizers. The increase in exposure to ranolazine by co-administration of paroxetine was $< 20\%$. There was no overt evidence for diminished tolerability of ranolazine in the CYP 2D6 EM subjects after they became phenotypically CYP 2D6 PM subjects.

- ***Renal Impairment***

Renal impairment increases the exposure to ranolazine 1.5 fold.

The sponsor conducted a study in subjects with mild, moderate or severe renal impairment who received multiple doses of ranolazine 500 mg bid. Relative to the control subjects the patients with mild, moderate or severe renal impairment showed respective increases in median C_{max} and AUC of 53.5% and 17.4%, 37.0% and 59.1% and 47.2% and 73.4%. The population PK analysis by the sponsor did not identify creatinine clearance as a significant covariate.

Based on the consistently elevated exposure measures for ranolazine found in renal impairment patients (Study CVT 3016), renal function is considered a significant covariate for the PK of ranolazine

The population PK-PD analysis performed by the Agency did not indicate that renal impairment impacted the ranolazine plasma concentration to QTc or ETT relationship.

Patients with severe renal failure experienced an increase in diastolic blood pressure of 10 mm Hg to 15 mmHg after 500 mg ranolazine bid. Thus, monitoring the blood pressure prior to and after initiation of a treatment with ranolazine is required.

- ***Hepatic Impairment***

Liver disease is a significant covariate affecting the relationship between ranolazine concentration and effect on QTc. In addition, moderate liver impairment is a significant covariate for the PK of ranolazine.

The sponsor conducted a study in subjects with mild or moderate hepatic impairment who received multiple doses of ranolazine 500 mg bid (Study CVT 3018). Median C_{max} and AUC in patients with mild hepatic impairment were 27.9% and 10.9%, respectively, greater than in the control subjects. Median C_{max} and AUC of ranolazine in the patients with moderate liver impairment increased by 74.8 % and 89.7 %, respectively, relative to control subjects. Moderate liver impairment should be considered a significant covariate for the PK of ranolazine.

The PK-PD analysis performed by the Agency showed that the slope of the ranolazine plasma concentration to QTc relationship was significantly increased to 0.00710 msec/1000 ng/mL in patients with mild or moderate hepatic impairment compared to a slope of 0.00256 sec/1000ng/ml in subjects without liver impairment. This corresponds to an increase in the steepness of the ranolazine concentration to QTc relationship by a factor of 2.8.

The ranolazine concentration to ETT relationship is not affected by hepatic impairment.

- ***Congestive Heart Failure***

Congestive heart failure is not a significant covariate for the PK or PK-PD of ranolazine and a dosage adjustment of ranolazine in patients with CHF appears not to be necessary.

The sponsor conducted a study in female and male patients with congestive heart failure (HF) NYHA Class III and IV with right ventricular ejection fraction < 35%. CHF did not importantly impact the PK of ranolazine.

The population analysis performed by the Agency did not identify CHF as a significant covariate for the PK-PD relationship of ranolazine.

- **Diabetes**

The population analysis of the PK- PD relationships of ranolazine did not identify diabetes as a significant covariate for ranolazine. The mean plasma concentrations in patients with diabetes in pivotal trials CVT Studies 3031 and 3033 tended to be 10% to 22% lower than in nondiabetic patients. This difference is too small to consider diabetes to be a significant covariate for the PK of ranolazine.

A summary of the significant intrinsic covariates and resulting “increase factors” for the PK and PK-PD of ranolazine are provided in Table 4:

Table 4. Significant Intrinsic Covariates for Ranolazine

Intrinsic Covariate	Factors ^a		
	PK C _{max}	PK-PD ETT	QTc
Typical Patient	1.0	1.0	1.0
Female	1.0	0.3-0.5	1.0
Hepatic Impairment			
Mild	1.3	1.0	2.8
Moderate	1.7	1.0	2.8
Renal Impairment			
Mild	1.5	1.0	1.0
Moderate	1.4	1.0	1.0
Severe ^c	1.5	1.0	1.0

^a Factors by which mean C_{max}, ETT or QTc of ranolazine change in the presence of a covariate
^b Mean dQTc_{max} does not exceed 5 msec
^c Diastolic blood pressure increase at 500 mg ranolazine bid

E. What Are the Extrinsic Factors that Influence Exposure or Response?

- **Drug-Drug Interactions**

In Vitro

The results of in vitro studies indicate that among the CYP 450 enzymes ranolazine is mainly metabolized by CYP 3A4 and to a small extent by CYP 2D6. Investigations with CYP 3A4 inhibitors have shown that the metabolism of ranolazine to RS-94287 (CVT-2738) is mainly by CYP 3A4, whereas the formation of RS-88390 (CVT- 2514) is catalyzed by CYP 2D6.

In Vivo

The impact of co-administered ketoconazole, diltiazem, verapamil, cimetidine, simvastatin and paroxetine on the PK of ranolazine was tested in young healthy male volunteers. Table 5 summarizes the results of the clinically significant interaction studies testing the impact of other drugs on ranolazine:

Table 5. Clinically Significant Drug Interactions Impacting Ranolazine

Extr. Covariate	Daily Dose, mg		Factor ^a C _{max}
	Drug	SR Ranolazine	
Typical Patient	NA	1000-2000	1.0
Ketoconazole	400	750	2.6
	400	2000	3.2
Diltiazem	180 SR	2000	1.9 ^b
			1.5 ^c
	240 SR	2000	2.4 ^b
			1.9 ^c
	360 SR	2000	2.8 ^b
			2.3 ^c
180 IR	2000	1.5 ^b	
		1.8 ^c	
Verapamil	120 SR	2000	1.9

^a Factor by which C_{max} of ranolazine in presence of extrinsic covariate increases ^b On treatment day 4 subjects had received 3.5 daily doses of diltiazem and 1 dose of ranolazine ^c On treatment day 8 subjects had received 7.5 daily doses of diltiazem and 7 doses of ranolazine

The potent CYP 3A4 inhibitors ketoconazole, diltiazem and verapamil increase the exposure to ranolazine by a factor of about 2.0 or more and the impact on the PK of ranolazine is clinically significant.

The impact of diltiazem on ranolazine's PK appears to depend on the dose and formulation of diltiazem. The effect on the exposure measures of ranolazine is initially (Day 4) greater than after more extended dosing (Day 8). A similar time dependency of the effect on C_{max} of ranolazine was not observed with immediately released diltiazem. The same daily dose of slowly and immediately released diltiazem appears to exert similar effects on C_{max} and AUC on Day 3 of the treatments. In the case of verapamil an inhibition of ranolazine's transport by P-glycoprotein cannot be excluded.

The drug interactions of the tested potent CYP 3A4 inhibitors ketoconazole, diltiazem and verapamil are clinically significant (Table 5). The co-administration of other untested, strong and intermediate CYP 3A4 inhibitors is predicted to also increase exposure to ranolazine clinically significantly.

Co-administered paroxetine, simvastatin, digoxin and cimetidine have no clinically relevant effects on the PK of ranolazine as shown in Table 6:

Table 6. Drug Interactions with No Significant Impact on Ranolazine

Extr. Covariate	Daily Dose, mg		Factor ¹ C _{max}
	Drug	Ranolazine	
Paroxetine	20	SR 2000	1.2
Cimetidine	1200	IR 523	1.1
Simvastatin	80	SR 2000	1.1
Digoxin	0.125	SR 2000	1.1

¹ Factor by which C_{max} of ranolazine in presence of covariate increases

A dose adjustment of ranolazine in the presence of these drugs is not required. The small impact of < 20% on the exposure measures of ranolazine by paroxetine, a potent CYP 2D6 inhibitor, indicated that only a minor fraction of ranolazine is metabolized by this enzyme. Thus, a relevant increase in the exposure to ranolazine is not likely in genotypically or phenotypically poor metabolizers of CYP 2D6. Ranolazine can be co-administered with paroxetine and other potent CYP 2D6 inhibitors. Ranolazine can also be administered to poor metabolizers of CYP 2D6.

The results of drug interaction studies in which ranolazine impacted the PK of other drugs clinically significantly are summarized in Table 7:

Table 7. Drug Interactions with Ranolazine Impacting the PK of Other Drugs Clinically Significantly

Drug	Daily Dose, mg		Factor ^a		Signific.	Labeling
	Drug	Ranolaz.	Cmax	AUC		
Digoxin	0.125	SR 1500	1.7	1.9	Yes	TDM ^b
	0.125	SR 2000	1.5	1.6		
	0.250 ^c	IR 1026	2.3	1.4		
Diltiazem	180 IR	SR 2000	1.1	1.1	No	No
Simvastatin	80	SR 2000	2.3	1.4	Yes	LFT ^c
Warfarin (+) R- (-) S- PT ^d	5	IR 1026	0.88	1.1	Yes	PT ^e
			0.89	1.1		
			1.4	1.2		
Dextrometorphan	30	SR 2000	NA ^f		Possible	No ^g

^a Factor by which exposure of other drug in presence of ranolazine increases
^b Therapeutic drug monitoring ^c Study in CHF patients of both genders, other studies in healthy young male volunteers
^c Liver function test ^d Prothrombin time ^e not applicable, dextrometorphan/dextrophan ratio significantly increased ^g Phase 4 study required

Co-administered ranolazine interacts clinically significantly with simvastatin, digoxin and warfarin. Ranolazine increases the exposure to digoxin and simvastatin. In the presence of ranolazine warfarin exerted an increased effect on prothrombin time without increasing the exposure to (-) S- or (+) R warfarin. The IR formulation of ranolazine exerted a greater effect on Cmax of digoxin than the SR tablet, but this finding has no bearing since only the SR tablet of ranolazine is proposed for marketing. Ranolazine also increased the dextrometorphan/dextrophan ratio statistically significantly, suggesting a possible inhibition of CYP 2D6 by ranolazine and/or a metabolite. However, this finding requires confirmation by a better-controlled Phase 4 clinical pharmacology study. Co-administered ranolazine did not affect the PK of diltiazem.

Of the 10 in vivo drug interaction studies conducted by the sponsor 9 were in healthy, male volunteers. One of the 3 digoxin studies enrolled CHF patients of both genders. An enrollment of more women in the interaction studies would have been desirable.

Studies with CYP3A4 or CYP 2D6 inducers and ranolazine have not been performed in vitro or in vivo.

III. BIOPHARMACEUTICS

A. Was an Adequate Link Established between the Clinical and to be Marketed Formulations of Ranolazine?

Yes.

The clinical formulations of the SR tablets were used in the pivotal trials (Studies CVT 3031 and 3033). The in vivo bioequivalence of the to be marketed and service formulations has been demonstrated for the 500 mg tablet (Study CVT 301-15).

Based on submitted data on the composition and comparable dissolution performance of the 375 mg and 500 mg tablets the sponsor requested a biowaiver.

The composition of the 375 mg and 500 mg SR tablets are proportionately similar and the dissolution profiles of the 375 mg and 500 mg tablets in 4 media, water and buffers of pH 1.2, 4.5 and 6.8 are sufficiently similar as evidenced by the results of the f2 test. Based on the demonstrated compositional and dissolution similarity of the 375 mg and 500 mg tablets the reviewer proposes granting of the biowaiver.

Unsuccessful attempts were made to establish an IVIVC using SR tablets with slightly modified release characteristics.

B. Was There an Impact of Food on the Bioavailability of Ranolazine?

No.

Food did not affect either extent or rate of unchanged ranolazine.

C. Are the Sponsor Proposed Dissolution Medium and Specifications Acceptable?

[REDACTED]

Condition	FDA Recommendation
[REDACTED]	[REDACTED]

IV. A. What are Issues that were not Adressed by the Sponsor?

- The effective and safe dose range of ranolazine in the studied patients is uncertain and is unknown in the target population with refractory angina
- The exercise improving effect of ranolazine in the dose range of 500 mg to 1500 mg in females has not been shown to be statistically significantly different from placebo
- The results on the exercise improving effects and associated ranolazine plasma concentrations were not consistent in some of the clinical trials casting doubt about the least effective concentration of ranolazine (RAN 1514 vs. CVT 3031)
- Uncontrolled factors in the pivotal clinical trials including circadian rhythm of the PK and interaction of co-administered diltiazem with ranolazine may have affected the results on exercise duration
- Sponsor's exclusion of subjects with hepatic impairment from population analysis of the relationship between ranolazine concentrations and the effect on QTc resulted in imprecise estimates of the slope and consequently of the risk associated with administration of ranolazine to this subpopulation
- There is a lack of evidence in support of developing racemic ranolazine
- The extent to which co-administered ranolazine increases exposure of drugs predominantly metabolized by CYP 2D6 was not determined in humans

IV.B. What are the Recommendations for the Labeling?

The effective and safe dose range of ranolazine in the studied patients is uncertain and is unknown in the target population with refractory angina. Thus, definitive recommendations for the labeling cannot be made.

The submission provides evidence that ranolazine can exert an exercise improving effect in the presence and absence of other antianginals. The submitted data also indicate that ranolazine prolongs the QTc interval dose- and concentration dependently. There is uncertainty about the least effective concentration of ranolazine. Doses in excess of 750 mg ranolazine are associated with mean peak QTc prolongations > 5 msec in patients without additional risk factors. Ranolazine is a QT prolonging drug at a dose level of 1000 mg bid. The exercise improving effect of ranolazine in females is importantly reduced and has not been shown to be statistically significantly different from placebo in the dose range between 500 mg and 1500 mg. It is likely that the data from the "better responding male" subpopulation would have provided improved estimates of extent and time duration of the exercise improving effect of ranolazine at the tested dose levels.

Patients on ketoconazole, diltiazem or verapamil or on other potent CYP 3A4 inhibitors when receiving ranolazine experience clinically significant increased ranolazine levels (Table 5). Patients with liver impairment display a clinically significant increased sensitivity to the QTc prolonging effects of ranolazine (Table 4). Renal impairment increases mean Cmax by a factor of about 1.5. In patients with severe renal impairment blood pressure should be monitored after initiation of treatment or up-titration of the dose.

Ranolazine is a drug with high intersubject variation in both PK and PK-PD. Monitoring of the QTc interval before and after initiation of a treatment with ranolazine or after uptitrating the dose is required. But, practicing Cardiologists should realize that with ranolazine QTc monitoring is a tool with very limited sensitivity to detect a true drug related increase.

V. What is the Overall Conclusion regarding NDA 21-526?

Overall the clinical pharmacology and biopharmaceutics section is acceptable.

REFERENCES

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LABELING RECOMMENDATIONS

CLINICAL PHARMACOLOGY

Description:

1. Change the chemical description of ranolazine so that the racemic character of the compound is recognizable. The amended sentence should read: "***Ranolazine is racemic and chemically described as (\pm)-4-[2-hydroxy-3- (O-methoxyphenoxy)propyl]-1-[piperazineaceto-2',6'-xylylidide and has the structural formula:***"
2. Delete racemic mixture.... The amended sentence should read: ***Ranolazine is insoluble in dichloromethane and methanol;***"

Pharmacokinetics

3. Change t_{max} to 2-5 hours. The amended sentence should read: "***After oral administration of Ranexa peak plasma concentrations are observed between 2-5 hours***"
4. Delete sentence "***The elimination half life of ranolazine is 1.4-1.9 hours***".
5. Change the value of terminal half life to 5-9 hours and change peak/trough ratio to 1.6 -3.0. The amended sentence should read: "***After dosing to steady-state with Ranexa, the apparent terminal half life ranges from 5 to 9 hours and the peak/trough ratio of ranolazine plasma concentration ranges between 1.6 to 3.0.***"

Absorption

6. Change value for absorption to 77%. The amended sentence should read: "***Ranolazine is absorbed to 77% after oral administration as a solution.***"
7. Delete sentence: "***The absolute bioavailability after oral administration of an immediate release (IR) formulation ranged between 35% to 50%***" and replace it by the sentence: "***The bioavailability of ranolazine from Ranexa relative to that from a solution is 76 %.***"

Distribution

8. Change the respective values for volume of the central compartment to 45 L and for the volume of distribution at steady state to 83 L. The amended sentence should read: "***The apparent volume of the central compartment (V_c) is approximately 45 L and the volume of distribution at steady-state is (V_{ss}) is approximately 83 L.***"

Metabolism and Excretion

9. In the first paragraph: Change oral dose of ranolazine in solution to oral dose of radiolabeled ranolazine administered in solution. The amended sentence should read: ***"Following a single oral dose of radiolabeled ranolazine administered in solution, approximately 73% of the dose is excreted in urine and approximately 25% in feces. "***

10. Delete reference to liver and statement of fraction of an oral dose excreted in the feces as unchanged ranolazine. The amended sentence should read: ***"Ranolazine is metabolized rapidly mainly by the cytochrom P450 isozyme CYP 3A4 and to lesser extent by CYP 2D6."***

In the second paragraph: Change first sentence as follows: ***"After dosing with 500 mg to 1500 mg bid to steady state, the four most abundant metabolites in plasma had AUC values of between about 5% to 33% relative to ranolazine."***

Special Populations

Age, Gender and Race

11. Delete the entire paragraph and replace it by: ***"A study investigating the impact of age on the pharmacokinetics of ranolazine has not been conducted. The mean plasma concentrations of ranolazine in patients with the target disease in the age ≥ 65 years were on average about 10 % greater than in patients < 65 years. A population analysis of the respective relationships between ranolazine concentration and effect on exercise or QTc interval showed no impact of age. A dose modification for age is not required for ranolazine (see DOSAGE AND ADMINISTRATION.)"***

A single dose study in young healthy volunteers with administration of 342 mg ranolazine using an immediate release tablet showed a statistically significantly greater oral clearance and shorter half life in females than in males. However, the mean plasma concentrations in male and female patients with the target disease were comparable.

A population analysis of the relationship between ranolazine concentration in plasma and exercise duration in patients with angina showed that the exercise duration at identical plasma concentrations in women is reduced to between about 28% and 42% of that in men, indicating a significantly smaller extent and time duration of the exercise performance improving effect of ranolazine in women. The reduced exercise improving effects of ranolazine in women have not been shown to be statistically significantly different from placebo. A population analysis of the relationship between ranolazine plasma concentration and QTc prolongation using data from patients with the target disease, patients with renal and hepatic disease and healthy subjects showed no impact of gender.

A study investigating the impact of race on the pharmacokinetics and pharmacodynamics of ranolazine has not been conducted and possible requirements for a dosage modification of ranolazine for race are not known."

Renal Impairment

12. Add to first sentence information on dose. The amended sentence should read: ***"The disposition of ranolazine at steady state at the 500 mg bid dose level has been studied in 29***

subjects with various degrees of renal function.” Reword the second sentence as follows: “ *In subjects with impaired renal function ranolazine peak plasma concentrations increased 1.5 fold in mild (CLcr 51 to 80 mL/min), 1.4-fold in moderate (Clcr 30 to 50 mL/min) and 1.5-fold in severe renal renal impairment (CLcr<30 mL/min) compared to healthy subjects (CLcr>80 mL/min). the pharmacokinetics of ranolazine in patients on dialysis have not been studied. In six subjects with severe renal impairment mean diastolic blood pressure increased by approximately 10 to 15 mmHg.*”

Hepatic Impairment

12. Add to the first sentence information on the dose administered. The amended sentence should read: “ *The disposition of ranolazine at steady state at the 500 mg bid dose level has been studied in patients with mild or moderate liver impairment*”. The second and third sentences should read: “*Subjects with mild hepatic impairment (Child-Pugh Class A) had pharmacokinetic parameters similar to subjects with normal hepatic function. Ranolazine peak plasma concentrations increased 1.7 fold in subjects with moderate hepatic impairment (Child-Pugh Class B). In the 16 subjects with mild or moderate hepatic impairment QTc prolongation relative to the plasma concentration of ranolazine was increased by a factor of about 2.8 in comparison with subjects without hepatic impairment.*”

Congestive Heart Failure

13. Replace first sentence with the following: “ *The mean plasma concentrations of ranolazine in patients with congestive heart failure (CHF) (NYHA Class I to IV) and patients without CHF were comparable.*”

Diabetes Mellitus

14. Replace the first sentence by the following: “ *The mean plasma concentrations of ranolazine in patients with diabetes mellitus tended to be about 16% smaller than in patients without diabetes mellitus.*”

Drug-Drug Interactions

15. The following 3 paragraphs that replace the current 3 paragraphs should be added after the first sentence: “*To examine the impact of other drugs on the disposition of ranolazine, drug interaction studies in healthy male subjects were conducted with the potent 3A4 inhibitors ketoconazole (400 mg/day), diltiazem (up to 360 mg/day), and verapamil (360 m/day). Other studies in healthy male subjects investigated the impact of simvastatin (80 mg/day), cimetidine (1200mg/day), digoxin (0.125 mg/day or 0.250 mg/day) and paroxetine (20 mg/day) on the plasma concentrations of ranolazine.*

CYP 3A4 Inhibitors

Peak plasma levels of ranolazine were clinically significantly increased by the potent CYP 3A4 inhibitors ketoconazole (2.6- to 3.2-fold increase), diltiazem (1.5 to 2.8 fold increase, dose and time dependently) and verapamil (1.9 fold increase). Ranolazine 500 mg bid in the presence of ketoconazole (400 mg/day,) diltiazem (240 mg/day and 360 mg/day) and verapamil (360 mg/day) increases the peak QTc interval > 5msec. Other, strong or intermediate CYP 3A4 inhibitors are predicted to also interact clinically significantly with ranolazine. Ranolazine is a substrate of P-glycoprotein and the increase in the exposure of ranolazine by verapamil may also be caused by verapamil's known inhibition of P-glycoprotein. Simvastatin, a weak inhibitor of CYP 3A, had no impact on the pharmacokinetics of ranolazine (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Other Drugs

Cimetidine, digoxin and paroxetine do not clinically relevantly increase the exposure to ranolazine and a dose adjustment of ranolazine in the presence of these drugs is not necessary. No dose adjustment is required when Ranexa is co-administered with drugs inhibiting CYP 2D6.

In vitro or in vivo studies investigating the impact of strong CYP 3A4 inducers such as e.g. rifampicin on the exposure to ranolazine have not been conducted. Thus, a diminished exposure to and response of ranolazine in the presence of a strong CYP 3A4 inducer cannot be excluded that could require an adjustment of the dose of ranolazine (see PRECAUTION and DOSAGE AND ADMINISTRATION).“

Effects of Ranolazine on Other Drugs

15. Amend the second paragraph as follows: *“Clinical studies have shown that the levels of simvastatin, active simvastatin metabolites, and HMG-CoA reductase inhibitory activity were increased up to 2 fold by ranolazine (see PRECAUTIONS). The pharmacokinetics of diltiazem were not affected by co-administered ranolazine.*

16. Add the following paragraph on warfarin: *“ Co-administration of ranolazine increased the effect of warfarin on the prothrombin time by a factor of 1.4. without increasing the exposure to (-)S- or (+)R warfarin. The mechanism underlying this drug interaction is unknown (see PRECAUTIONS.)”*

CONTRAINDICATIONS

17. the effective and safe dose range of ranolazine in the studied patient population is uncertain and unknown in patients with refractory angina pectoris. Therefore definitive statements regarding contraindications of ranolazine in patients with hepatic impairment and in patients on potent CYP 3A4 inhibitors cannot be made.

WARNINGS

QT Prolongation

18. The statement in the second sentence on the observed mean maximum increases in QTc is premature. The effective and safe dose range of ranolazine in the tested population is uncertain and is unknown in patients with refractory angina.

Metabolic Interactions

19. The statement proposed in the second sentence is premature. The effective and safe dose range of ranolazine in the tested population is uncertain and is unknown in patients with refractory angina.

PRECAUTIONS

Use in Patients with Impaired Hepatic Function

20. The statement proposed in the second paragraph is premature. The effective and safe dose range of ranolazine in the tested population is uncertain and is unknown in patients with

Use in Patients with Impaired Renal Function

21. The statement on the dosage adjustment in renally impaired patients is premature. The effective and safe dose range of ranolazine in the tested population is uncertain and is unknown in patients with refractory angina.
the following sentence should be added: "*In patients with severe renal failure blood pressure should be carefully monitored.*"

Information of Patients

21. 22. The statement made in bullet 4 is premature. The effective and safe dose range of ranolazine in the tested population is uncertain and is unknown in patients with

Drug- Drug Interactions

Pharmacokinetic Interactions: Effects of Other Drugs on Ranolazine

Ketoconazole

23. Change the wording of the first sentence as follows: "*As a potent inhibitor of CYP 3A4, ketoconazole (400 mg/day) increased steady-state peak plasma concentrations of ranolazine by a factor of 2.6 to 3.2*". The statement in the second sentence is premature.

Diltiazem

24. Replace the first sentence by the following: *“As a potent inhibitor of CYP3A4, diltiazem (180 to 360 mg daily) caused dose dependent mean increases in the ranolazine peak plasma concentrations of 1.5- to 2.8- fold.”* The statement in the second sentence is premature.

Verapamil

25. Replace the first sentence by the following: *“Verapamil 360 mg/day increased ranolazine steady-state peak plasma concentrations 1.9 fold.”* The statement in the second sentence is premature.

Cimetidine

26. Replace the first sentence by the following: *“Co-administration of cimetidine (1200 mg/day) did not impact the plasma levels or ranolazine clinically relevantly.”*

Paroxetine

27. Replace the first sentence by the following: *“Co-administration of the potent CYP 2D6 inhibitor paroxetine (20 mg/day) did not impact the plasma levels of ranolazine clinically relevantly.”*

Pharmacokinetic and Pharmacodynamic Interactions: Effects of Ranolazine on Other Drugs

Simvastatin

28. Amend the paragraph as follows: *“Co-administration of ranolazine and simvastatin (80 mg) resulted in an up to 2-fold increase in the plasma concentrations of simvastatin, its active metabolites and the HMG-CoA reductase inhibitory activity indicating that ranolazine inhibits CYP 3A4 in vivo. Liver function should be tested before and repeatedly after initiation of concomitant treatment with ranolazine and simvastatin, and other statins metabolized by CYP 3A4 such as levostatin and atorvastatin.”*

Warfarin

29. Replace the paragraph by the following: *“Co-administered ranolazine increases warfarin’s effect on prothrombin time by a factor of 1.4. Prothrombin time should be measured before and repeatedly after initiation of a treatment with ranolazine. An adjustment of the warfarin dose based on prothrombin time may be required.”*

DOSAGE AND ADMINISTRATION

30. The respective statements in the second sentence of the first paragraph regarding dose range, in the second paragraph on gender and in the fourth paragraph on dose adjustments in renally impaired patients and in patients on CYP 3A4 inhibitors are premature. The effective and safe dose range of ranolazine in the tested population is uncertain and is unknown in patients with

APPENDIX I

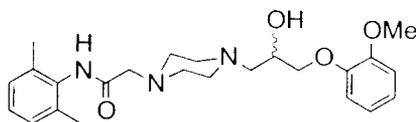
2.1 Proposed Labeling

Ranexa™
(ranolazine)

DESCRIPTION

Ranexa™ (ranolazine) is available as a tablet for oral administration. Ranolazine is a member of a new class of drugs whose anti-anginal and anti-ischemic effects are believed to result from partial inhibition of fatty acid oxidation (pFOX inhibition). Ranolazine inhibits enoyl-CoA hydratase and carnitine acyl carnitine translocase, enzymes that mediate the beta-oxidation of fatty acids. Ranolazine is pharmacologically unrelated to calcium channel blockers, beta-blockers, and nitrates.

Ranolazine is racemic and chemically described as (\pm)-4-[2-hydroxy-3-(O-methoxyphenoxy)propyl]-1-[piperazineaceto-2',6'-xylylidide and has the structural formula:



The molecular weight of ranolazine is 427.54.

Ranolazine is a white to off-white solid. Ranolazine is soluble in dichloromethane and methanol; sparingly soluble in tetrahydrofuran, ethanol, acetonitrile, and acetone; slightly soluble in ethyl acetate, isopropanol, toluene, and ethyl ether; and very slightly soluble in water.

Ranexa is a film-coated, extended release tablet for oral administration containing 375 mg or 500 mg of ranolazine. Each tablet also contains carnauba wax, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer (Type C), microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium hydroxide, titanium dioxide, and either FD&C Blue #2 Lake (375 mg tablets) or FD&C Yellow #6 Lake (500 mg tablets).

CLINICAL PHARMACOLOGY

Mechanism of Action

The anti-anginal and anti-ischemic effects of ranolazine are believed to result from partial inhibition of fatty acid oxidation (pFOX inhibition) which consequently stimulates glucose oxidation during ischemia, when free fatty acid levels are known to increase. Shifting the increase in fatty acid oxidation that occurs during myocardial ischemia toward glucose oxidation results in more oxygen-efficient production of adenosine triphosphate (ATP), because less oxygen is required to yield a given amount of ATP during glucose oxidation. The relative increase in glucose oxidation is believed to improve cardiac efficiency and to reduce ischemia-induced increases in lactic acid and cellular acidosis. These metabolic effects of ranolazine do not result from beta-adrenergic blockade, calcium channel antagonism, or vasodilation.

The effects of ranolazine on the surface electrocardiogram are believed to result from inhibition of the fast and slow inward rectifying potassium currents, I_{Kr} and I_{Ks} , which prolong

ventricular action potential, and from inhibition of the late sodium current, late I_{Na} , which shortens ventricular action potential. Ranolazine preferentially inhibits the late I_{Na} current relative to the peak sodium current (or V_{max}) by at least 5-fold.

Pharmacokinetics

After oral administration of Ranexa, peak plasma concentrations (C_{max}) of ranolazine are observed between 2 and 5 hours. Steady-state is generally achieved within 3 days of dosing b.i.d. At steady-state, over the dose range 500 to 1000 mg b.i.d., C_{max} and AUC_{0-7} increase slightly more than proportionally to dose (2.5- and 2.7-fold, respectively). After dosing to steady-state with Ranexa, the apparent terminal elimination half-life is 5 to 9 hours and the peak/trough ratio of ranolazine plasma concentrations ranges between 1.6 and 3.0.

The C_{max} and AUC data from food-effect studies involving administration of Ranexa to healthy volunteers under fasting conditions and with a high-fat meal indicated that exposure to the drug was not affected by food. Therefore, Ranexa may be taken without regard to meals.

Absorption

Ranolazine is absorbed to 77% after oral administration as a solution. The bioavailability of ranolazine from Ranexa relative to that from a solution is 76%.

Distribution

After intravenous administration, ranolazine distributes according to a two-compartment model. The apparent volume of the central compartment (V_c) is approximately 45 L, and the volume of distribution at steady-state (V_{ss}) is approximately 83 L. Over the concentration range of 0.25 to 10 $\mu\text{g/mL}$, ranolazine is approximately 65% bound to human serum proteins. Ranolazine binds mainly to α -1 acid glycoprotein and weakly to albumin.

The ratio of ranolazine concentrations in human red blood cells relative to plasma ranges from 0.62 to 0.88, indicating that ranolazine distributes preferentially to the plasma compartment.

Metabolism and Excretion

Following a single oral dose of radiolabeled ranolazine administered in solution, approximately 73% of the dose is excreted in urine and 25% in feces. Ranolazine is metabolized rapidly and extensively; less than 5% is excreted unchanged in urine.

After dosing to steady-state with 500 mg to 1500 mg b.i.d., the four most abundant metabolites in plasma had AUC values of between about 5% and 33% relative to ranolazine with elimination half-lives ranging from 6 to 22 hours. Ranolazine is metabolized mainly by the cytochrome P450 isozyme CYP3A4 and to a lesser extent by CYP2D6.

Special Populations

Age, Gender, and Race

A study investigating the impact of age on the pharmacokinetics of ranolazine has not been conducted. The mean plasma concentrations of ranolazine in patients with the target disease in the age ≥ 65 years were on average about 10% greater than in patients < 65 years. A population analysis of the respective relationships between ranolazine concentrations and effect on exercise or QTc showed no impact of age. A dose modification of ranolazine for age is not required.

A single dose study in young healthy volunteers with administration of 342 mg ranolazine using an immediate release tablet showed a statistically significantly greater oral clearance and shorter half life in females than in males. However, the mean concentrations of ranolazine in male and female patients with the target disease were comparable. A population analysis of the relationship between ranolazine concentration and exercise duration in patients with angina showed that the exercise duration at identical ranolazine concentrations in women is reduced to between 28% and 42% of that in men, indicating a significantly smaller extent and time duration of the exercise improving effect of ranolazine in women. The reduced exercise improving effects of ranolazine in women have not been shown to be statistically significantly different from placebo. A population analysis of the relationship between ranolazine plasma concentration and QTc prolongation using data from patients with the target disease, patients with renal and hepatic disease and healthy volunteers showed no impact of gender. A dose modification of ranolazine in females is not recommended.

A study investigating the impact of race on the pharmacokinetics and pharmacodynamics of ranolazine has not been conducted and possible requirements for a dosage modification of ranolazine for race are not known.

Pediatric

The pharmacokinetics of ranolazine have not been investigated in patients < 18 years of age.

Renal Insufficiency

The disposition of ranolazine at steady-state at the 500 mg bid dose level was studied in 29 subjects with various degrees of renal function. Ranolazine clearance was significantly correlated with creatinine clearance (CLcr). In subjects with impaired renal function, ranolazine peak plasma concentrations increased 1.5-fold in mild (CLcr 51 to 80 mL/min), 1.4-fold in moderate (CLcr 30 to 50 mL/min), and 1.5-fold in severe renal impairment (CLcr < 30 mL/min) compared to healthy subjects (CLcr > 80 mL/min). The pharmacokinetics of ranolazine in patients on dialysis have not been assessed. In six subjects with severe renal impairment on ranolazine 500 mg b.i.d., mean diastolic blood pressure increased approximately 10 to 15 mmHg (see **DOSAGE AND ADMINISTRATION**).

Hepatic Insufficiency

The disposition of ranolazine at steady-state at the 500 mg bid dose level has been studied in subjects with mild or moderate hepatic impairment. Subjects with mild hepatic impairment (Child-Pugh Class A) had pharmacokinetic parameters similar to subjects with normal hepatic function. Ranolazine peak plasma concentrations increased 1.7 fold in subjects with moderate hepatic impairment Child-Pugh Class B). In the 16 subjects with mild or moderate hepatic impairment the QTc prolongation relative to the plasma concentration of ranolazine was increased by a factor of 2.8 compared to subjects without hepatic impairment.

Congestive Heart Failure

The mean plasma concentrations of ranolazine in patients with congestive heart failure (CHF) (NYHA Class I-IV) and patients with CHF were comparable. Ranolazine has been used in patients with angina and NYHA Class I or II heart failure with minimal effects on heart rate or blood pressure. In a placebo-controlled study of 81 patients with NYHA Class III or IV CHF, treatment with ranolazine 750 mg b.i.d. for one week had minimal effects on heart rate or blood pressure.

Diabetes Mellitus

The mean plasma concentrations of ranolazine in patients with diabetes mellitus tended to be about 16% smaller than in patients without diabetes mellitus. Decreases in HbA_{1c} have been observed during treatment with ranolazine (see **PRECAUTIONS, Laboratory Tests**).

Drug-Drug Interactions

Effects of Other Drugs on Ranolazine

Ranolazine is primarily metabolized by CYP3A4. To examine the impact of other drugs on the disposition of ranolazine drug interaction studies in healthy male subjects were conducted with the potent 3A4 inhibitors ketoconazole (400 mg/day), diltiazem (up to 360 mg/day) and verapamil (360 mg/day). Other studies in healthy male volunteers investigated the impact of simvastatin (80 mg/day), cimetidine (1200 mg/day), digoxin (0.125mg/day) and paroxetine (20 mg/day) on the plasma concentrations of ranolazine.

CYP 3A4 Inhibitors

Peak plasma levels of ranolazine were increased by the potent CYP 3A4 inhibitors ketoconazole (2.6 to 3.2 fold increase), diltiazem (1.5 to 2.8 fold, dose and time dependently) and verapamil (1.9 fold). Ranolazine is a substrate of P-glycoprotein and the increase in the exposure of ranolazine by verapamil may also be caused by verapamil's known inhibition of P-glycoprotein. Simvastatin, a weak inhibitor of CYP 3A4 had no impact on the pharmacokinetics of ranolazine. However, caution should be exercised when other weak or intermediate inhibitors of CYP 3A4 ; such as fentanyl, are co-administered with ranolazine (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Other Drugs

Cimetidine, digoxin and paroxetine do not clinically relevantly increase the exposure to ranolazine and a dose adjustment of ranolazine in the presence of these drugs is not necessary. No dose adjustment is required when Ranexa is co-administered with drugs inhibiting CYP 2D6.

In vitro or in vivo studies investigating the impact of strong CYP 3A4 inducers such as e.g. rifampicin on the exposure to ranolazine have not been conducted. Thus, a possibly diminished exposure to and response of ranolazine in the presence of a strong CYP 3A4 inducer cannot be excluded, and could require an adjustment of the dose of ranolazine (see PRECAUTIONS and DOSAGE AND ADMINISTRATION)

Effects of Ranolazine on Other Drugs

In vitro studies indicate that ranolazine and its O-demethylated metabolite are weak inhibitors of CYP3A4 and CYP2D6. Ranolazine and its most abundant metabolites are not known to inhibit the metabolism of substrates for CYP1A2, 2C9, 2C19 or 2E1 in human liver microsomes, suggesting that ranolazine is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes.

Clinical studies have shown that the levels of simvastatin, active simvastatin metabolites, and HMG-CoA reductase inhibitory activity were increased up to 2-fold by ranolazine. The pharmacokinetics of diltiazem were not affected by ranolazine.

The inhibitory effects of ranolazine on CYP2D6 have been evaluated through phenotyping with dextromethorphan before and after dosing with ranolazine to steady-state. The results demonstrate that ranolazine and/or metabolites partially inhibit CYP2D6, but not to the extent that a general shift from extensive to poor metabolizer phenotype is seen. Concomitant use of Ranexa with other drugs metabolized by CYP2D6 has not been formally studied but may require lower doses of the other drug than usually prescribed.

Ranolazine increased digoxin concentrations 1.4- to 1.6-fold, probably due to inhibition of P-gp (see PRECAUTIONS).

Co-administration of ranolazine increased the effect of warfarin on the prothrombin time by a factor of 1.4 without increasing the exposure to (-)S- or (+) R-warfarin. The mechanism underlying this drug interaction is not known (see PRECAUTIONS).

Smoking

Based on *in vitro* studies using human liver enzymes, ranolazine is not a substrate for CYP1A2. Smoking is not expected to affect the pharmacokinetics of ranolazine.

Pharmacodynamic Effects

Hemodynamic Effects

Minimal changes in mean heart rate (<2 bpm), systolic blood pressure (<3 mmHg), and rate-pressure product were observed in patients with chronic angina treated with ranolazine as monotherapy or in combination with other anti-anginal medications in controlled studies. Similar results were observed in subgroups of patients with NYHA Class I or II heart failure, diabetes, or reactive airway disease, and in elderly patients.

Electrocardiographic Effects

Dose and plasma concentration-related increases in the QTc interval (see **WARNINGS**), reductions in T wave amplitude and, in some cases, notched T waves, have been observed in patients treated with ranolazine.

Other Pharmacodynamic Effects

In clinical pharmacology studies, at plasma concentrations up to 4-fold higher than those produced by recommended doses of ranolazine, subjects frequently developed paresthesia, diplopia, and confusion that in some cases culminated in syncope. No arrhythmias were observed during constant electrocardiographic monitoring in these subjects.

CLINICAL STUDIES

The anti-anginal and anti-ischemic efficacy and the safety of Ranexa have been demonstrated in two randomized, double-blind, placebo-controlled studies in patients with chronic angina and severe coronary artery disease (Duke Treadmill Exercise Score \leq -10) and in three additional randomized, double-blind, placebo-controlled chronic angina studies using an IR ranolazine formulation. Of the 1596 patients (aged 28–92 years) in these five studies, 745 patients received Ranexa, 576 received ranolazine IR, and 1018 patients received placebo. Because four of these five trials were of crossover design, many of these patients received both placebo and ranolazine, during separate treatment periods. Sublingual nitrates were used in these studies as needed. Thirty-two percent (421/1321) of the patients treated with ranolazine in these trials were receiving a concomitant beta-blocker and 40% (529/1321) were receiving a concomitant calcium channel blocker.

In these studies, efficacy and safety were also demonstrated in subgroups of chronic angina patients in whom other anti-anginal drugs may be inadequate or not tolerated, including patients with:

- Low blood pressure, heart rate, and/or prolonged AV nodal conduction in whom initiation or upward dose titration of a long-acting nitrate, beta-blocker, or calcium channel blocker is not recommended;
- Reactive airway disease, in whom use of a beta-blocker is not recommended due to the potential for bronchospasm;
- Congestive heart failure, in whom calcium channel blockers are not recommended due to the potential for decompensated heart failure; and
- Diabetes, in whom beta-blockers should not be used because these drugs can mask the symptoms of hypoglycemia.

In the CARISA (Combination Assessment of Ranolazine in Stable Angina) trial, 823 patients (who continued on daily doses of atenolol 50 mg, amlodipine 5 mg, or diltiazem CD 180 mg) were randomized to receive 12 weeks of treatment with twice daily Ranexa 750 mg, 1000 mg, or placebo. In the MARISA (Monotherapy Assessment of Ranolazine In Stable Angina) trial, 191 patients on no other anti-anginal drugs were randomized to treatment with twice daily Ranexa 500 mg, 1000 mg, 1500 mg, and matching placebo, each for one week in a crossover design. In both trials, statistically significant ($p < 0.05$) increases in modified Bruce treadmill exercise duration and time to angina were observed for each Ranexa dose versus placebo, at both trough (12 hours after dosing) and peak (4 hours after dosing) plasma levels, with minimal effects on blood pressure and heart rate. The changes vs placebo in exercise parameters at recommended doses are given in Tables 1 and 2. In the CARISA trial, the changes from baseline in exercise duration at trough were 91.7 sec for placebo, 115.4 sec for Ranexa 750 mg b.i.d., and 115.8 sec for Ranexa 1000 mg b.i.d. Angina attacks and nitroglycerin consumption decreased in patients on Ranexa in comparison with patients on placebo (Table 3).

Table 1. Treadmill Exercise Results (CARISA)

Ranexa Dose	Difference from Placebo (sec)	
	750 mg b.i.d.	1000 mg b.i.d.
Exercise Duration	trough	23.7*
	peak	34.0*
	trough	24.0*
	peak	26.1*
Time to Angina	trough	29.7*
	peak	38.0*
	trough	26.0*
	peak	37.9*
Time to 1 mm ST Depression	trough	19.9
	peak	40.8*
	trough	21.1

34.5*

Primary efficacy population N = 791
*p-value <0.05

Table 2. Treadmill Exercise Results (MARISA)

Ranexa Dose	Difference from Placebo (sec)	
	500 mg b.i.d.	1000 mg b.i.d.
Exercise Duration	trough	
	peak	
	trough	
	peak	
Time to Angina	23.8*	
	29.3*	
	33.7*	
	50.1*	
Time to 1 mm ST Depression	27.0*	
	35.5*	
	45.9*	
	56.4*	
Time to 1 mm ST Depression	27.6*	
	38.8*	
	44.5*	
	55.6*	

Primary efficacy population N = 175
*p-values ≤0.005

Table 3. Angina Frequency and Nitroglycerin Use (CARISA)

	Placebo	Ranexa 750 mg b.i.d.	Ranexa 1000 mg b.i.d.
Angina Frequency (attacks/week)			
	N		
	258	272	261
	Mean at baseline		
	4.6	4.4	4.4
	Mean on treatment		
	3.31	2.47	2.13
	<i>p-value vs. placebo</i>		
	—	0.006	<0.001
Nitroglycerin Use (number/week)			
	N		
	247	258	244
	Mean at baseline		

4.1

4.0

3.7

Mean on treatment

3.14

2.11

1.76

p-value vs. placebo

—

0.016

<0.001

In a population analysis of efficacy data, the anti-anginal and anti-ischemic effects of ranolazine were not dependent upon the age of the patients. The effects of ranolazine were also generally consistent across subgroups defined by baseline standing systolic blood pressures ≤ 100 mmHg, heart rates ≤ 60 bpm, or PR intervals ≥ 200 msec, and in patients with concomitant reactive airway disease, heart failure, or diabetes.

The ability of ranolazine to increase exercise performance in patients with chronic angina has been demonstrated within 3 hours after the first dose. Tolerance to ranolazine did not develop after 12 weeks of therapy. Rebound increases in angina, as measured by exercise duration, have not been observed following abrupt discontinuation of ranolazine.

INDICATIONS AND USAGE

Ranexa is indicated for the treatment of chronic angina in patients with severe coronary artery disease, and should be reserved for use in patients in whom other anti-anginals are inadequate or not tolerated (see **CLINICAL STUDIES**). Ranolazine prolongs the QTc interval (see **WARNINGS**). Some other drugs that prolong the QTc interval are associated with torsade de pointes, a potentially fatal ventricular arrhythmia. Whether ranolazine will cause torsade de pointes or increase the rate of sudden death is not yet known; however, because of the effect of ranolazine on QTc, consideration should be given to alternative treatments. Ranexa may be used alone or in combination with beta-blockers, calcium channel blockers, and/or nitrates.

CONTRAINDICATIONS

Ranexa is contraindicated in patients with a known hypersensitivity to any component of the product. In a pharmacokinetic study, eight subjects with mild and eight subjects with moderate hepatic impairment exhibited an average increase in QTc of 7.10 msec per 1000 ng/mL compared to 2.56 msec per 1000 ng/mL ranolazine plasma concentration in populations with no hepatic impairment. The predicted maximum increase in mean QTc in subjects with hepatic impairment exceeds 10 msec at the 500 mg dose level.

Co-administration of ketoconazole (400 mg/day) increased the mean peak plasma concentrations of ranolazine by a factor of 3.2 and the associated mean increase of QTc at [peak is predicted to amount to 9.2 msec at the 500 mg dose level.

WARNINGS

QT Prolongation

Treatment with ranolazine has been associated with small, dose-dependent increases in the QTc interval. A population analysis of the relationship between ranolazine concentration and QTc prolongation using data from patients with angina and healthy volunteers of both genders predicted mean maximum increases in QTc of 2.9 msec, 4.9 msec and 6.3 msec, respectively, for the dose levels 500 mg, 750 mg and 1000 mg. Age, weight, gender, race, heart rate, CHF NYHA Class I to IV, and diabetes had no significant effect on the slope of the relationship between ranolazine plasma level and increase in QTc. The relationship between ranolazine levels and QTc remains linear over a concentration range up to 4-fold greater than the concentrations produced by 1000 mg b.i.d., and is not affected by changes in heart rate.

The clinical significance of the QTc change is unknown. Prolongation of the QTc interval for certain other drugs has been associated with an increased risk of torsade de pointes and sudden death. The relationship between QT prolongation and torsade de pointes is clearest for larger increases in QTc, but it is possible that smaller QTc prolongations may also increase the risk for life-threatening arrhythmias, or increase the risk in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of ranolazine in premarketing studies, experience is too limited to rule out a potential risk. Because some other drugs that prolong QTc are associated with life-threatening ventricular arrhythmias, the use of Ranexa generally should be avoided in patients with QT prolongation (including congenital long QT syndrome) or a known history of ventricular tachycardia.

Pharmacodynamic studies with ranolazine and other drugs that prolong the QT interval have not been performed. An additive effect of ranolazine and other drugs that prolong the QT interval cannot be excluded. Therefore, the use of Ranexa generally should be avoided with other drugs that prolong the QT interval, including but not limited to, dofetilide, sotalol, quinidine, and other Class Ia and III anti-arrhythmics, and mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, moxifloxacin, gatifloxacin, sparfloxacin, erythromycin, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, or tacrolimus. The use of Ranexa generally should be avoided with drugs that have a pharmacodynamic effect of causing QT prolongation that is described in the full prescribing information as a contraindication or a boxed or bolded warning.

Metabolic Interactions

Ranolazine is primarily metabolized by CYP3A4, and its plasma level is increased by inhibitors of CYP3A4. (see **PRECAUTIONS, Drug-Drug Interactions**).

PRECAUTIONS

Use in Patients with Impaired Hepatic Function

(see **CLINICAL PHARMACOLOGY, Special Populations** and **CONTRAINDICATIONS**).

Use in Patients with Impaired Renal Function

In patients with severe renal failure blood pressure should be carefully monitored. (see **CLINICAL PHARMACOLOGY, Special Populations** and **DOSAGE AND ADMINISTRATION**).

Use in Patients with Congestive Heart Failure

No dosage adjustment is required in patients with CHF (NYHA Class I to IV) (see **CLINICAL PHARMACOLOGY, Special Populations**).

Use in Patients with Diabetes Mellitus

No dosage adjustment is required in patients with diabetes (see **CLINICAL PHARMACOLOGY, Special Populations**).

Laboratory Tests

Average elevations of serum creatinine by 0.1 mg/dL and of blood urea nitrogen (BUN) by 0.5 to 1.2 mg/dL have been observed in healthy volunteers and angina patients. In patients with renal impairment, the percentage increase in creatinine from pretreatment values was of the same magnitude as in angina patients; BUN did not increase. The mechanism of this effect of ranolazine is not known. These elevations have a rapid onset, are generally dose-dependent for BUN, show no signs of progression during long-term therapy, and are rapidly reversible after discontinuation of ranolazine. Urinalysis results are unaffected by ranolazine.

HbA_{1c} decreased by approximately 0.5 to 0.9 percentage units from baseline in diabetic patients treated with Ranexa as compared to no change in patients on placebo. Both insulin-dependent and non-insulin-dependent patients responded similarly. The decreases in HbA_{1c} developed gradually over approximately 100 days and continued during a subsequent long-term safety study. The mechanism of this effect of ranolazine is not known. Hypoglycemia attributed to ranolazine was not observed.

Transient eosinophilia was observed infrequently on ranolazine. Small mean decreases in hematocrit (1.1%) were also observed on ranolazine; however, there was no evidence of occult fecal blood loss.

Information for Patients

To ensure safe and effective use of Ranexa, the following information and instructions should be communicated to the patient when appropriate.

Patients should be advised:

- that Ranexa may produce changes in the electrocardiogram (QTc interval prolongation)
- to inform their physician of any personal or family history of QTc prolongation, congenital long QT syndrome, or proarrhythmic conditions such as hypokalemia or hypomagnesemia
- that Ranexa generally should be avoided in patients receiving drugs that prolong the QTc interval such as Class Ia (e.g., quinidine, procainamide or Class III (e.g., amiodarone, sotalol) anti-arrhythmic agents, erythromycin, and antipsychotics
-
- to inform their physician of any other medications when taken concurrently with Ranexa, including over-the-counter medications
- to contact their physician if they experience palpitations or fainting spells while taking Ranexa
- that Ranexa may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile, or machinery, or engage in activities requiring mental alertness or coordination
- that Ranexa may be taken with or without meals
- that Ranexa tablets should be swallowed whole and not crushed, broken, or chewed

Drug-Drug Interactions (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions; and DOSAGE AND ADMINISTRATION)

Pharmacokinetic or Pharmacodynamic Interactions: Effects of Other Drugs on Ranolazine

Ketoconazole

As a potent inhibitor of CYP3A4, ketoconazole (400 mg/day) increased average steady-state

peak plasma concentrations of ranolazine 2.6- to 3.2 -fold (see **WARNINGS**).

Diltiazem

As a potent inhibitor of CYP 3A4 diltiazem (180 mg mg/day to 360 mg/Day) caused a dose dependent mean increase in the ranolazine plasma concentrations of 1.5 to 2.8 fold (see DOSAGE AND ADMINISTRATION).

Verapamil

Verapamil 360 mg/day increased the ranolazine steady-state peak plasma concentrations of ranolazine 1.9 fold. Ranexa should be discontinued during treatment with verapamil in doses >360 mg/day(see DOSAGE AND ADMINISTRATION).

Cimetidine

Co-administration of cimetidine (1200 mg/day) did not impact the plasma levels of ranolazine clinically relevantly.. No dose adjustment of Ranexa is required in patients treated with cimetidine.

Paroxetine

Co-administration of paroxetine (20 mg/day) did not impact the plasma levels of ranolazine clinically relevantly. No dose adjustment of Ranexa is required in patients treated with paroxetine.

Pharmacokinetic Interactions: Effects of Ranolazine on Other Drugs

Digoxin

As a result of an interaction at the P-glycoprotein level, co-administration of ranolazine and digoxin (0.125 mg/day or 0.250 mg/day) results in a 1.4- to 1.6-fold elevation of digoxin plasma concentrations. Digoxin levels should be measured following initiation of Ranexa therapy.

Simvastatin

Co-administration of ranolazine and simvastatin (80 mg/day) resulted in an up to 2-fold increase in the plasma concentrations of simvastatin and the HMG-CoA reductase inhibitory activity at steady-state for both drugs, indicating that ranolazine inhibits CYP3A4 *in vivo*. Liver function should be tested before and repeatedly after initiation of concomitant treatment with ranolazine and simvastatin and other statins such as levostatin or atorvastatin that are metabolized mainly by CYP 3A4 .

Warfarin

Co-administered ranolazine increases warfarin's effect on prothrombin time by a factor of 1.4 without increasing the exposure to (-)S- or (+)R-warfarin. Prothrombin time should be measured before and repeatedly after initiation of a treatment with ranolazine. An adjustment of the warfarin dose based on prothrombin time may be required in the presence of ranolazine.

Drug/Laboratory Test Interactions

Ranolazine is not known to interfere with any laboratory test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Ranolazine demonstrated no mutagenic potential in the following assays: Ames bacterial mutation assay, Saccharomyces assay for mitotic gene conversion, chromosomal aberrations assay in Chinese hamster ovary (CHO) cells, mammalian CHO/HGPRT gene mutation assay and mouse bone marrow micronucleus assay.

There was no evidence of carcinogenic potential in mice or rats. The highest oral doses used in carcinogenicity studies were 150 mg/kg/day for 21 months in rats (900 mg/m²/day) and 50 mg/kg/day for 24 months in mice (150 mg/m²/day). These doses are equivalent to 0.8 times and 0.1 times, respectively, the maximum recommended human dose (MRHD) of 2 grams on a mg/m² basis and represent the maximum tolerated doses in those species.

Ranolazine did not affect the fertility or reproductive capacity of male or female rats at the highest oral doses of 300 mg/kg/day or 1800 mg/m²/day (1.5 times the MRHD on a mg/m² basis).

Pregnancy -- Pregnancy Category C

Ranolazine was not teratogenic in rats or rabbits at highest oral doses of 400 mg/kg/day (2400 mg/m²/day) and 150 mg/kg/day (1275 mg/m²/day), respectively. These doses are equivalent to up to 2.0 times the MRHD. At the highest dose that caused maternal toxicity in rats, but not in rabbits, there was a reduction in fetal weight and a decrease in skeletal ossification. There are no adequate well-controlled studies in pregnant women. Ranexa should be used during pregnancy only when the potential benefit to the patient justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether ranolazine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from ranolazine in nursing infants, a decision should be made whether to discontinue nursing or to discontinue Ranexa, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of chronic angina patients in studies of ranolazine, 521 (51%) were ≥ 65 years of age, and 116 (11%) were ≥ 75 years of age. No overall differences in safety or efficacy were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Over 2600 patients/subjects have been exposed to one or more doses of ranolazine in various formulations during the ranolazine clinical development program, corresponding to approximately 1170 patient/subject years. Adverse events were assessed in a total of 2103 patients with chronic angina in controlled parallel and crossover design studies; of these, 749 were treated with Ranexa, and 988 were treated with ranolazine immediate-release (IR). Of the patients treated with Ranexa, 745 were enrolled in two double-blind, placebo-controlled, randomized studies (CARISA and MARISA) of up to 12 weeks duration. In addition, upon study completion, 550 patients from CARISA and MARISA received continued treatment with Ranexa in open-label, long-term studies. Data are included for 276 patients continuously exposed to Ranexa for more than 1 year and 101 patients for more than 2 years. Subgroup evaluations in patients with reactive airway disease, CHF, diabetes and low blood pressure, heart rate, and/or prolonged AV node conduction were also conducted. These conditions did not alter the general nature or frequency of treatment-emergent adverse events observed in the broader ranolazine-treated population.

In general, the adverse events reported with ranolazine were mild to moderate in severity. The most frequently reported treatment-emergent adverse events (incidence of 5% or greater) observed in controlled clinical studies in angina patients were dizziness (8.1%), constipation (6.5%), and nausea (5.7%). In open-label, long-term treatment studies, a similar adverse event profile was observed among patients treated with ranolazine. Adverse events typically appear during the first 1 to 2 weeks after the start of treatment.

Most adverse events were well-tolerated, with <10% of patients discontinuing due to an adverse event. The most commonly reported adverse events which led to discontinuation more frequently on ranolazine than on placebo were dizziness (1.7% vs 1.1%) and nausea (1.3% vs 1.0%).

Small, reversible elevations in serum creatinine and BUN levels have been observed in angina patients treated with ranolazine. These elevations were observed without evidence of renal toxicity; however, the mechanism for these effects is unknown (see **PRECAUTIONS, Laboratory Tests**).

Adverse Events Occurring at an Incidence of $\geq 2\%$ Among Angina Patients in the CARISA and MARISA Trials

Adverse event data for chronic angina patients from controlled safety and efficacy studies is presented in Table 4. The most commonly observed treatment-emergent adverse events that occurred in ranolazine-treated patients at a higher frequency than placebo-treated patients were dizziness, constipation, nausea, asthenia, headache, and dyspepsia, and of these, the incidences of dizziness, constipation, nausea, and asthenia were dose-dependent.

Table 4: Treatment-Emergent Adverse Events (≥2%)

Number (%) of Angina Patients

CARISA Trial
b.i.d. dosing for up to 12 weeks
MARISA Trial
b.i.d. dosing 1 week each treatment

	Placebo N = 269	750 mg N = 279	1000 mg N = 275	Placebo N = 179	500 mg N = 181	1000 mg N = 180
Any AE	71 (26.4)	87 (31.2)	90 (32.7)	26 (14.5)	28 (15.5)	37 (20.6)
Body as A Whole	28 (10.4)	22 (7.9)	29 (10.5)	10 (5.6)	6 (3.3)	9 (5.0)
Abdominal Pain	2 (0.7)	2 (0.7)	7 (2.5)	1 (0.6)		

	1 (0.6)
	2 (1.1)
Asthenia	
	6 (2.2)
	5 (1.8)
	13 (4.7)
	3 (1.7)
	0
	3 (1.7)
Headache	
	4 (1.5)
	7 (2.5)
	6 (2.2)
	4 (2.2)
	1 (0.6)
	2 (1.1)
Pain	
	3 (1.1)
	2 (0.7)
	1 (0.4)
	0
	2 (1.1)
	4 (2.2)
Cardiovascular	
	29 (10.8)
	35 (12.5)
	28 (10.2)
	16 (8.9)
	9 (5.0)
	11 (6.1)
Angina pectoris	
	12 (4.5)
	11 (3.9)
	8 (2.9)
	8 (4.5)
	8 (4.4)
	2 (1.1)

Digestive System

18 (6.7)
36 (12.9)
41 (14.9)
3 (1.7)
2 (1.1)
8 (4.4)

Constipation

2 (0.7)
18 (6.5)
20 (7.3)
0
0
3 (1.7)

Dyspnea

4 (1.5)
7 (2.5)
5 (1.8)
0
1 (0.6)
1 (0.6)

Nausea

2 (0.7)
9 (3.2)
14 (5.1)
0
1 (0.6)
2 (1.1)

Nervous System

9 (3.3)
17 (6.1)
28 (10.2)
4 (2.2)
3 (1.7)
15 (8.3)

Dizziness

5 (1.9)
10 (3.6)

19 (6.9)
1 (0.6)
2 (1.1)
9 (5.0)

Adverse Events Occurring Among All Ranolazine-Treated Patients with Chronic Angina

Ranolazine was evaluated in 1737 patients with chronic angina in controlled clinical trials. The most frequently reported adverse events ($\geq 2\%$) were consistent with those observed in CARISA and MARISA (dizziness, constipation, nausea, asthenia, headache, and dyspepsia).

Of the 1737 angina patients evaluated in controlled clinical trials, the following additional adverse events occurred at an incidence of >0.5 to $<2.0\%$ in patients treated with ranolazine and were greater than the incidence observed in placebo-treated patients. Other more rare ($<0.5\%$) but potentially medically important adverse events are also included (noted with an *):

Body as a Whole – accidental injury, allergic reaction, back pain, chest pain, infection, pain, viral infection

Cardiovascular System – coronary artery disorder*, hypertension, hypotension*, palpitation, peripheral edema*, postural hypotension, myocardial infarction*, myocardial ischemia*, syncope, tachycardia, vasodilation

Digestive System – diarrhea, anorexia, dry mouth, vomiting

Metabolic and Nutritional Disorders – BUN increased*, creatinine increased*, hypercholesterolemia, hyperglycemia, hyperlipemia

Musculoskeletal System – myasthenia

Nervous System – confusion*, hypesthesia*, insomnia, tremor, vertigo

Respiratory System – bronchitis, cough increased, dyspnea, pharyngitis, respiratory disorder, rhinitis, sinusitis

Skin and Appendages – rash

Special Senses – abnormal vision*, sweating, tinnitus

Urogenital – urine abnormality, hematuria*

DRUG ABUSE AND DEPENDENCE

Ranolazine does not have any potential for abuse or dependence.

OVERDOSAGE

No cases of intentional or accidental overdose with ranolazine have been reported. In the clinical development program, safety and tolerability have been documented at ranolazine plasma concentrations up to 4-fold those typically seen at the 1000 mg b.i.d. dosage level. In the event of overdose, the expected symptoms would be dizziness, nausea/vomiting, diplopia, paresthesia, and confusion. Syncope with prolonged loss of consciousness may develop. Because the QTc interval increases with ranolazine plasma concentration, continuous ECG monitoring may be warranted in the event of overdose. If required, general supportive measures should be initiated. Possible disturbances of cardiac rhythm should be treated

appropriately.

Since ranolazine is about 65% bound to plasma proteins, complete clearance of ranolazine by hemodialysis is not likely.

DOSAGE AND ADMINISTRATION

Therapy with Ranexa should be individualized according to each patient's response and the physician's clinical judgment.

Dose adjustments are generally not required on the basis of age or gender, or in patients with CHF or diabetes mellitus.

Ranexa may be taken with or without meals. The concomitant use of Ranexa with other commonly administered cardiovascular medications (beta-blockers, anti-hypertensive agents, calcium antagonists, and nitrates) is well-tolerated.

In subjects with impaired renal function ranolazine peak plasma concentrations increased 1.5 fold in mild (Clcr 51 to 80 mL/min), 1.4 fold in moderate (Clcr 30 to 50 mL/min) and 1.5 fold in severe renal impairment (Clcr<30 ml/min) compared to healthy subjects (Clcr>80 ml/min). In patients with severe renal impairment blood pressure should be monitored after initiation of treatment with Ranexa.

Peak plasma levels of ranolazine were increased by the strong CYP 3A4 inhibitors ketoconazole (2.6-3.2 fold increase), diltiazem (1.5 to 2.8 fold, dose and time dependently) and verapamil (1.9 fold).

The exposure to and the response of ranolazine after co-administration of strong CYP 3A4 inducers may be diminished and an adjustment of the dose of Ranexa may be required (see PRECAUTIONS and Drug-Drug Interactions).

Ranexa tablets should be swallowed whole and not crushed, broken, or chewed.

Rebound increases in angina have not been observed following abrupt discontinuation of Ranexa.

HOW SUPPLIED

Ranexa (ranolazine) is supplied as film-coated, oblong-shaped tablets containing the following amount of ranolazine:

Strength

Color

Marking

375 mg

pale blue

CVT 375

500 mg

light orange

CVT 500

Ranexa™ (ranolazine) Tablets are available in:

Strength

NDC Code

Unit-of-Use Bottle (60 Tablets)

375 mg

67159-AAA-AA

500 mg

67159-BBB-BB

Pharmacy Bottle (500 Tablets)

375 mg

67159-XXX-XX

500 mg

67159-YYY-YY

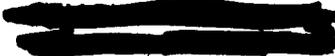
Store at controlled room temperature, 59° to 86° F (15° to 30° C).

REFERENCES

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Manufactured for:
CV Therapeutics, Inc.
Palo Alto, CA 94304 USA

By:



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PHARMACOMETRICS REVIEWS

Effectiveness and Safety (Other than QT)

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Compound:	Ranolazine
Submission Dates:	12/27/02
	03/15/03
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Sponsor:	CV Therapeutics
Pharmacometrics Reviewer:	B. Nhi Nguyen, Pharm.D.
Pharmacometrics Team Leader:	Joga Gobburu, Ph.D.

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1. Abbreviations

Abbreviation	Definition
ATP	Adenosine 5'-triphosphate
bid	twice daily
bsl	baseline
CHF	congestive heart failure
DM	Diabetes mellitus
EC_{50}	concentration that produces half the maximal response
Eff	effect
ETT	exercise treadmill test
h	hour
IR	immediate release
L_{max}	maximal learning
min	minutes
mg	milligram
NYHA	New York Heart Association
pbo	placebo
PPK	population pharmacokinetic
PD	pharmacodynamic
PK PD	pharmacokinetic pharmacodynamic

pts	patients
q	every
qd	daily
SD	standard deviation
SE	standard error
sec	seconds
SR	sustained release
tid	three times a day
TV	typical value
tx	treatment
wk	weeks

2. Introduction

Ranolazine (NDA 21-526) is proposed for the treatment of chronic angina in patients with severe coronary artery disease when other anti-anginals are inadequate or intolerable.

Objectives of the analysis: Determine the relationship between plasma concentrations and effect on duration of exercise treadmill test (ETT) and safety (other than QT).

Background: Ranolazine is believed to partially inhibit fatty acid uptake and oxidation. Ranolazine appears to shift ATP production away from fatty acid oxidation in favor of more oxygen-efficient carbohydrate oxidation. Thereby reducing oxygen demand without decreasing the ability of the heart to do work. It is claimed to have minimal effects on blood pressure and heart rate. Its antianginal effects appear to be via optimization of myocardial metabolism during ischemia, rather than reduction in cardiac work. The proposed dose is ranolazine SR (sustained release) 500 mg –1000 mg twice daily.

Population PK (PPK) analysis: The sponsor conducted a formal population PK analysis, however, this was a stand alone analysis and was not used in any of the PK/PD (pharmacokinetic/pharmacodynamic) analysis. See Dr. Atul Bhattaram's review of the PPK analysis.

PK/PD analysis: The relationship between concentration and duration on exercise treadmill in patients with cardiac angina was modeled. The observed peak and trough concentrations were used to drive the PD effectiveness model.

3. Executive Summary

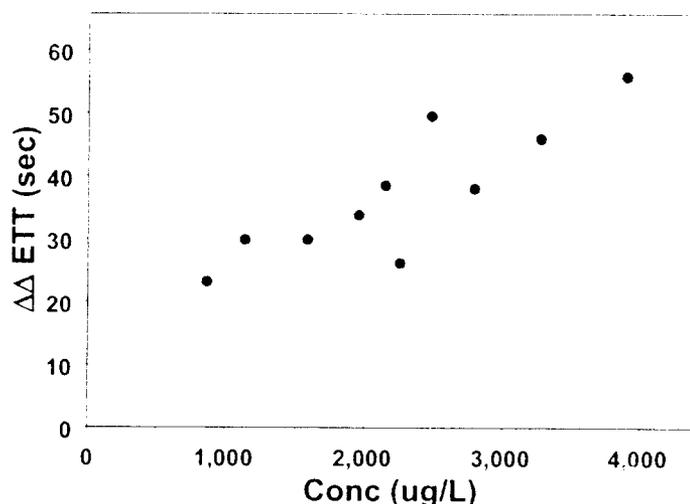
There is a significant nonlinear relationship between ranolazine plasma concentrations and effectiveness. Females have less proportional (effect relative to placebo) benefit from ranolazine than males: ~ 70 % and 60 % less proportional benefit from ranolazine SR 500 mg q 12 h and 1000 mg q 12 h, respectively. The time for 50 % reduction from peak effect is ~8-10 hours for the SR 500 mg and ~15-17 hours for the SR 750 mg, SR 1000 mg and SR 1500 mg dose in males. The time for 50% reduction from peak effect in females is approximately 8-11 hours, but the peak effect in females is lower. Learning to walk on the treadmill gradually increased and eventually reached a plateau in studies RAN 1514, CVT 3031 and CVT 3033. Learning to walk followed a linear model in RAN 080. Patients with CHF have proportionally more benefit from ranolazine than patients without CHF, although the maximal learning capacity in patients with CHF is smaller than in patients without CHF. Drug effect is independent of CHF. There does not seem to be a carryover effect on effectiveness in the cross-over study CVT 3031. Russian center #710 does not seem to significantly influence the ETT duration.

4. Question Based Review – Effectiveness

5. Is there a ranolazine concentration dependent change in ETT duration from placebo ($\Delta\Delta\text{ETT}$)?

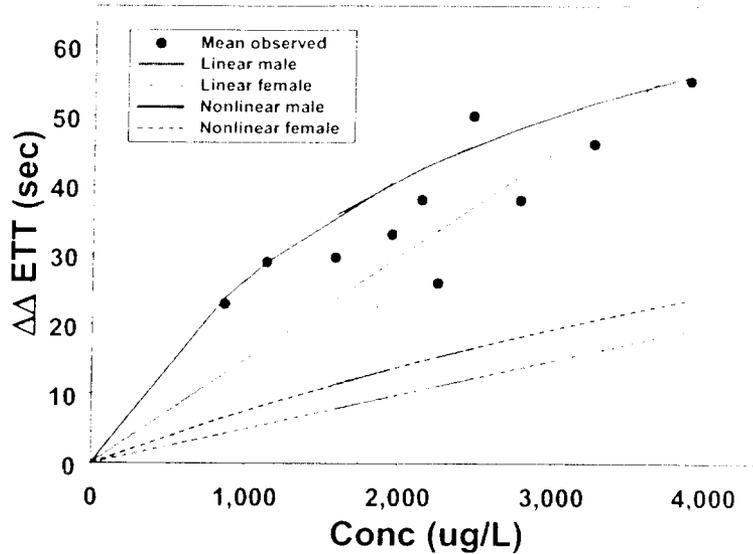
Figure 1 shows the relationship between observed mean peak and trough concentrations of the doses used in the two pivotal trials CVT 3031 and CVT 3033 and the observed mean $\Delta\Delta\text{ETT}$ in seconds. (See 0 for mean concentrations by dose.) Figure 1 suggests that there is a concentration effect relationship.

Figure 1. Observed mean peak and trough concentration vs. observed mean $\Delta\Delta\text{ETT}$ in CVT 3031 and CVT 3033



The reviewer found a significant nonlinear relationship between ranolazine plasma concentrations and ETT duration. The model with a drug effect was significantly better than the model with no drug effect (maximal effect = 0). The reviewer also tested a linear effectiveness model, because the sponsor's final model was linear. Figure 2 shows the observed mean $\Delta\Delta\text{ETT}$ and the model predictions for both linear and nonlinear models. The reviewer's final model was a nonlinear effectiveness model because it better predicted the observed mean $\Delta\Delta\text{ETT}$ duration, especially at lower concentrations, and was significantly better than the linear model. The linear model underpredicted the observed mean drug effect ($\Delta\Delta\text{ETT}$) of the SR 500 mg q 12 h dose. The difference between observed mean and model predicted is smaller with the nonlinear model. Because there was a significant gender difference, the model predictions in Figure 2 are separated by gender. It is noted that the data contained 78 % males, and males had a greater drug effect than females. Predicted mean $\Delta\Delta\text{ETT}$ of males, as one would expect, are higher than the naïve average of observed $\Delta\Delta\text{ETT}$. Thus, combining the gender data would result in a model predicted line closer to the observed mean $\Delta\Delta\text{ETT}$.

Figure 2. Reviewer's model predicted and observed mean $\Delta\Delta ETT$



The reviewer's final model predicted $\Delta\Delta ETT$ at trough and peak concentrations are shown in 0. Combining the genders results in predictions close to observed except for the SR 1000 mg dose in study CVT 3033 (discussion to follow). The $\Delta\Delta ETT$ was calculated using the mean trough and peak concentrations in studies CVT 3031 and CVT 3033 (0).

Table 3. Reviewer's final model predicted peak and trough mean $\Delta\Delta ETT$ (seconds)

	Males		Females	
	Trough	Peak	Trough	Peak
500 mg SR q 12h – CVT 3031	23.8	28.9	6.6	8.4
750 mg SR q 12h – CVT 3033	35.8	42.5	11.4	14.7
1000 mg SR q 12h – CVT 3031	40.4	45.7	13.6	16.5
1000 mg SR q 12h – CVT 3033	43.6	48.3	15.3	18.2
1500 mg SR q 12h – CVT 3031	51.9	55.7	20.6	23.5

The reviewer generated 0. The numbers are slightly different from the sponsor's for reasons discussed in Reviewer's Comments (61, page 339).

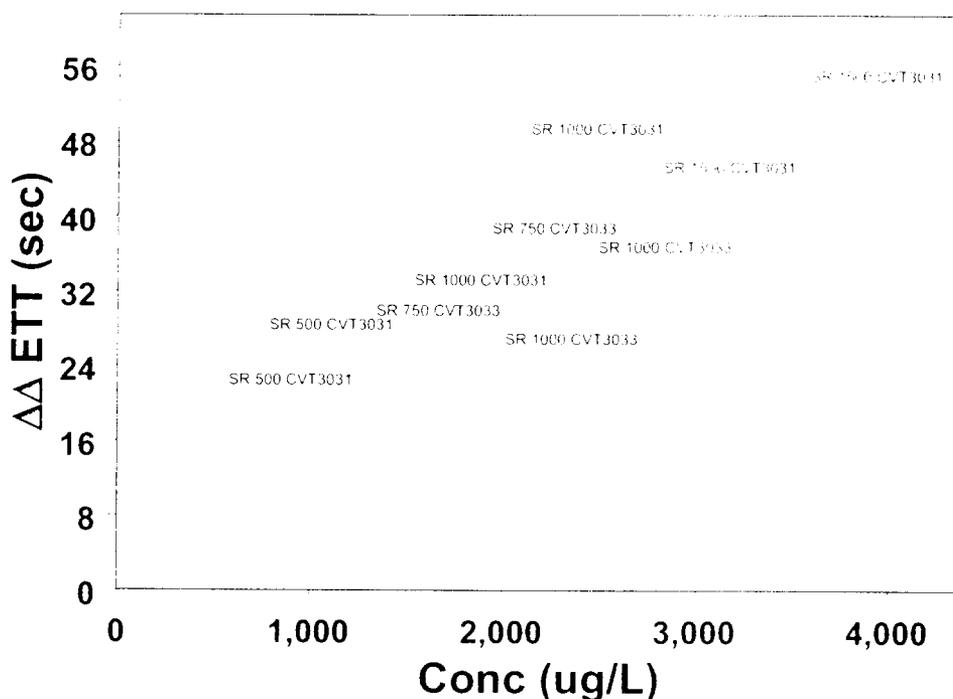
Table 4. Peak and trough concentrations in CVT 3031 and CVT 3033

	SR 500 mg	SR 750 mg	SR 1000 mg	SR 1000 mg	SR 1500 mg
	CVT 3031	CVT 3033	CVT 3031	CVT 3033	CVT 3031
Trough (ug L)	864 ± 720	1585 ± 1076	1954 ± 1425	2255 ± 1550	3264 ± 1917
Peak (ug L)	1136 ± 721	2145 ± 1235	2473 ± 1522	2785 ± 1537	3891 ± 2021

(mean ± SD)

The observed mean $\Delta\Delta\text{ETT}$ from the SR 1000 mg BID dose in study CVT 3033 (parallel study) was 24.0 and 26.1 seconds at trough and peak, respectively. However, the same dose in study CVT 3031 (cross-over study) had a mean $\Delta\Delta\text{ETT}$ of 33.7 and 50.1 seconds at trough and peak, respectively. Figure 3 shows that the 1000 mg dose in CVT 3033 does not follow the same trend as the rest of the data, yet the 750 mg dose, also used in study CVT 3033, follows the same trend as the doses used in CVT 3031. The reviewer cannot explain this.

Figure 3. Observed mean peak and trough concentration vs. observed mean $\Delta\Delta\text{ETT}$ in CVT 3031 and CVT 3033 – data shown by dose and study



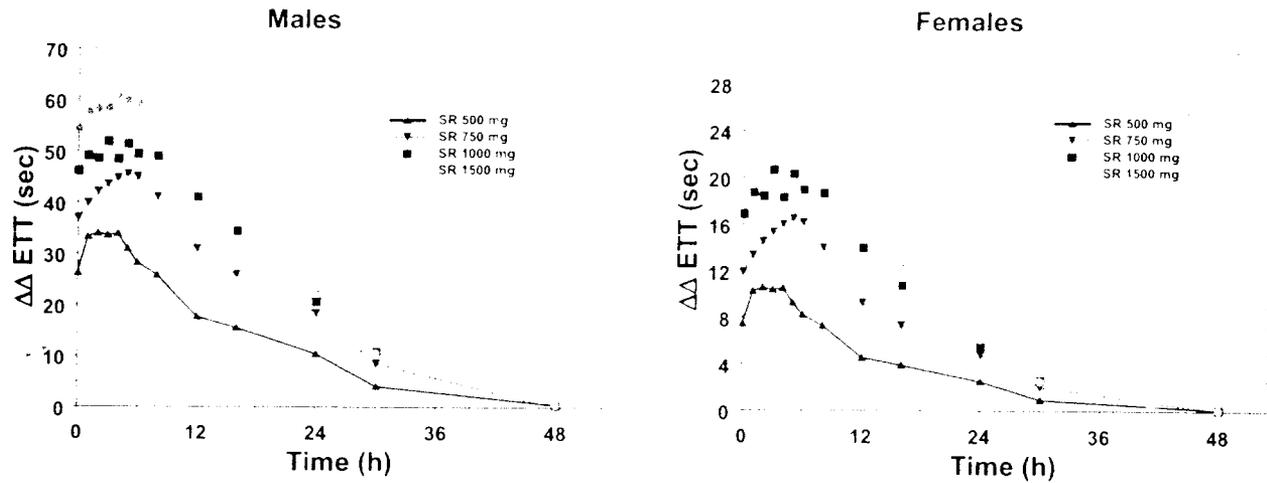
6. What is the time course of effectiveness of ranolazine?

Figure 4 shows the model predicted time course of effectiveness at steady state for ranolazine SR dosed every 12 h for 24 hours in males and females. The time for 50 % reduction from peak effect is ~8-10 hours for the SR 500 mg and ~15-17 hours for the SR 750 mg, SR 1000 mg and SR 1500 mg dose in males. The time for 50 % reduction from peak and is approximately 8-11 hours in females for all doses, but the peak effect in females is lower.

The reviewer generated Figure 4 by using observed mean steady state plasma concentrations from studies RAN 0114 (SR 500, 750, 1000mg) and RAN 0201 (SR 1500 mg) in the final model. Although healthy male volunteers participated in these studies, there are no considerable differences in pharmacokinetics between patients and volunteers, nor are there considerable differences in pharmacokinetics between genders. In general, RAN 0114 and RAN 0201 had lower mean troughs and higher mean peaks by ~300 ug/L compared to that observed in studies CVT 3031 and CVT 3033. Notably, the mean peak for SR 1500 mg was higher than that in CVT

3031 by ~ 1000 ug/L. However, the differences in mean concentrations are within the variability of the drug.

Figure 4. Model predicted time course of effectiveness at steady state for SR ranolazine q 12 h – Note the different y-axes range



7. Is there a gender difference in baseline walking time?

Yes, at baseline females walk for a shorter time on a treadmill than males. The typical value of the baseline treadmill duration in a 64 year old (median age in effectiveness analysis) patient in study CVT 3033 is 5.47 minutes if female and 6.27 minutes if male. Thus, at baseline, females walk 48 seconds less than males.

8. Is there a gender difference in effectiveness?

Yes, females have less of an effect from ranolazine compared to males. See Table 22, page 352 for a comparison of effectiveness at peak and trough.

The smaller baseline duration and higher concentrations required for effectiveness translate into a smaller proportional effect (effect relative to placebo) in females. For example, a 64 year old female given ranolazine SR 500 mg q 12 h in study CVT 3031 would have the following effect at trough relative to placebo.

$$\frac{\text{Drug Eff}}{\text{Pbo ETT duration}} \cdot 100 = \frac{\text{Drug Eff}}{TV_{BSL} + TV_{TMAX}} \cdot 100 = \frac{6.54 \text{ sec}}{5.47 \text{ min} + 3.19 \text{ min}} \cdot \frac{1 \text{ min}}{60 \text{ sec}} \cdot 100 = 1.3 \%$$

where TV_{BSL} is the typical baseline ETT (min) and TV_{TMAX} is the typical maximal learning (min).

A 64 year old female receiving SR 500 mg q 12 h would typically have 1.3 % higher ETT duration than one receiving placebo.

A 64 year old male given ranolazine SR 500 mg q 12 h in study CVT 3033 would have the following effect at trough relative to placebo.

$$\frac{\text{Drug Eff}}{\text{Pho ETT duration}} \cdot 100 = \frac{\text{Drug Eff}}{TV_{BSL} + TV_{LMAX}} \cdot 100 = \frac{23.76 \text{ sec}}{6.27 \text{ min} + 3.19 \text{ min}} \cdot \frac{1 \text{ min}}{60 \text{ sec}} \cdot 100 = 4.2 \%$$

A 64 year old male receiving SR 500 mg q 12 h would typically have 4.2 % higher ETT duration than one receiving placebo.

Thus, a lower baseline treadmill duration and a smaller drug effect in females translate into approximately 70 % $\left(\frac{1.26 - 4.19}{4.19} \right)$ less proportional benefit from ranolazine SR 500 mg q 12 h than males. Because the concentration-effect relationship is nonlinear, the proportional benefit decreases with higher doses. For the 1000 mg dose and 1500 mg dose, females have approximately 60 % and 55 % less proportional benefit than males, respectively. Administering relatively higher doses to females might not be feasible because of the concentration dependent QTc prolongation. (See Dr. Bhattaram's review of QT prolongation.)

9. Do patients with CHF benefit more from ranolazine?

Patients with CHF have proportionally more benefit from ranolazine than patients without CHF.

The typical value of the maximal learning in a 64 year old male without CHF in study CVT 3033 is 3.19 minutes (SE, $\pm 6.6 \%$). Patients with CHF have ~25 % less maximal learning capacity than patients without CHF, or 2.39 minutes (SE, $\pm 23.5 \%$) vs. 3.19 minutes. However, the drug effect is independent of the presence or absence of CHF. Thus, a 64 year old male with CHF given ranolazine SR 500 mg q 12 h in study CVT 3033 would have the following effect relative to placebo,

$$\frac{\text{Drug Eff}}{\text{Pho ETT duration}} \cdot 100 = \frac{\text{Drug Eff}}{TV_{BSL} + TV_{LMAX}} \cdot 100 = \frac{23.76 \text{ sec}}{6.27 \text{ min} + 2.39 \text{ min}} \cdot \frac{1 \text{ min}}{60 \text{ sec}} \cdot 100 = 4.6 \%$$

A similar patient without CHF would have the following effect relative to placebo.

$$\frac{\text{Drug Eff}}{\text{Pho ETT duration}} \cdot 100 = \frac{\text{Drug Eff}}{TV_{BSL} + TV_{LMAX}} \cdot 100 = \frac{23.76 \text{ sec}}{6.27 \text{ min} + 3.19 \text{ min}} \cdot \frac{1 \text{ min}}{60 \text{ sec}} \cdot 100 = 4.2 \%$$

Therefore, a patient with CHF has approximately 10 % $\left(\frac{4.6 - 4.2}{4.2} \right)$ more proportional benefit than a patient without CHF.

10. Do concomitant medications significantly affect the effectiveness of ranolazine?

The sponsor examined if the following medications affected the effectiveness: beta-blockers, atenolol, diltiazem, verapamil, amlodipine, calcium channel blockers and nitrates. The sponsor

did not find a significant effect of these concomitant medications on the effectiveness of ranolazine. The analysis done by the sponsor is satisfactory to the reviewer.

Additionally, the reviewer examined if diltiazem or verapamil affected the effectiveness in the reviewer's final model. The concomitant drugs were tested on baseline treadmill duration to determine if there were baseline differences in treadmill duration in patients receiving the concomitant medication compared to patients not receiving the concomitant medication. There were no differences at baseline between the two groups. When the concomitant drug was tested on the drug effect, neither drug significantly affected the effectiveness.

It should be noted that there are pharmacokinetic effects with verapamil and diltiazem on ranolazine. Increases in ranolazine concentrations are observed. See Dr. Hinderling's review of the drug drug interactions.

11. Is there a carry-over effect on the effectiveness in study CVT 3031?

The reviewer believes that a carryover effect in the cross-over study CVT 3031 is unlikely. Patients in study CVT 3031 received four treatments for one week each without an interim washout between treatments. There are two scenarios that can result in a carryover effect,

1. Long pharmacokinetic half-life of parent or active metabolite and/or
2. Persistent pharmacodynamic effect after active moiety is eliminated because of slow onset or offset.

Regarding the pharmacokinetics, the half-life of the parent drug is approximately 7 hours. Therefore, the parent drug is completely eliminated in less than 7 days. In the mass balance study, 83% of the total radioactivity was recovered by 48 hours post dose. By one week, ~ 98% of total radioactivity was recovered. Thus, the parent drug and any metabolites are completely eliminated within one week. For these reasons, it is unlikely that pharmacokinetics would contribute to a carryover effect.

Regarding the pharmacodynamics, if there were a carryover effect, then the significance of the drug effect would not be maintained in a cross-over study. The reviewer separated data from the four studies used in the population PK/PD analysis by study design (cross-over or parallel). Studies RAN 080, RAN 1514 and CVT 3031 were all cross-over study designs with no interim washout and study CVT 3033 was a parallel study. Each data set was analyzed with and without drug effect. The analysis showed a significant drug effect, $p < 0.0001$, in both the parallel and cross-over studies. Additionally, the parameter estimates of the analysis with drug effect for both the parallel and cross-over studies are similar to the final model (Table 21). It should also be noted that our model accounts for the learning effect across the study duration. This analysis supports no carryover effect from persistent pharmacodynamics.

12. Does Russian center 710 in study CVT 3033 have more influence on the effectiveness than the other centers?

It is unlikely that Russian center 710 has more influence on the effectiveness than the other study centers.

Possible reasons for Russian center 710 to have more influence on the effectiveness include:

1. Higher concentrations.
2. Different patient characteristics.
 - 2a. Were the baseline ETTs lower in Russian, leading to proportionally more effect?
3. More pharmacodynamic effect.

Point 1 - concentrations

Concentrations in the 42 patients in Russian center 710 seem higher than all other patients in the PK /PD analysis of effectiveness (studies CVT 3033, CVT 3031, RAN 080 and RAN 1514) (Table 5). Yet patients at center 710 were equally (n=14) randomized to placebo, 750 mg and 1000 mg. The 1st quartile concentration is almost double, and the median concentration is higher than the rest of the world. Thus, if one ignores concentration data and only analyzes the effectiveness by dose, one may falsely conclude that there is more effect in center 710 when the reason why center 710 may seem to have more effectiveness may be because concentrations are higher, especially at trough. The reviewer's analyses of the effectiveness uses concentration and not dose. Thus, the reviewer did not find center 710 to have more effectiveness.

Table 5. Concentrations (ug/L) in Russian center 710 & the rest of the world

	Russian center 710	Rest of the world
1 st Quartile	1,118.00	636.23
Median	1,765.00	1,460.30
Mean	1,837.00	1,777.10
3 rd quartile	2,313.00	2,500.00

It is noted that all patients in study CVT 3033 received the same formulation, DSM sustained release tablet. Thus, possible differences in formulation are excluded.

Point 2 –patient characteristics

Other than a higher percentage of patients with CHF and concomitant diltiazem in site 710, the baseline demographics were similar (See Table 6).

Table 6. Baseline characteristics of patients in site 710 and all sites in study CVT 3033

	Russian center 710	Study 3033
Males	75 %	78 %
CHF	97 %	29 %
Weight (kg)	80.5 ± 10.3	80.6 ± 12.9
Height (cm)	169.3 ± 6.3	170.0 ± 8.6
Age (years)	56.7 ± 6.1	64.4 ± 9.2
Baseline ETT time (min)	7.6 ± 2.0	7.3 ± 1.9
Concomitant diltiazem	36 %	21 %

Mean ± SD

Of the patients in Russian site 710, mean concentrations of those patients taking diltiazem were not different from those patients not taking diltiazem (see Table 7).

Table 7. Ranolazine concentrations of patients in Russian center 710 by diltiazem treatment

	On diltiazem	No diltiazem
--	---------------------	---------------------

750 mg	1597 ± 307	1781 ± 647
1000 mg	2025 ± 708	1694 ± 562
Mean ± SD		

To determine if there were differences at baseline, center 710 was first tested as a covariate on the baseline treadmill duration and then on maximal learning. The results indicated that patients in center 710 did not have different baseline treadmill durations or maximal learning ($p > 0.05$).

Point 3 - pharmacodynamics

To determine if there were differences in pharmacodynamics, the reviewer first tested if a significant drug effect was preserved when the Russian data were removed (42 patients removed). The drug effect was significant ($p < 0.05$). Thus, removing the Russian data still preserves a significant drug effect that was also found with the final model.

Second, the parameter estimates of the drug effect model without Russian center 710 data were similar to the final model. Specifically the EC_{50} s are similar between the final model and the drug effect model without Russian center 710 data. These data support that there are no differences in pharmacodynamics.

Table 8. EC_{50} of reviewer's final model and final model without Russian center 710

	Final model	Model without Russian center
EC_{50} male (ug/L)	2,400	2,690
EC_{50} female (ug/L)	10,980	11,000

Because of differences in concentrations, similar patient characteristics and pharmacodynamics, it is unlikely that Russian site 710 has more influence on the effectiveness.

13. Is the every 12 hour dosing regimen optimal?

The development program for ranolazine induced angina with exercise. This suggests that ranolazine may be more suitable for patients with angina on exertion. Another possibility is to aim for effective ranolazine concentrations during the day when patients are active. The actual data for an every 12 hour regimen shows that the time for 50 % reduction from peak effect is ~8 hours for the SR 500 mg and ~15-17 hours for the SR 750 mg, SR 1000 mg and SR 1500 mg dose (See Section 6, page 309).

The reviewer simulated the concentrations when ranolazine is dosed twice a day at other times. Employing the sponsor's population PK model for simulations was inevitable due to the lack of observed concentrations for different twice daily (not q 12 h) regimens. However, a nominal factor of 60% was added to the simulated concentrations to account for the underprediction by the sponsor's population PK model. The simulated concentrations were used in the final model to predict the $\Delta\Delta ETT$. Note that the predictions of $\Delta\Delta ETT$ (Figure 5) for the q 12 hour simulation are similar to predicted $\Delta\Delta ETT$ using actual data (0).

Figure 5 shows the steady state effect when 500 mg is dosed twice daily at different times in males and females. To maintain a $\Delta\Delta ETT$ of at least 12 seconds (Tiazac 120 mg dose trough $\Delta\Delta ETT$ in label) at trough, then in males all regimens are effective, however in females, dosing

at 0 and 6 hours or 0 and 8 hours are the regimens that may achieve this effect at the end of a 12 hour period.

Figure 5. $\Delta\Delta\text{ETT}$ from 500 mg BID regimens in males (left) and females (right) – Note the different y-axis range

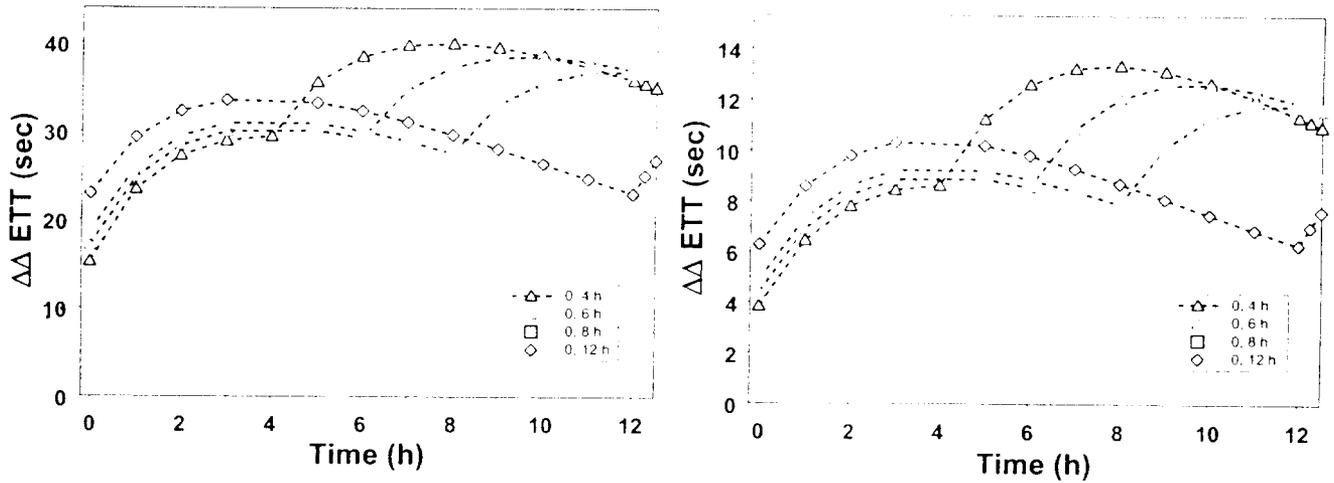
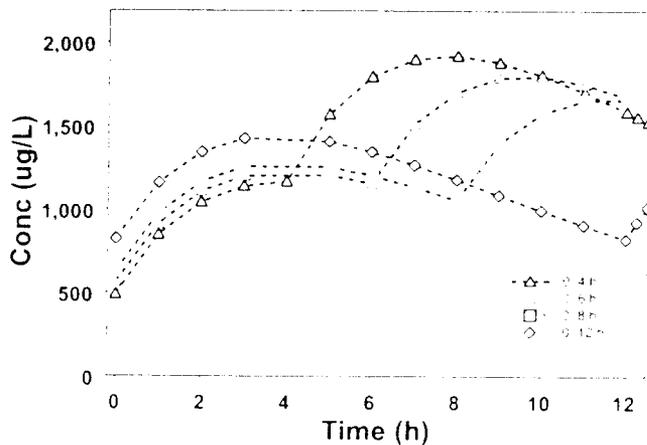


Figure 6 shows the concentration over time. The concentrations required for effectiveness with each dosing schedule should be considered with respect to safety also. Dosing at 0 and 4 hours does not seem to provide added benefit at 12 hours, compared to dosing at 0 and 6 hours or 0 and 8 hours, however this dosing schedule produces higher concentrations and longer exposure to higher concentrations than the other dosing schedules.

Figure 6. Simulated concentrations 500 mg BID regimens



14. Question Based Review – Safety Other than QT

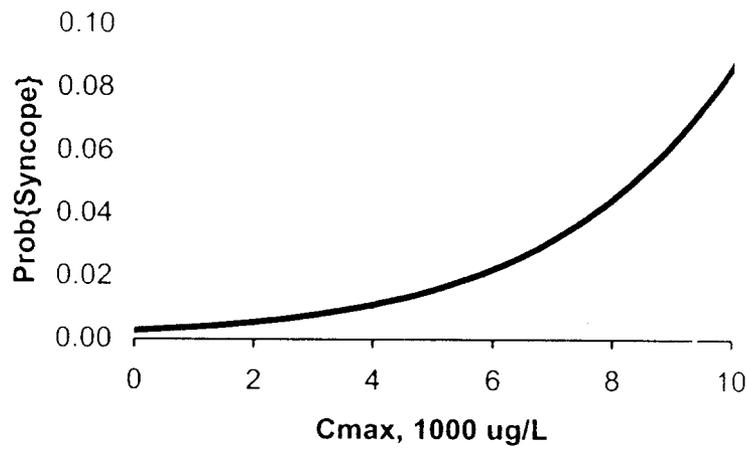
Data from 25 parallel studies (2,431 patients) were used in the safety analysis. These studies contain the longest exposure (12 weeks) and concentrations as high as 12,172 ug L. The mean maximum concentration was 1,960 ug L. C_{max} was used as a measure of exposure. It should

not be interpreted that the adverse event occurred at the maximum concentration. Since C_{max} and AUC are highly correlated, it was also likely that the adverse event was related to accumulated exposure.

15. Is syncope concentration dependent?

The reviewer found a significant concentration dependent effect on syncope. Figure 7 shows the probability of syncope as concentrations increase.

Figure 7. Probability of syncope



Concentrations as high as 9,000 ug/L observed with the SR 1000 mg bid dose translates into ~6% probability of syncope. Only one patient with syncope, out of 51 reports, also had hypotension reported.

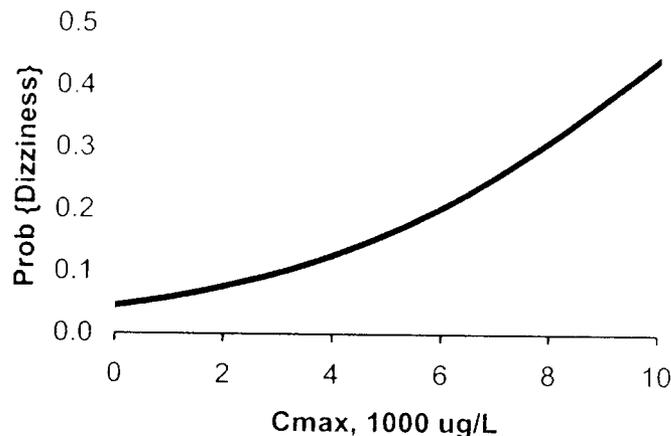
16. Is asthenia concentration dependent?

In the entire safety data set there were 760 reports of asthenia in 387 patients. There were 160 patients with asthenia in the parallel studies. We did not find a concentration dependent effect on asthenia.

17. Is dizziness concentration dependent?

The reviewer found a significant concentration dependent effect on dizziness. Figure 8 shows the probability of having dizziness as concentrations increase.

Figure 8. Probability of dizziness



Concentrations as high as 9,000 ug/L observed with the SR 1000 mg bid dose translates into ~35% probability of dizziness.

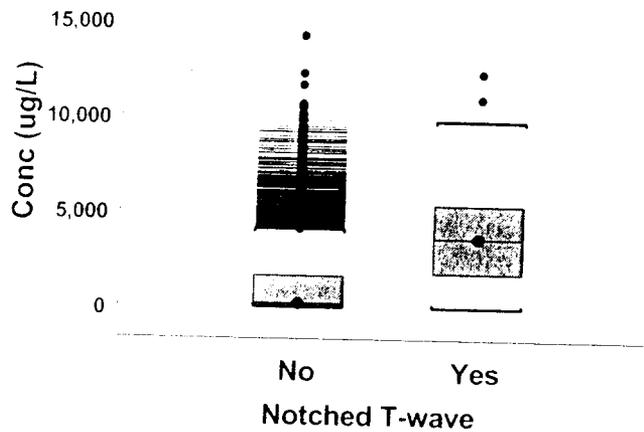
18. Are notched T-waves concentration dependent?

Fourteen studies with information on notched t-waves were available for analysis. This data set was the same one as that used in the population QTc analysis minus five studies because notched t-wave data were not reported. Thirty-one observations where the dose was zero and the concentration was greater than zero were removed by the reviewer. The removed observations did not contain notched t-waves. There were a total of 1271 patients, 458 of these patients continued on to the open label study. There were 283 reports of notched T-waves, 14,588 reports of no notched T-waves and 3 reported as unknown. Table 9 and Figure 9 show the concentrations of those with notched T-waves and those without. Overall, there seems to be a concentration dependent relationship, but the data are variable.

Table 9. Concentration (ug/L) of notched and no notched T-wave

Notch	Number pts	observations	Mean \pm SD	Median
No	1,728	14,588	1,035 \pm 1,532	180
Yes	118	283	3,758 \pm 2,604	3,660

Figure 9. Concentration of notched and no notched T-waves



19. Comments to the sponsor

- The sponsor used two different compilers for their analysis, yet the statistical results from different compilers cannot be directly compared. Most of the models were run using the compiler g77 version 2.95 19990728 release from FSF-g77 version 0.5.25 19990728 release. The final model was run using Compaq Digital Fortran compiler version 6.6 (update A). It is recommended that only one compiler be used for all analysis so that the statistical results can be directly compared.
- The sponsor used Excel for data manipulation. Software programs with manual manipulation, such as Excel, are highly discouraged for data manipulation because changes to the data set cannot be tracked or reproduced. It is highly recommended that software packages that keep a record of changes to the data set, such as SAS or Splus, be used for data manipulation. The NONMEM data set had two notable problems.
 - patients assigned to placebo had measurable plasma concentrations, and
 - patients assigned to drug had no plasma concentrations.
 It is possible that the samples were mishandled, however, it is also possible that during the data manipulation to create the NONMEM data set, the data were mixed up because manual manipulation was used.
- On a minor note, in the PK PD analysis plan the sponsor specified that the bias and precision would be calculated and compared against a pre-specified value. Unfortunately, the pre-specified value is expressed as percentage while the calculations were absolute differences. A more appropriate method of calculating the bias and (im)precision would have been to consider relative (to observed values) deviations.

- In the future, the sponsor is strongly encouraged to conduct exposure-toxicity analysis such as that performed by the reviewer, particularly when data are available.

20. Sponsor's Methods - Effectiveness

21. Design of CVT 00204 – Concentration - Effectiveness Analysis

vol. 284, p.183 - 319

The sponsor conducted a population PK/PD analysis (CVT 00204) of ranolazine plasma concentrations and treadmill exercise duration in patients with chronic stable angina enrolled into one of four randomized, double-blind, placebo-controlled, multiple dose studies:

- RAN 080 (Vol. 211, p.1 - 396)
- RAN 1514 (Vol. 237, p. 1 - 358)
- CVT 3031 (Vol. 64, p. 1 - 386)
- CVT 3033 (Vol. 78, p. 1 - 389)

Table 10 that starts on the next page summarizes the four studies.

Table 10. Description of studies used in concentration-effectiveness analysis

	RAN 080	RAN 1514	CVT 3031 Pivotal monotherapy trial	CVT 3033 Pivotal combination therapy trial
n	158 entered - 101 exercised on ETT - 57 exercised on bicycle	310	191	823
Design	Three-way, cross-over with no interim washout	Five-way (four treatment), cross-over with no interim washout	Four-way, cross-over with no interim washout	Multicenter, parallel with a rebound assessment two days after the last dose
Primary objective	Time to onset of angina during exercise testing at peak (1 hour post dose)	Exercise treadmill time to onset of angina at trough	Exercise treadmill time at trough	Symptom-limited exercise treadmill time at trough
Treatments (tx)	Ranolazine IR 400 mg tid Atenolol 100 mg qd Placebo	Ranolazine IR 267 mg tid Ranolazine IR 400 mg bid Ranolazine IR 400 mg tid Placebo	Ranolazine SR 500 mg bid Ranolazine SR 1000 mg bid Ranolazine SR 1500 mg bid Placebo	Ranolazine SR 750 mg bid. Ranolazine SR 1000 mg bid or Placebo
Treatment duration	7-10 days each	1 wk each	1 wk each	12 wks
				Stratified by background antianginals <ul style="list-style-type: none"> • diltiazem 180 mg qd • atenolol 50 mg qd or • amlodipine 5 mg qd Antianginal started at least 5 days prior to ranolazine or placebo.

2

Total treatment duration	4 wks	1 tx repeated 5 th wk 5 wks	4 wks	12 wks

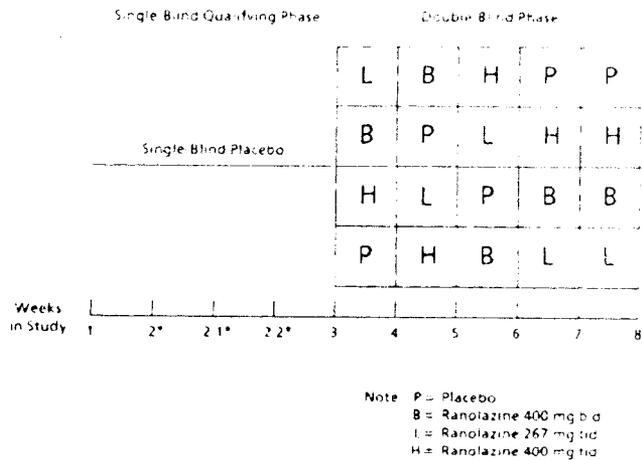
11

Table 7. Description of studies used in concentration-effectiveness analysis (continued)

	RAN 080	RAN 1514	CVT 3031 Pivotal monotherapy trial	CVT 3033 Pivotal combination therapy trial
Actual time of trough ETT assessment	N/A	7 AM to 10 AM Trough - 8 h after the last dose for the tid tx & 12 h after the next to last dose of the previous day for the bid tx.	7 AM to 12 PM	7 AM to 12 PM
Plasma concentration collection	Peak: 1 hour after study drug intake, before the ETT, for a total of three samples taken per patient. However, only one ranolazine sample per patient.	Trough & peak during each of the five ETT visits Trough - 8 ± 1 h after the last dose of the previous day or 12 ± 1 hour after the second to last dose of the previous day. Peak - 1 ± 0.25 hours after the AM dose. early withdrawal - trough taken	Trough & peak before the ETTs (Day 7, 14, 21 & 28) Trough - ~ 12 h after the last dose Peak 4 h after the in-clinic dose Eight total samples per patient.	Trough: 12 ± 0.5 hours after the last dose of study medication in the morning of visits 3, 4, 5, and 6 (end of Week 2, 6, 12 and Week 12 Day 2 of the treatment phase). Peak: 4 ± 0.5 hours after the in clinic dose at Visits 3 and 5 (end of Week 2 and 12 of the treatment phase).
Other notes	Investigators were allowed to use bicycle or treadmill for the exercise test.	Concomitant antianginals remained constant. Patients could not take long-acting nitrates or digoxin.	Study sites: U.S., Canada, Czech republic & Poland	118 study sites in 15 countries

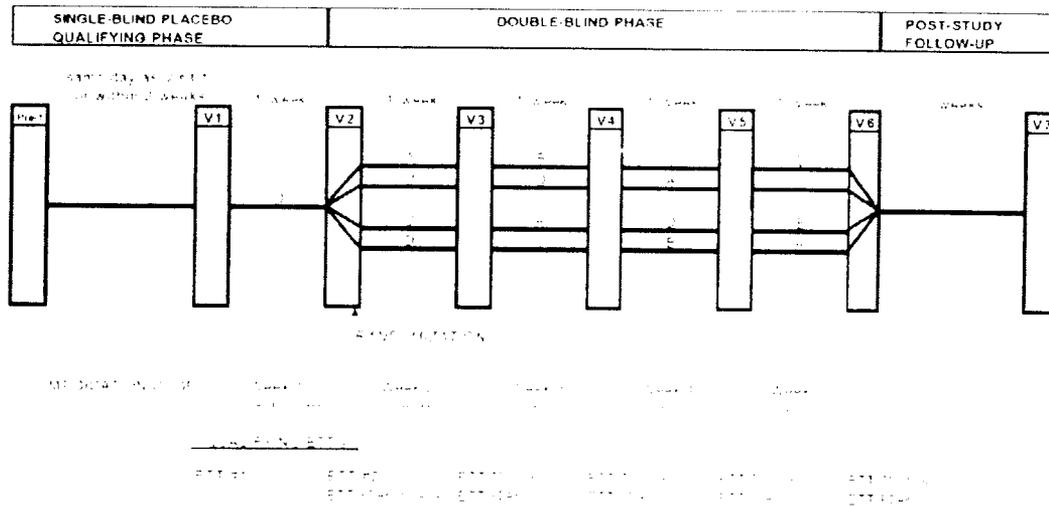
A schematic of the study procedures for RAN 1514, CVT 3031 and CVT 3033 are shown in Figure 10, Figure 11, and Figure 12, respectively.

Figure 10. Study procedures RAN 1514



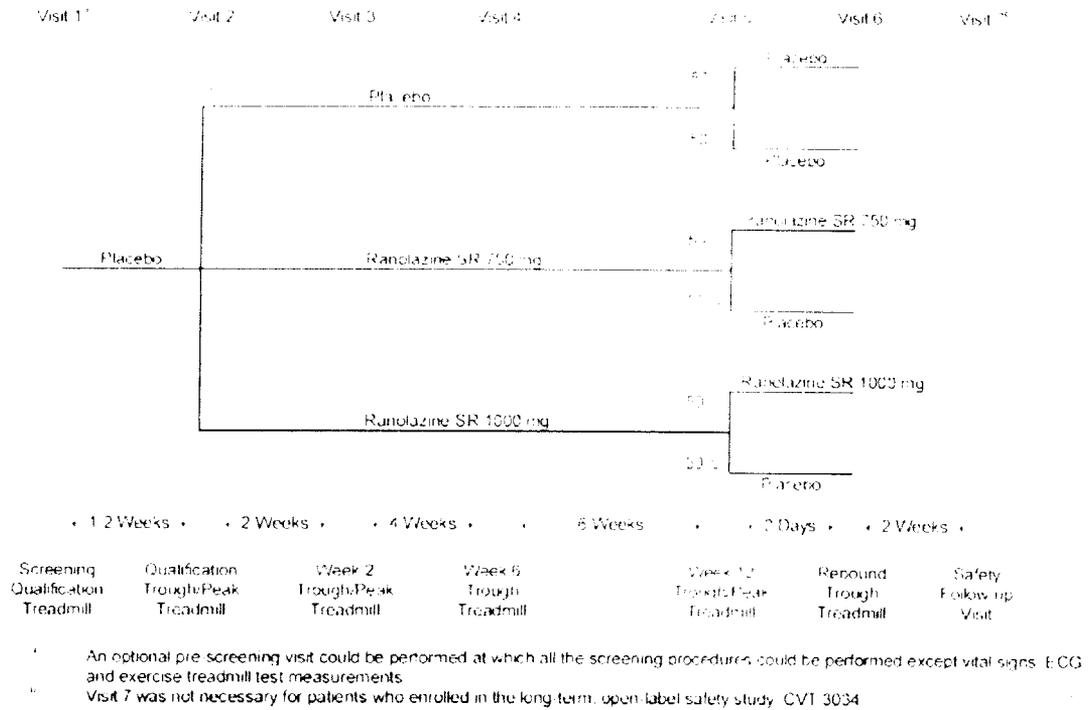
* Single-blind placebo could be given two additional weeks in order to qualify for entry. Evaluations at weekly visits during the double-blind phase included: exercise treadmill tests and hemodynamic data at trough and peak, weekly diary data, ECG at rest, laboratory tests, compliance, concomitant medications, adverse events, and blood samples for Ranolazine plasma concentrations at trough and peak.

Figure 11. Study procedures CVT 3031



A = 500 mg Ranolazine SR BID
 B = 1000 mg Ranolazine SR BID
 C = 1500 mg Ranolazine SR BID
 D = Placebo

Figure 12. Study procedures CVT 3033



22. Data

The patient demographics between studies were similar (Table 11).

Table 11. Demographics of patients used in sponsor's PK/PD analysis

	RAN 80	RAN 1514	CVT 3031	CVT 3033
n (m/f)	74 (69/5)	309 (226/83)	191 (140/51)	823 (638/185)
age (years)	59 ± 7 (41 – 73)	64 ± 9 (32 – 84)	64 ± 9 (39 – 85)	64 ± 9 (36 – 92)
ht (cm)	not recorded	171 ± 10 (135 – 203)	171 ± 9 (147 – 193)	170 ± 9 (149 – 195)
wt (kg)	80 ± 11 (55 – 115)	82 ± 16 (42 – 141)	83 ± 15 (43 – 133)	81 ± 13 (41 – 150)
Race (W/B/A/O)	(73/0/1/0)	265/21/7/16	174/10/4/3	803/3/5/12
CHF (NYHA I/II)	4 (class not recorded)	10 (class not recorded)	32 (10/22)	242 (103/139)
DM	5	64 (2 unknown)	46	189

mean ± SD (min, max)

m/f = male/female

W/B/A/O = white/ black/asian/other

CHF = congestive heart failure, NYHA = New York Heart Association

DM = diabetes mellitus

The demographics by gender are also similar (Table 12).

Table 12. Description of patients used in PK/PD analysis by gender

	Males	Females
n (%)	1073 (77.0%)	324 (23.0%)
Age	64 ± 9	64 ± 9
Weight (kg)	84 ± 14	73 ± 14
Race % (W/B/A/O)	94.2 / 1.3 / 2	93.4 / 0.6 / 3
CHF %	19	25
DM %	21	26

mean ± SD

W/B/A/O = white/black/asian/other

CHF = congestive heart failure

DM = diabetes mellitus

23. Pharmacokinetics

Although, the sponsor developed a population PK model (Report CVT00200, Item 6, vol. 284), this model was not used in the concentration effectiveness analysis. Observed concentrations were employed to drive the PD model.

A total of 1397 patients (1073 m/324 f) for a total of 10,998 observations were included in the sponsor's analysis. Plasma concentrations below the limit of quantitation were coded as zero and included in the data set.

Data Exclusion - The sponsor states that the following observations were excluded from the concentration effectiveness analysis:

- Missing PK sample or time of the treadmill test,
- Quantifiable concentrations during the placebo treatment phase (applicable for studies 3031 and 3033). For placebo treatment data in study RAN 1514, the data were coded as "PLA" and these data were not reported in study RAN 080. (See Reviewer's first comments in on regarding the Sponsor's analysis on page 339.)

24. Pharmacodynamics

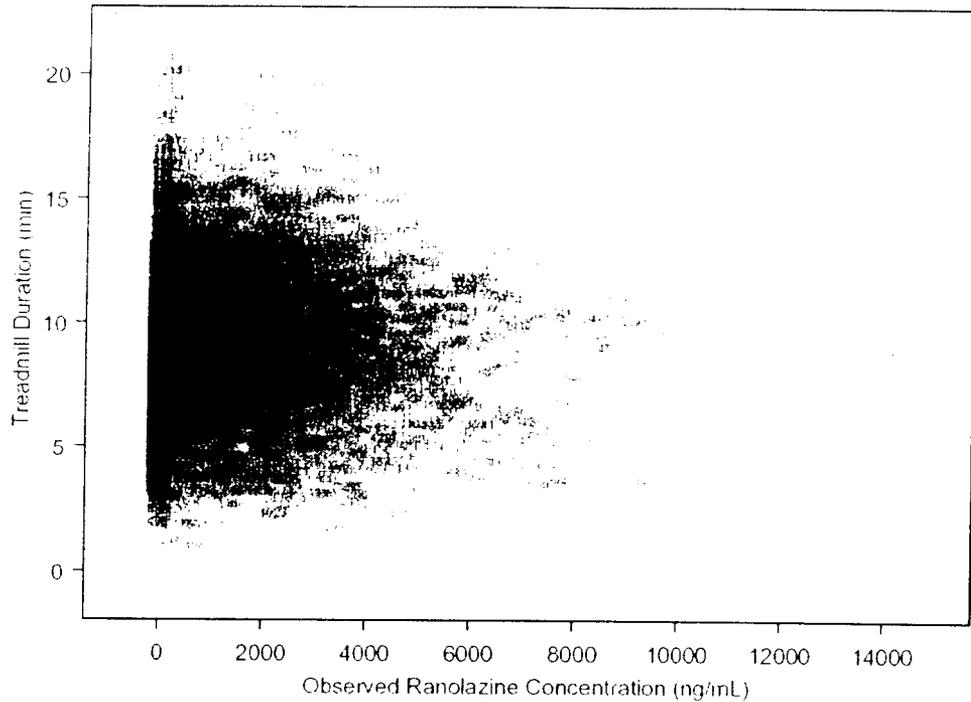
Baseline treadmill assessments in all four studies differed. For the sponsor's analysis, baseline treadmill duration was defined as the treadmill duration obtained during the single-blind phase.

The double-blind placebo phase data were used to define the placebo response.

The sponsor states that for study CVT 3031 and CVT 3033, any placebo treatment records with quantifiable ranolazine plasma concentrations with date and time of plasma sampling and treadmill duration data with date and time of the ETT were excluded from the concentration-effect analysis. (See Reviewer's first comment in Data 6L.)

Figure 13 shows the concentration treadmill duration relationship for the studies used in the PK/PD model.

Figure 13. Ranolazine concentration vs. treadmill duration in RAN 080, RAN 1514, CVT 3031 & CVT 3033



25. Study RAN 080

26. Pharmacokinetics

In this cross-over study, 74 patients were included in the analysis. Only 64 patients had measurable peak plasma ranolazine samples (one concentration per subject). Peak ranolazine concentrations of these patients were 1726 ± 1046 ug L (mean \pm SD), lower than the mean of all 143 plasma samples (2039 ± 1201 ug L). The range of concentrations used in the analysis was 37 – 4911 ug L. The limit of detection of the assay was not reported.

Data for the atenolol treatment arm were not included in the analysis.

27. Pharmacodynamics

The primary objective was to compare the time to onset of angina during exercise at peak concentrations between ranolazine IR 400 mg TID, atenolol 100 mg QD and placebo. Both treatments were taken for 7-10 days. An ETT was performed at the end of each treatment period at one hour post dose (peak).

There were 117 evaluable patients; 74 exercised on treadmill and 43 exercised on bicycle. Patients that exercised on bicycle were excluded from the analysis because a significant treatment by exercise method interaction was found where the average difference in exercise duration between active ranolazine and placebo periods was less for centers

using bicycles versus those using treadmill (eight seconds for centers using the bicycles and 50 seconds for centers using the treadmill).

28. Study RAN 1514

29. Pharmacokinetics

In this cross-over study, 318 patients (230 males, 88 females) were enrolled, 310 received double-blind placebo treatment. Table 13 generated by the reviewer summarizes the plasma concentration data in study RAN 1514 that was used for the reviewer's analysis. These numbers are slightly different from that reported by the sponsor for reasons cited in Reviewer's Comments, section 61, page 339).

Table 13. Peak and trough plasma concentrations in study RAN 1514

	IR 400 bid	IR 267 mg tid	IR 400 mg tid
Trough (ug/L)	n = 312 268 ± 334 (15 - 2220)	n = 306 367 ± 436 (12 - 4296)	n = 317 533 ± 502 (17 - 3877)
Peak (ug/L)	n = 323 1796 ± 1120 (29 - 7174)	n = 319 1298 ± 830 (16 - 6174)	n = 321 2101 ± 1206 (58 - 7788)

n = number of plasma samples

Data are mean ± SD (minimum, maximum)

Nine patients out of 318 were excluded from the analysis. At the time of the writing of this review, the reviewer is waiting for the reasons for exclusion.

30. Pharmacodynamics

The primary variable endpoint was exercise treadmill time to onset of angina at trough (8 ± 1 hour post dose or 12 ± 1 hour post dose). During the double-blind phase, trough and peak treadmill performances were assessed at each visit for a maximum total of ten ETTs (five troughs and five peaks) per patient.

Of the 318 patients, 29 withdrew, thus 289 patients completed the study. Six of the 318 had no ETT data thus leaving 312 in the all pt analysis with both peak and trough ETT data. All 318 patients were included in the safety analysis.

Primary endpoint:

This study did not find a statistically significant difference at trough between each ranolazine IR regimen and placebo for time to onset of angina, duration of exercise, or time to 1 mm ST segment depression in either the per protocol or the all patient analyses.

31. Study CVT 3031

32. Pharmacokinetics

Table 14 describes the plasma concentration data for those patients that were included in the reviewer's analysis. These numbers are different from the sponsor's for reasons stated in Reviewer's Comments, section 61, page 339).

Table 14. Peak and trough plasma concentrations in CVT 3031

	SR 500 mg	SR 1000 mg	SR 1500 mg
Trough (ug L)	n = 170 864 ± 720 (96 - 3560)	n = 174 1954 ± 1425 (86 - 8090)	n = 165 3264 ± 1917 (405 - 11,000)
Peak (ug L)	n = 167 1136 ± 721 (98 - 3800)	n = 172 2473 ± 1522 (228 - 8650)	n = 165 3891 ± 2021 (543 - 14,300)

n = number of plasma samples

Data are mean ± SD (minimum, maximum)

33. Pharmacodynamics

Of the 191 patients randomized, fifteen patients discontinued because of an adverse effect and one patient died. Therefore, 175 patients were included in the primary efficacy analysis and all 191 were included in the safety analysis.

Results of this study are thoroughly discussed in the medical and statistical review.

34. Study CVT 3033

35. Pharmacokinetics

Table 15 describes the peak and trough ranolazine concentrations used in the reviewer's analysis. These numbers are different from the sponsor's for reasons stated in Reviewer's Comments, section 61, page 339).

Table 15. Peak and trough plasma concentrations in CVT 3033

	SR 750 mg	SR 1000 mg
Trough (ug/L)	n = 907 1585 ± 1076 (52 - 8850)	n = 855 2255 ± 1550 (57 - 9172)
Peak (ug/L)	n = 508 2145 ± 1235 (81 - 7860)	n = 481 2785 ± 1537 (314 - 9020)

n = number of plasma samples

Data are mean ± SD (minimum, maximum)

36. Pharmacodynamics

The primary efficacy variable was defined as the change from baseline in ETT duration at the time of trough ranolazine concentration using the last observation carried forward.

Trough ETTs (at 12 ± 0.5 hours post dose) were performed at the end of Weeks 2, 6, 12 and Week 12 Day 2 (rebound ETT) while peak ETTs (at 4 ± 0.5 hours post dose) were performed at the end of Weeks 2 and 12.

Results of this study are thoroughly discussed in the medical and statistical review.

37. Data Checking

The data were formatted to be compatible with NMTRAN/NONMEM. Diagnostics were performed to check for any gross errors during the compilation of the data set. Further modifications were made in Excel. All data sets underwent quality control checks at GloboMax® LLC.

38. Models

39. Pharmacokinetics

40. Structural Model

Although the sponsor developed a population PK model (see Dr. Atul Bhattaram's review), it was not used for the PK/PD analysis. The sponsor used the actual concentration data to drive the PD analysis.

41. Pharmacodynamics

42. Structural Model

The sponsor's structural model can be divided into the following three models: baseline, placebo effect and drug effect. The summation of these three models results in the response model.

43. Baseline model

Studies RAN 080, CVT 3031 and CVT 3033 were grouped together to estimate one baseline because individual estimates (the intercepts) for these studies were similar (6.74, 6.68, 6.86 minutes, respectively). The baseline exercise duration for study RAN 1514 was estimated separately (9.19 minutes). However, there were no distinguishing differences in design, demographics, etc. between the three studies grouped together versus RAN 1514. The grouping was made simply because of similar baseline treadmill

duration estimates. The equation for the typical value (TV) of the baseline (BSL) treadmill duration in minutes was:

$$TVBSL = \mu_{BSL(RAN\ 080,\ CVT\ 3031,\ CVT\ 3033)} \text{ or } \mu_{BSL(RAN\ 1514)} \quad (\text{Eq 1})$$

where

TVBSL is the typical value of the baseline treadmill duration,

$\mu_{BSL(RAN\ 080,\ CVT\ 3031,\ CVT\ 3033)}$ is the mean baseline ETT duration if the patient is in study RAN 080, CVT 3031 or CVT 3033 and

$\mu_{BSL(RAN\ 1514)}$ is the mean baseline ETT duration if the patient is in study RAN 1514

Covariate analysis revealed that gender and age affected the baseline treadmill duration. The final equation for the typical value of the baseline treadmill duration in minutes is described by the following:

$$TVBSL = (\mu_{BSL(RAN\ 080,\ CVT\ 3031,\ CVT\ 3033)} \text{ or } \mu_{BSL(RAN\ 1514)}) + \Delta\mu_{BSL(\text{female})} + \Delta\mu_{BSL(\text{age}-64\ \text{years})} \quad (\text{Eq 2})$$

where

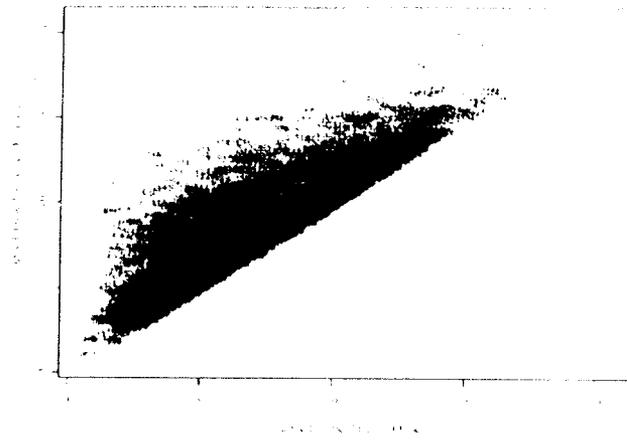
$\Delta\mu_{BSL(\text{female})}$ is the mean difference from males in baseline treadmill duration for females. This value is zero if the patient is male.

$\Delta\mu_{BSL(\text{age}-64\ \text{years})}$ is the mean difference from age 64 in baseline treadmill duration. This value is centered on the median age, 64 years old, of the patient population.

The reasons for use of exercise duration instead of time to onset of angina are discussed below.

Exercise duration vs. time to onset of angina: The sponsor modeled the duration of treadmill exercise. A plot of the observed duration of the treadmill versus the time to onset of angina (Figure 14) indicated that the two variables are highly correlated ($r^2 = 0.75$), thus the sponsor chose to model the duration of treadmill exercise as the response. There are no data below the line of unity because onset of angina only occurred after walking on the treadmill.

Figure 14. Observed exercise duration vs. observed time to angina



44. Placebo effect model

The placebo effect model (Peff) includes a treadmill learning effect for studies RAN 1514, CVT 3031 and CVT 3033. No learning effect was included for study RAN 080. An Emax-type model, describes this learning effect (Eq 3). According to this model, each patient gradually, over time, learns to walk greater distances, until a plateau is reached.

$$P_{eff} = \frac{(TVL_{max} \cdot time)}{(time + TVL_{50})} \quad (Eq \quad 3)$$

where

Peff is the placebo effect in minutes,

TV Lmax is the typical value of maximal learning in minutes if the patient is in study RAN 1514, CVT 3031 and CVT 3033,

time is in weeks, and

TVL₅₀ is the typical time in weeks to reach half the maximal treadmill learning.

Patients in different studies had different rates of learning. Equation 4 describes the typical value of the time (in weeks) to reach half the maximal learning effect for three studies.

$$TVL_{50} = \mu_{L_{50} \text{ RAN 1514}} \text{ OR } \mu_{L_{50} \text{ CVT 3031}} \text{ OR } \mu_{L_{50} \text{ CVT 3033}} \quad (Eq \quad 4)$$

where

$\mu_{L_{50} \text{ RAN 1514}}$ is the mean L₅₀ in weeks for patients in study RAN 1514,

$\mu_{L_{50} CVT3031}$ is the mean L_{50} in weeks for patients in study CVT 3031, and
 $\mu_{L_{50} CVT3033}$ is the mean L_{50} in weeks for patients in study CVT 3033.

Covariate analysis shows that the presence of congestive heart failure (CHF) affects the maximal treadmill learning. The final model for the placebo treadmill learning effect (in minutes) is described by equation 5.

$$TVL_{max} = \mu_{L_{max}} + \Delta\mu_{L_{max}CHF} \quad (\text{Eq 5})$$

where

$\mu_{L_{max}}$ is the mean L_{max} in minutes.

$\Delta\mu_{L_{max}CHF}$ is the mean difference in L_{max} in minutes for patients with CHF.

This value collapses to zero if the patient does not have CHF.

45. Concentration effect model

A linear model (Eq 6) describes the concentration-effect (Eff) relationship.

$$Eff = TVSLP \cdot Conc \quad (\text{Eq 6})$$

where

Eff is the concentration effect,

TVSLP is the typical value of the slope of the concentration- effect relationship,

and

Conc is the drug concentration in $\mu\text{g/L}$

Covariate analysis shows that gender affects the slope of the drug effect. The final drug effect equation is described by Equation 7.

$$TVSLP = \mu_{SLP} + \Delta\mu_{SLP_{gender}} \quad (\text{Eq 7})$$

where

μ_{SLP} is the mean slope for males, and

$\Delta\mu_{SLP_{gender}}$ is the mean difference from the male slope. This value collapses to zero if the patient is male.

46. Random Effects Models

Between subject variability (BSV or Ω^2) was tested on all parameters in the model. Between subject variability of the baseline treadmill time (Ω^2_{BSL}), maximal treadmill learning ($\Omega^2_{L_{max}}$), time to reach half the maximal treadmill learning ($\Omega^2_{T_{1/2}}$), and slope (Ω^2_{SLP}), were assumed to be normally distributed. Both additive and proportional

residual error models were tested to explain unknown residual error when predicting exercise treadmill duration from parameters estimated from the population model. The final residual error model was additive, with a variance of σ^2 .

47. Model Selection

All modeling was performed using first order conditional estimation (FOCE)

48. Initial Model Selection

Model selection was based on a reduction in objective function value of approximately 10 points, AIC (Akaike Information Criterion), a decrease in the residual error, randomness of the individual weighted residuals distribution against the predicted observations, randomness of the observed effect distribution versus individual and mean predicted effect values across the identity line.

49. Covariate Analysis

Relationships between covariates and individual model parameters were graphically explored. The following covariates were explored: age, weight, gender, race, CHF (presence of absence of), NYHA (Class I or II), diabetes (presence of absence of), concomitant antianginal medications, study and formulation (Syntex SR tablet, DSM SR tablet and Syntex IR capsule).

All continuous covariate values were available for the final analysis. For categorical covariates, two subjects missing diabetes status were excluded from the assessment of diabetes as a covariate.

Population covariate analysis of the effect of demographics, disease status, and the presence of concomitant medications on the specific model parameters was performed. NONMEM regression analysis was performed on the model with covariate parameters being added in the model building process and subtracted in the model reduction process.

The effect of covariates was tested individually on each model parameter. The Log Likelihood Ratio Test (LRT) was used to evaluate the significance of covariate effects in the population model. A difference of greater than 10 in the objective function after inclusion of the covariate was regarded significant. For covariates that caused a modest decrease in the objective function of 7 to 10 points, other diagnostic criteria were considered to determine if the covariate was significant. After all significant individual covariates were determined, model building continued by incorporating the significant covariates into the model simultaneously.

50. Final Model Selection

After the full model was defined, the statistical significance of each covariate-parameter relationship was tested individually in a stepwise deletion method. Significance was defined as an increase in OFV of 10 units with no substantial increase in the corresponding random effect parameter. After all covariates were individually deleted from the full model, the least significant covariate was then removed. This cycle was repeated until only significant parameters remained. The resulting model is known as the final NONMEM model.

51. Software

Data sets were formatted for each study individually and then combined into one data set. Diagnostics were performed to check for any gross errors during the compilation of the data set. Further modifications were made in Excel. PK/PD analysis were performed using NONMEM version V, level 1.1, NM-TRAN version III, level 1.0 and PREDPP version IV, level 1.0. Most of the models were run using the compiler g77 version 2.95 19990728 release from FSF-g77 version 0.5.25 19990728 release. The final model was run using Compaq Digital Fortran compiler version 6.6 (update A).

52. Sponsor's Results

53. Sponsor's Final Model - Linear

54. Parameter estimation results

Similar parameter estimates of the sponsor's final model were obtained by the Agency (0). These parameter estimates were obtained using all 10,998 observations since these are the data the sponsor used. The purpose of the Agency's run of the sponsor's model was to reproduce the sponsor's results. Below is the interpretation of the parameter estimates obtained by the sponsor. The control stream for the Sponsor's Base Model and the Sponsor's Final Model are included in Appendix I.

55. Baseline treadmill duration

The sponsor's model shows that the typical value of the baseline treadmill duration was 6.85 minutes for a median aged (64 years old) male in studies RAN 080, CVT 3031 or CVT 3033. The baseline duration was 8.25 minutes for a median aged male in study RAN 1514.

Females have lower baseline treadmill durations than males. The typical value of the baseline treadmill duration is 0.76 minutes less for a 64 year old female than a male (i.e., 6.08 minutes for a median age female in study RAN 080, CVT 3031 or CVT 3033 and 7.49 minutes for a median age female in study RAN 1514).

The baseline treadmill duration decreased by 0.03 minutes (or 1.8 seconds) for each year older than 64 and increased by 0.03 minutes for each year younger than 64.

56. Learning effect

The maximal learning capacity on the treadmill was similar between males and females. The most learning that occurred in studies RAN 1514, CVT 3031 and CVT 3033 was 2.89 minutes.

Patients with CHF had less maximal learning capacity (1.98 minutes) than patients without CHF.

The time to reach half the maximal learning was shorter in study RAN 1514 compared to CVT 3031 and CVT 3033, indicating that patients in RAN 1514 learned to walk on the treadmill at a faster rate than patients in studies CVT 3031 and CVT 3033. Patients in study RAN 1514 reached half the maximal learning capacity in 0.84 weeks, while

patients in study CVT 3031 and CVT 3033 reached half maximal learning capacity in 2.75 weeks and 2.31 weeks, respectively.

57. Concentration effect

The slope of the concentration effect in males was 0.278 minutes (or 16.7 seconds) per 1000 ug/L of ranolazine.

Females were less sensitive to the drug than males. The slope of the drug effect in females was 0.106 minutes (or 6.4 seconds) per 1000 ug/L of ranolazine.

Table 16. Parameter estimates of sponsor's final model

Compiler	Sponsor's final model		Sponsor's final model ran by the Agency	
	Compaq Digital Fortran compiler version 6.6 (update A)		Compaq Fortran Optimizing Compiler Version 6.5	
Objective function value	19644.579		19654.65	
No. observations	10,998		10,998	
	Mean (SE %)	BSV, % CV (SE %)	Mean (SE %)	BSV, % CV (SE %)
BSL_{RAN 080,CVT 3031,CVT 3033} (minutes)	6.85 (1.6)	24.8 (7.2)	6.84 (1.6)	23.8 (7.4)
BSL_{RAN 1514} (minutes)	8.25 (3.1)		8.20 (0.1)	
ΔBSL_{female} (minutes)	-0.76 (16.9)		-0.75 (16.4)	
BSL_{age} (minutes)	-0.03 (20.2)		-0.03 (19.9)	
L_{max}_{RAN 1514,CVT 3031,CVT 3033} (minutes)	2.89 (5.2)	91.7 (6.7)	2.91 (4.4)	88.7 (6.6)
ΔL_{max}_{CHF} (minutes)	-0.91 (23.9)		-0.91 (22.6)	
L₅₀_{RAN 1514} (weeks)	0.84 (21.7)	185.7 (35.0)	0.81 (15.2)	66.7 (29.6)
L₅₀_{CVT 3031} (weeks)	2.75 (7.4)		2.70 (7.5)	
L₅₀_{CVT 3033} (weeks)	2.31 (13.9)		2.25 (14.0)	
Slope of DE_{male} (minutes per 1000 ug/L)	0.278 (6.5)	68.3 (25.1)	0.277 (6.6)	68.6 (25.6)
ΔSlope of DE_{females} (minutes per 1000 ug/L)	-0.172 (16.0)		-0.172 (16.3)	
Residual error (additive) (σ²) (minutes)	SD=1.14 (3.67)		SD=1.14 (3.7)	

BSV= between subject variability calculated as SD mean. For situations with more than one mean, the lowest mean parameter was used, so that the largest BSV was reported. For example, BSV for L₅₀ was calculated as 1.7 0.84. The BSL of 0.84 is the lowest of the three.

BSL=baseline treadmill duration
Lmax = maximal learning
L₅₀ = time to reach 1/2 of maximal learning
DE = drug effect

58. Goodness of fit

Unlike the population predictions of treadmill duration (Figure 15), there was a good fit between the observed treadmill durations and the individual predicted treadmill durations (Figure 16).

Figure 15. Observed treadmill duration vs. population predicted treadmill duration

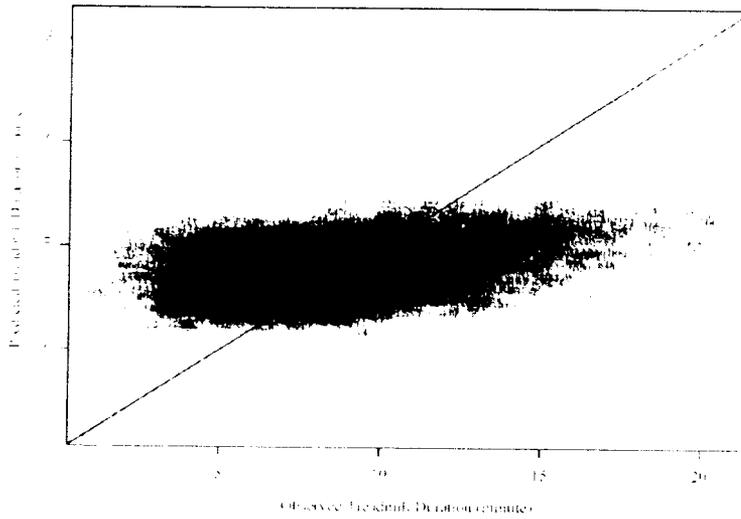
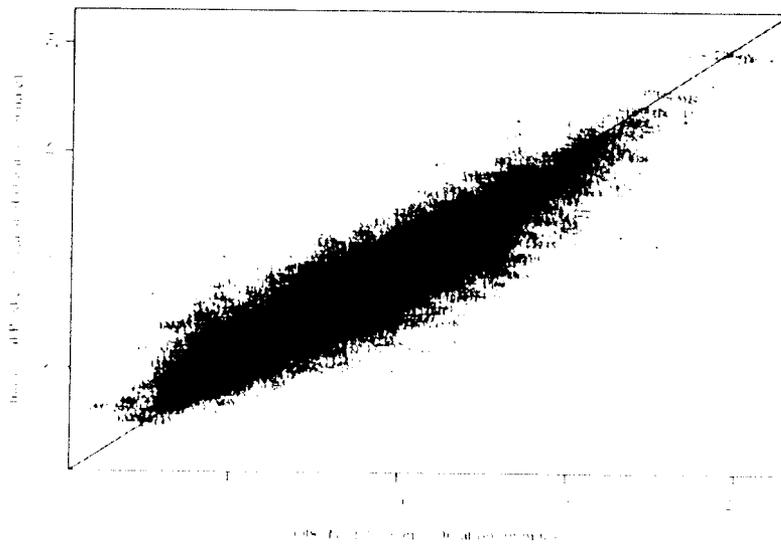


Figure 16. Observed treadmill duration vs. individual predicted treadmill duration



59. Model Qualification

Except for the final model, the sponsor developed all models with an index data set that contained 70 % of the data (randomly chosen). The last model obtained with the index data set was used to determine individual predictions for subjects in the qualification data set (30 % of the data). In the estimation step in NONMEM, the maximum-evaluations (MAXEVAL=0) option was set to zero and the individual predictions of effect were obtained. Because an additive residual error model was selected, the 95 % confidence interval for the mean prediction error and the mean squared prediction error were calculated.

The qualification data set was fitted to the final model, and subsequently the entire data set was fitted to the final model. The parameter estimates for the final model fitted to the entire data set and the last model fitted to the index data set were close. The final model fitted to the entire data set contained more precise (lower % SE) parameter estimates and less BSV.

60. Reviewer's Comments of Sponsor's Analysis

61. Data

- The sponsor used 10,998 observations in their analysis. The sponsor stated that quantifiable concentrations during the placebo treatment phase were excluded from the analysis, however this was not entirely true. Thirty-seven observations (from a total of 27 patients) contained measurable concentrations for patients assigned to placebo. This is particularly disturbing for 19 patients in the parallel study (CVT 3033). The analysis should not have included these 37 observations. At the time of the writing of this review, the sponsor was informed of this issue and has rerun the analysis without the 37 observations. The sponsor stated that the estimates are similar, but have not yet submitted the revised report to the Agency.
- Additionally, concentrations reported as zero when the patient was reportedly taking ranolazine (252 observations) should not have been used in the sponsor's analysis. It is not clear if the concentration data or drug dosing data are incorrect, thus the data were removed from the reviewer's analysis and for the tables of mean peak and trough concentrations generated by the reviewer.
- For study RAN 1514, the numbers in Table 13 generated by the reviewer differ from that in the study report (Volume 237, Table 41) for the following reasons:
 - The reasons stated in the preceding bullets concerning concentration data.
 - The values in Table 13 have been corrected for the salt.
 - Sixty-six plasma samples (from 45 patients) were not used in the NONMEM analysis. Thus, they were not used in the calculation of mean peak and trough concentrations. Fifteen of 66 plasma samples (from five patients) were not used because no baseline ETT was available. At the time of the writing of this review, the Agency is still waiting for the sponsor to explain why plasma samples were not used.

- The reviewer agrees with the sponsor's choice to exclude the bicycle data in study RAN 080 from the analysis. Because it was a different method of exercise, the results should not be merged with data obtained by treadmill.

62. Model

- We attempted to run the sponsor's base and final model submitted to the Agency, however due to different compilers between the sponsor and the Agency, we were unable to reproduce the sponsor's base and final models as submitted. Most of the sponsor's models were run using the compiler g77 version 2.95 19990728 release from FSF-g77 version 0.5.25 19990728 release. The sponsor's final model was run using Compaq Digital Fortran compiler version 6.6 (update A). In one of our last attempt to reproduce the results of the final model, we used the final parameter estimates as the initial estimates. This run successfully minimized, but resulted in different parameter estimates than the sponsor's.

Alternatively, we modified the initial estimates of some of the model parameters and successfully reproduced the sponsor's results using our compiler (Compaq Visual Fortran Optimizing Compiler Version 6.5).

- The sponsor analysis of covariates is unclear. It is unclear if all covariates were tested individually in the model, or if specific covariates were tested and other covariates were examined graphically. At the time of the writing of this review, the Agency is waiting for the sponsor to explain exactly how the covariate analysis was done.

63. The significance of the results

64. Gender

Females have lower baseline treadmill durations than males, and females are less sensitive to ranolazine. This translates into less of a proportional effect (ratio of drug effect to placebo duration) in females, ~ 60 % of that in males.

For example, a 64 year old female in study CVT 3033 would have the following proportional effect,

$$\frac{\text{Drug Eff}}{\text{Pho ETT duration}} = \frac{\text{Drug Eff}}{TV_{BSL} + TV_{MAX}} = \frac{0.106 \text{ min } 1000\mu\text{g } \cdot L}{6.08 \text{ min} + 2.89 \text{ min}} = 1.18\% \text{ per } 1000\mu\text{g } \cdot L$$

where TV_{BSL} is the typical baseline ETT and TV_{MAX} is the typical maximal learning.

A 64 year old male in study CVT 3033 would have the following proportional effect,

$$\frac{\text{Drug Eff}}{\text{Pho ETT duration}} = \frac{\text{Drug Eff}}{TV_{BSL} + TV_{MAX}} = \frac{0.278 \text{ min } 1000\mu\text{g } \cdot L}{6.85 \text{ min} + 2.89 \text{ min}} = 2.85\% \text{ per } 1000\mu\text{g } \cdot L$$

Thus, while the slope of the drug effect in females is ~60 % lower than that in males, the baseline treadmill duration in females is also ~10 % lower than that in males. These two effects translate into females having proportionally 60% less benefit from ranolazine than males.

65. CHF

Patients with CHF have ~31.5 % less maximal learning capacity than patients without CHF. However, the slope of the drug effect is independent of the presence or absence of CHF. Therefore, a 64 year old male in study CVT 3033 with CHF would have the following percent change from baseline,

$$\frac{\text{Drug Eff} + TV_{LMAX}}{TV_{LMAX}} = \frac{0.278 \text{ min} \cdot 1000 \text{ug} / L + 1.98 \text{ min}}{1.98 \text{ min}} = 1.14 = 14\% \text{ per } 1000 \text{ug} / L$$

A 64 year old male in study CVT 3033 without CHF would have the following percent change from baseline.

$$\frac{\text{Drug Eff} + TV_{LMAX}}{TV_{LMAX}} = \frac{0.278 \text{ min} \cdot 1000 \text{ug} / L + 2.89 \text{ min}}{2.89 \text{ min}} = 1.09 = 9\% \text{ per } 1000 \text{ug} / L$$

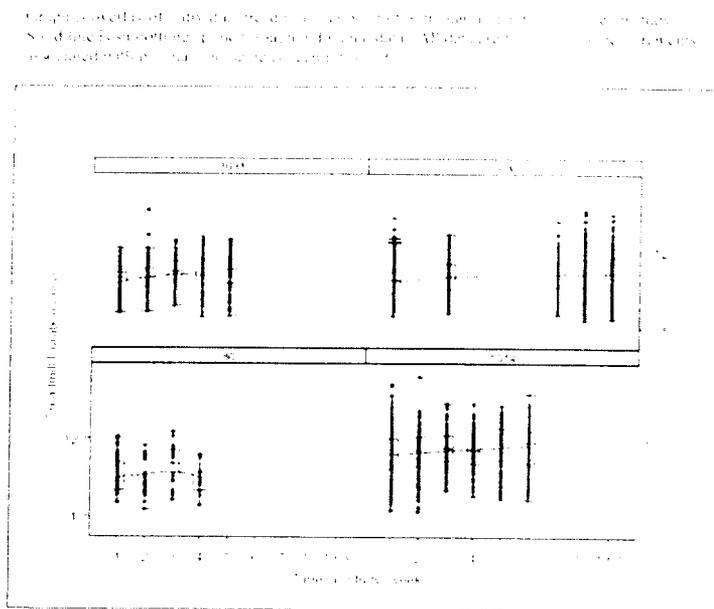
Therefore, a patient with CHF will walk 57.5 seconds (6.85 minutes • 0.14 per 1000 ug/L • 60 sec/min) more from baseline, and a patient without CHF will walk 37 seconds more from baseline. Thus, while the maximal learning capacity is smaller in patients with CHF, patients with CHF benefit more from ranolazine than patients without CHF.

66. The validity of the results

67. Learning Effect

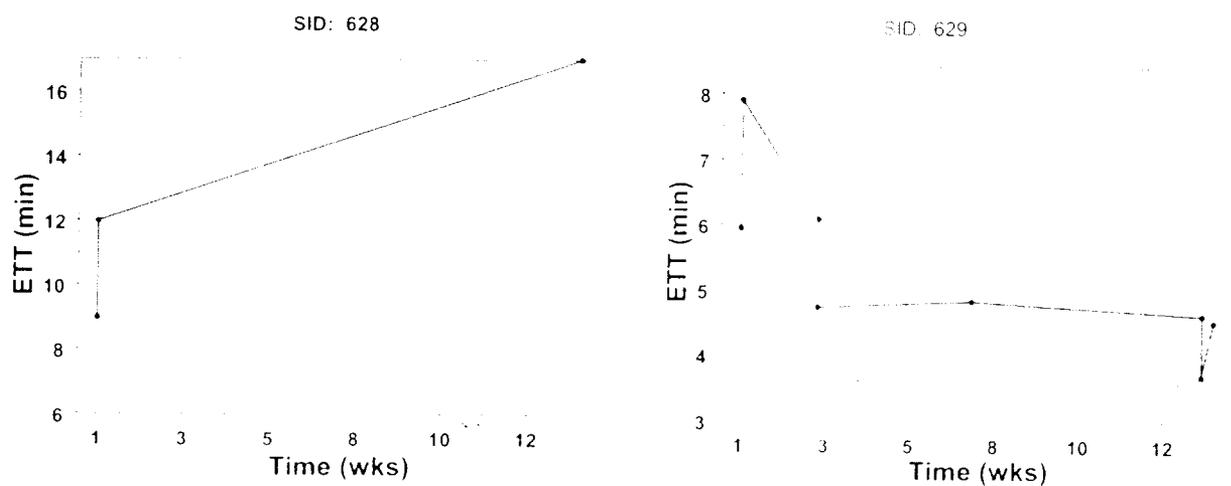
Because learning can occur after repeated exercise treadmill testing, the sponsor chose to use the observed duration of treadmill exercise rather than change from baseline in the model. Figure 17 helps explain why an Emax model was chosen to describe the learning effect. For studies RAN 1514, CVT 3031 and CVT 3033, the learning effect seemed to plateau. Since the treadmill duration in study RAN 080 appeared to peak and then decrease the last week, the sponsor assigned a separate slope term for study RAN 080 for the learning effect, rather than an Emax model that was used for the other three studies. The model did not converge and the 90% confidence interval included zero. After making other changes to the model, the sponsor obtained a poor estimate of the learning effect with the 90 % confidence interval including zero. Subsequently, the sponsor fixed the learning effect parameter for study RAN 080 to zero. This resulted in an insignificant increase (-1) in the objective function value (OFV). Based on the increase in OFV and the inclusion of zero in the 90 % confidence interval, the sponsor dropped this parameter from the model. Thus, no learning effect for study RAN 080 was included in the sponsor's final model.

Figure 17. Treadmill duration when ranolazine concentrations are zero



The reviewer made plots of ETT duration when plasma concentration was zero for each patient. Random inspection revealed that most patients walk longer on the treadmill after repeated treadmill tests. There were patients that had the inverse trend (walked for a shorter time on the treadmill with repeated treadmill tests) and there were patients that had no obvious learning effect. Figure 18 shows two examples of the learning effect from two different subjects.

Figure 18. ETT learning effect in two patients



Because learning occurred in the other three studies, the reviewer finds it difficult to believe that learning did not occur in the patients in study RAN 080.

68. Data set

The NONMEM analysis should have been run with 10,709 observations for the reasons mentioned in the Reviewer's Comments of the data (page 339).

69. Comments to sponsor

- The sponsor used two different compilers for their analysis, yet the statistical results from different compilers cannot be directly compared. Most of the models were run using the compiler g77 version 2.95 19990728 release from ESI-g77 version 0.5.25 19990728 release. The final model was run using Compaq Digital Fortran compiler version 6.6 (update A). It is recommended that only one compiler be used for all analysis.
- The sponsor used Excel for data manipulation. Software programs with manual manipulation, such as Excel, are highly discouraged for data manipulation because changes to the data set cannot be tracked or reproduced. It is highly recommended that software packages that keep a record of changes to the data set, such as SAS or Splus, be used for data manipulation. The NONMEM data set had two notable problems.
 - patients assigned to placebo had measurable plasma concentrations, and
 - patients assigned to drug had no plasma concentrations.It is possible that the samples were mishandled, however, it is also possible that during the data manipulation to create the NONMEM data set, the data were mixed up because manual manipulation was used.
- On a minor note, in the analysis plan the sponsor specified that the bias and precision would be calculated and compared against a pre-specified value. Unfortunately, the pre-specified value is expressed as percentage while the calculations were absolute differences. A more appropriate method of calculating the bias and (im)precision would have been to consider relative (to observed values) deviations.

70. Reviewer's Analysis of Effectiveness

71. Models

72. Linear effectiveness model - learning in all studies

Because it is difficult to understand why learning did not occur in study RAN 080, and there were no distinguishing differences between study RAN 080 and the other three studies where learning was modeled by the sponsor, we tested if learning in study RAN 080 was linear. We found that inclusion of a linear learning effect for study RAN 080 was statistically significant. The objective function value (OFV) was 12.844 less than the model without a learning effect for study RAN 080. Most parameter estimates were similar between the two models. However, the standard error for the learning effect for study RAN 080 was moderately large (62.7 %). We then tested if learning decreased after Week 3, using a piece-wise linear model, as depicted in Figure 17. There was no significant improvement in the fit, hence the linear model was used for the learning effect of study RAN 080.

Table 17. Parameter estimates of sponsor's final model & reviewer's learning in all studies linear effectiveness model

	Sponsor's Final Model Ran by the Agency		Reviewer's Learning in All Studies Linear Effectiveness Model	
Objective function value	19,654.65		19,641.81	
No. observations	10,998		10,998	
	Mean (SE %)	BSV, % CV (SE %)	Mean (SE %)	BSV, % CV (SE %)
BSL_{RAN 080,CVT 3031,CVT 3033} (minutes)	6.84 (1.6)	23.8 (7.4)	6.81 (1.7)	24.8 (7.2)
BSL_{RAN 1514} (minutes)	8.20 (0.1)		8.23 (3.1)	
ΔBSL_{female} (minutes)	-0.75 (16.4)		-0.75 (17.2)	
BSL_{age} (minutes)	-0.03 (19.9)		-0.03 (21.0)	
L_{max}_{RAN 1514,CVT 3031,CVT 3033} (minutes)	2.91 (4.4)	88.7 (6.6)	2.92 (5.2)	90.8 (6.8)
ΔL_{max}_{CHE} (minutes)	-0.91 (22.6)		-0.90 (25.8)	
Slope of learning in RAN 080	N/A	N/A	0.098 (62.7)	
L₅₀_{RAN 1514} (weeks)	0.81 (15.2)	66.7 (29.6)	0.83 (21.2)	66.3 (34.2)
L₅₀_{CVT 3031} (weeks)	2.70 (7.5)		2.72 (7.5)	
L₅₀_{CVT 3033} (weeks)	2.25 (14.0)		2.24 (14.2)	
Slope of DE_{male} (minutes per 1000 ug/L)	0.28 (6.6)	68.6 (25.6)	0.28 (6.7)	67.9 (25.8)
ΔSlope of DE_{females} (minutes per 1000 ug/L)	-0.17 (16.3)		-0.17 (16.5)	
Residual error (additive) (σ²) (minutes)	SD=1.14 (3.7)		SD=1.14 (3.7)	

BSV—between subject variability calculated as SD mean. For situations with more than one mean, the lowest mean parameter was used, so that the largest BSV was reported.

BSL—baseline treadmill duration

L_{max} – maximal learning

L₅₀ – time to reach ½ of maximal learning

DE – drug effect

After it was discovered that the data set was incorrect, the analysis was reran with the correct number of observations (10,709). The slope of the concentration effect remained fairly similar.

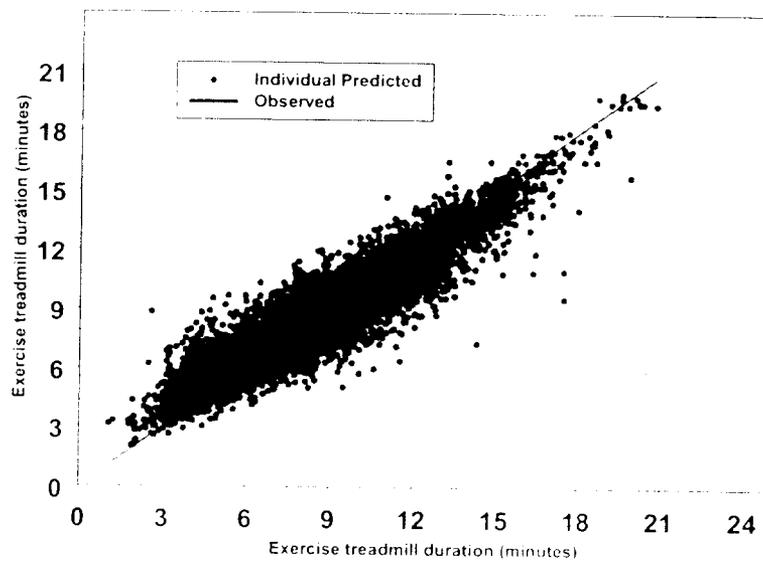
73. Linear effectiveness model – learning in all studies and random correlation

Usually, interindividual differences (parameter estimate of an individual minus the typical estimate) of different parameters, such as sensitivity and disease status at baseline, can be correlated. Sometimes this correlation cannot be explained with a known covariate. Thus, random correlation is explored to obtain a better description of the data.

We tested the random correlation between interindividual differences of various parameters by using an omega block in the NONMEM control stream of the learning in all studies linear model. The correlations between interindividual differences of slope of the concentration effect and the other parameters were small (< 0.50) so the random correlations for the slope of the concentration effect was taken out of the omega block.

Figure 19 shows the goodness of fit of the individual predicted concentrations for the final linear model (learning in all studies and random correlation).

Figure 19. Goodness of fit of the individual predicted concentrations using the reviewer's final linear effectiveness model (learning in all studies and random correlation)



With regard to the correlations (omega block), the analysis shows that patients with higher baseline treadmill duration have less maximal learning capacity. The correlations between baseline and L_{50} and L_{50} and L_{max} were small. When these correlations were removed the model successfully minimized, but standard error estimates could not be obtained.

Table 18. Parameter estimates of reviewer's final linear effectiveness model (learning in all studies and random correlation)

	Agency's final linear model	
	Mean (SE %)	BSV, % CV (SE %)
Objective function value	19,040.24	
No. observations	10,709	
BSL_{RAN 080,CVT 303L,CVT 3033} (minutes)	6.21 (2.8)	39.3 (9.0)
BSL_{RAN 1514} (minutes)	9.40 (2.7)	
ΔBSL_{female} (minutes)	-0.887 (14.4)	
BSL_{age} (minutes)	-0.03 (17.9)	
Lmax_{RAN 1514,CVT 303L,CVT 3033} (minutes)	3.26 (6.1)	105.8 (8.9)
ΔLmax_{CHF} (minutes)	-0.663 (28.2)	
Slope of learning in RAN 080 (minutes/week)	0.196 (33.1)	N/A
L₅₀ RAN 1514 (weeks)	4.60 (37.8)	71.8 (17.1)
L₅₀ CVT 3031 (weeks)	1.43 (28.2)	
L₅₀ CVT 3033 (weeks)	0.975 (12.2)	
Slope of DE_{male} (minutes per 1000 ug/L)	0.248 (7.3)	76.6 (25.4)
ΔSlope of DE_{females} (minutes per 1000 ug/L)	-0.166 (17.1)	
Residual error (additive) (σ^2) (minutes)	SD=1.11 (3.7)	
	correlations	
BSV_{BSL} and BSV_{L_{MAX}}	-0.556	
BSV_{BSL} and BSV_{L₅₀}	0.262	
BSV_{L₅₀} and BSV_{L_{MAX}}	0.112	

BSV = between subject variability calculated as SD mean. For situations with more than one mean, the lowest mean parameter was used, so that the largest BSV was reported.

BSL = baseline treadmill duration

Lmax = maximal learning

L₅₀ = time to reach 1/2 of maximal learning

DE = drug effect

7.4. Interpretation of reviewer's linear effectiveness model

The model was used to derive the drug effect or $\Delta\Delta$ ETT (Δ ranolazine - Δ placebo). The model underpredicted the actual $\Delta\Delta$ ETT for the SR 500 mg dose. For example, a typical

male taking ranolazine SR 500 mg BID has a predicted $\Delta\Delta$ ETT at trough of 12.8 ± 10.6 seconds (mean \pm SD). (Calculation shown below.)

$$\Delta\Delta \text{ ETT} = (0.248 \text{ min } 1000 \text{ ug L} \bullet 861 \pm 709 \text{ ug L}) \bullet 60 \text{ sec min} \\ = 12.8 \pm 10.6 \text{ sec}$$

where $861 \pm 709 \text{ ug L}$ is the mean \pm SD trough concentration of ranolazine SR 500 mg BID.

However, the reported $\Delta\Delta$ ETT for the SR 500 mg BID dose at trough was 23.8 seconds.

Table 19 shows the predicted $\Delta\Delta$ ETT at peak and trough for all doses by gender using the mean concentration data for the respective dose. Ranolazine had a smaller effect (0.087 minutes, 1000 ug L) in females. These data are separated for males and females since there was a significant drug effect by gender, whereas the numbers reported by the sponsor are the $\Delta\Delta$ ETT for all patients (e.g. Item 8, vol2, p123 table 15 and Item 8, vol2, p145 table 27).

Table 19. Reviewer's linear model predicted peak and trough mean $\Delta\Delta$ ETT (seconds)

	Males		Females	
	Trough	Peak	Trough	Peak
500 mg SR q 12h – CVT 3031	12.8	17.1	4.2	5.6
750 mg SR q 12h – CVT 3033	23.7	32.0	7.8	10.6
1000 mg SR q 12h – CVT 3033	33.4	41.2	11.1	13.6
1500 mg SR q 12h – CVT 3031	48.5	57.4	16.0	19.0

Table 20 shows the mean peak and trough data from the two pivotal trials, CVT 3031 (cross-over) and CVT 3033 (parallel). These numbers are different from the sponsor's for reasons discussed in Reviewer's Comments (61, page 339). The peak and trough data used in the reviewer's population PK/PD analysis were used to generate the $\Delta\Delta$ ETT. The $\Delta\Delta$ ETT for the SR 1000 mg dose was calculated using the data from the parallel study, CVT 3033, because there was no washout in the cross-over study.

Table 20. Peak and trough concentrations from pivotal trials CVT 3031 and CVT 3033

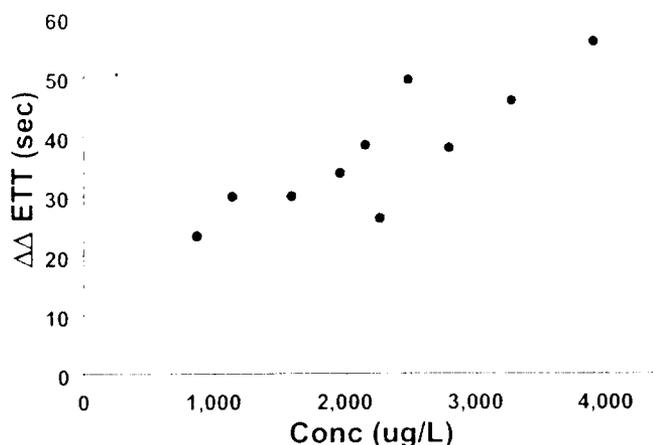
	SR 500 mg	SR 750 mg	SR 1000 mg	SR 1000 mg	SR 1500 mg
	CVT 3031	CVT 3033	CVT 3031	CVT 3033	CVT 3031
Trough (ug L)	861 ± 709	1591 ± 1079	1904 ± 1347	2245 ± 1536	3261 ± 1915
Peak (ug L)	1146 ± 729	2148 ± 1234	2455 ± 1508	2769 ± 1525	3857 ± 1991

Because the Agency's linear model was underpredicting at low concentrations, the Agency attempted a nonlinear model to better describe the effect at lower concentrations.

75. Reviewer's final model - nonlinear effectiveness model

Figure 20 shows the mean concentration, $\Delta\Delta$ ETT data from the two pivotal trials CVT 3031 and CVT 3033. The figure suggests that there is a concentration effect relationship. Linear regression of the mean data results in an intercept other than zero, suggesting that a linear model may not be the most appropriate model.

Figure 20. Mean concentration vs. $\Delta\Delta$ ETT from CVT 3031 and CVT 3033



Thus, a nonlinear model was tried and was significantly better than the linear model as evidenced by a drop in the objective function value of more than 112 ($p < 0.01$). Figure 21 and Table 20 shows the goodness of fit of the reviewer's final model. Most of the parameter estimates were similar to that of the linear model (See Table 21). Changes include a decrease in L_{50} for patients in study RAN 1514 of approximately 86 % from 4.6 weeks to 0.636 weeks.

Additionally, instead of a linear slope, an Emax type model now describes the concentration effect relationship. This was a "pseudo Emax" model because Figure 20 showed no clear plateau, yet a nonlinear model described the data better, so Emax was arbitrarily fixed to a value.

A nonlinear model can be fitted to the data in at least three ways:

1. Fit an Emax model.
2. Fit a log-linear model ($\Delta\Delta$ ETT = Int(conc))
3. Fit an empirical nonlinear model, such as a polynomial.

With regard to an Emax model, Figure 20 shows no sign of a plateau, so if used, an Emax should be arbitrarily fixed at some value. A log-linear model is an awkward model since the $\log(\text{conc} - 0)$ is undefined and best fits data only if the effect lies between 20% and 80% of maximal effects. This is most likely not the case with ranolazine. A polynomial model is also an awkward model to use since none of the model parameters reflect any

known pharmacodynamic phenomenon. Thus, covariate analysis and interpretation is extremely challenging with a polynomial model. Thus, a “pseudo Emax” model was chosen.

When the Emax was fixed to 1 minute the OFV increased to 18939.11 (Δ OFV +11) and when the Emax was fixed to 2 minutes, the OFV increased to 18932.96 (Δ OFV +4.791). Thus, 1.5 was chosen as the value to fix Emax. The EC₅₀ in males was 2,400 ug/L (2.4 mg/L) and in females was almost 11,000 ug/L (11 mg/L).

Table 21. Parameter estimates of reviewer’s final model (nonlinear)

Agency’s final model		
Objective function value	18928.173	
No. observations	10,709	
	Mean (SE %)	BSV, % CV (SE %)
BSL_{RAN 080,CVT 3031,CVT 3033} (minutes)	6.27 (2.7)	35.9 (9.9)
BSL_{RAN 1514} (minutes)	7.96 (3.5)	
ΔBSL_{female} (minutes)	-0.801 (15.9)	
BSL_{age} (minutes)	-0.0335 (16.7)	
Lmax_{RAN 1514,CVT 3031,CVT 3033} (minutes)	3.19 (6.6)	107.7 (9.1)
ΔLmax_{CHF} (minutes)	-0.805 (23.5)	
Slope of learning in RAN 080 (minutes/week)	0.167 (44.7)	
L₅₀ _{RAN 1514} (weeks)	0.636 (20.4)	67.3 (36.1)
L₅₀ _{CVT 3031} (weeks)	1.70 (11.2)	
L₅₀ _{CVT 3033} (weeks)	1.14 (12.8)	
Emax (minutes)	1.5 fixed	78.6 (24.7)
EC₅₀ _{male} (mg/L)	2.4 (17.6)	113 (29.3)
ΔEC₅₀ _{female} (mg/L)	8.58 (41.3)	
Residual error (additive) (σ^2) (minutes)	SD 1.10 (3.8)	
BSV_{BSL} and BSV_{LMAX}	correlations -0.594	

BSV – between subject variability calculated as SD mean. For situations with more than one mean, the lowest mean parameter was used, so that the largest BSV was reported.

BSL – baseline treadmill duration

Lmax – maximal learning

L₅₀ – time to reach 1/2 of maximal learning

E_{max} = maximal effect

EC_{50} = time to reach half maximal effect

DE= drug effect

Figure 21. Goodness of fit of the individual predicted concentrations of reviewer's final model (nonlinear)

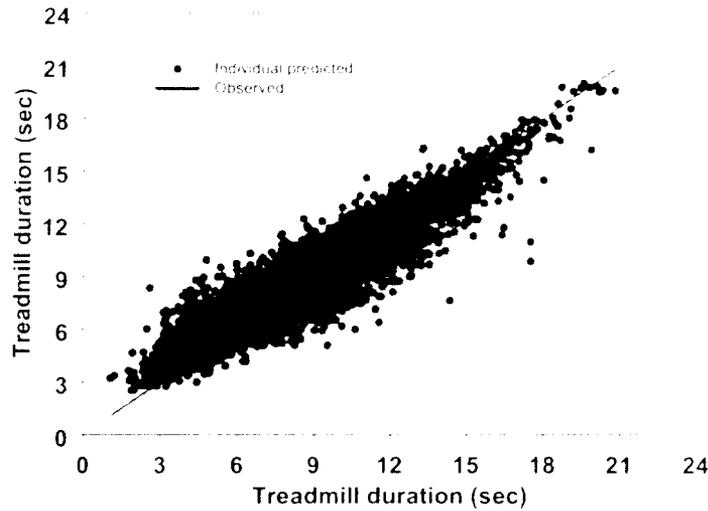
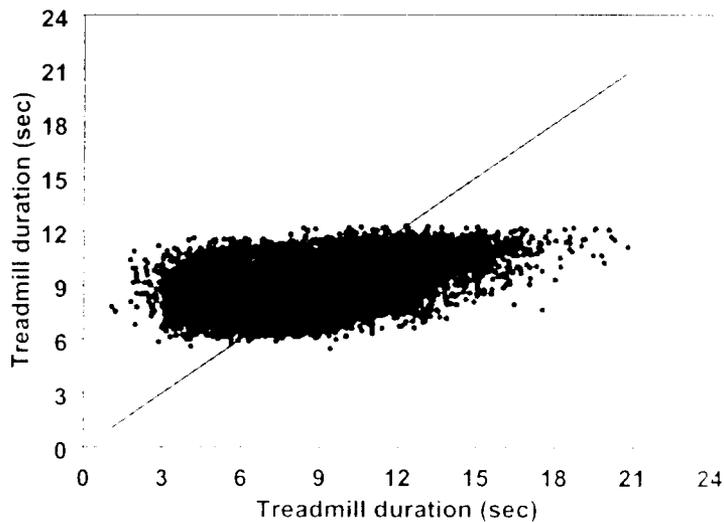


Figure 22. Goodness of fit of the population predicted concentrations of reviewer's final model (nonlinear)



7.6. Backward elimination of covariates

The covariates of gender and CHF were sequentially removed from the model to determine their importance. When gender was removed from the EC_{50} part of the model, the OFV increased to 18954.481 (Δ OFV =26) indicating that there is a significant gender

difference in drug effect. When CHF was removed from the maximal learning the OFV increased to 18944 (Δ OFV +15) indicating that patients with CHF have significantly different maximal learning capacity than patients without heart failure. Therefore, both covariates were important.

77. Software

NONMEM version 5 was used for the PK PD analysis. Compaq Fortran Optimizing Compiler Version 6.5 was used. SAS version 8.0 was used for data manipulation.

78. Interpretation of reviewer's final model

It should be noted that the selected model is a pseudo Emax model. This pseudo Emax model does not hold the standard mechanistic features of an Emax model. The Emax was arbitrarily fixed at 1.5 minutes for convenience. It should not be interpreted as the real Emax that could be achieved by ranolazine. The same applies to EC₅₀. The most important aspect is the $\Delta\Delta$ ETT. It is recommended that only $\Delta\Delta$ ETT be interpreted and no extrapolations of $\Delta\Delta$ ETT beyond the observed concentrations should be made. An advantage of the pseudo Emax model over the linear model is its ability to capture the lower concentration effects well, which are critical in the determination of the optimal dosing strategy.

79. Baseline treadmill duration

The Agency's model estimates that the typical value of the baseline treadmill duration for a median aged (64 years old) male in studies RAN 080, CVT 3031 or CVT 3033 was 6.27 minutes, 35 seconds less than the sponsor's final model of 6.85 minutes. The baseline duration for a median aged male in study RAN 1514 was 7.96 minutes, 15 seconds less than the sponsor's final model of 8.25 minutes.

Females have lower baseline treadmill durations than males (48 seconds less). The typical value of the baseline treadmill duration for a 64 year old female is 0.801 minutes less than males, compared to the sponsor's 0.76 minutes less, a difference of only 2.5 seconds. Thus, by our analysis, a 64 year old female would have a baseline treadmill duration of 5.47 minutes (sponsor's model: 6.09 minutes) compared to a male baseline treadmill duration of 6.27 minutes.

The baseline treadmill duration decreased by 0.03 minutes (or 1.8 seconds) for each year older than 64 and increased by 0.03 minutes for each year younger than 64. This finding is similar to the sponsor's final model, except that our model was a more precise estimate (standard error: 16.7%, reviewer versus 20.2%, sponsor).

Thus, our model predicts 15-35 second lower baseline treadmill duration than the sponsor's final model. Both models predict approximately the same decrease in baseline duration for females as well as age effect.

80. Learning effect

The maximal learning capacity on the treadmill was similar between males and females. The most learning that occurred in studies RAN 1514, CVT 3031 and CVT 3033 was 3.19 minutes, 18 seconds more than the sponsor's 2.89 minutes.

Patients with CHF had less maximal learning capacity (2.39 minutes) than patients without CHF. The sponsor's estimate of CHF maximal learning capacity was 1.98 minutes. The difference in learning capacity between the reviewer's model and the sponsor's was 24 seconds more in the reviewer's model.

The time to reach half the maximal learning was shorter in study RAN 1514 compared to CVT 3031 and CVT 3033, indicating that patients in study RAN 1514 learned to walk on the treadmill at a faster rate than patients in studies CVT 3031 and CVT 3033. Patients in study RAN 1514 reached half the maximal learning capacity in 0.636 weeks while patients in study CVT 3031 and CVT 3033 reached half maximal learning capacity in 1.70 weeks and 1.14 weeks, respectively. In the sponsor's model patients in study RAN 1514 also learned at a faster rate than patients in CVT 3031 and CVT 3033, however overall the rate of learning was slower in the sponsor's model.

The slope of the learning effect for patients in study RAN 080 was 0.167 minutes/week or 10 seconds per week.

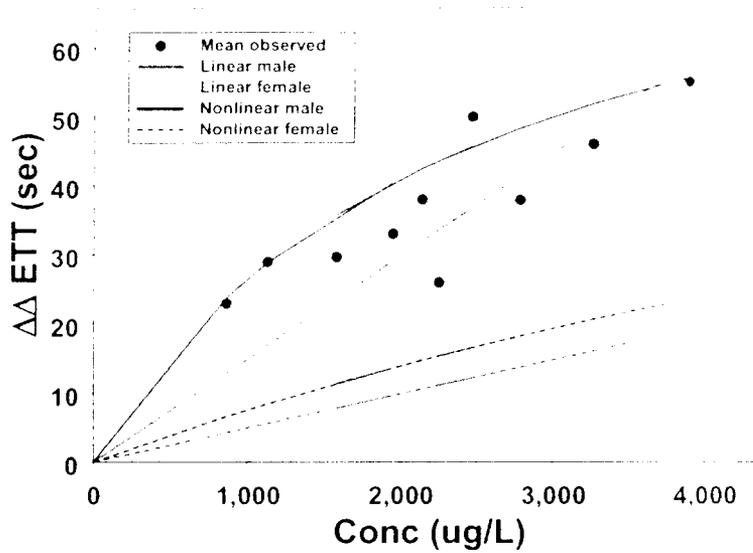
81. Drug effect

The predicted $\Delta\Delta\text{ETT}$ for trough and peak concentrations are shown in Table 22. These were calculated using the mean trough and peak concentrations in studies CVT 3031 and CVT 3033 (see Table 20). The nonlinear model better predicted the observed mean $\Delta\Delta\text{ETT}$ duration and was significantly better than the linear model (Figure 23). The linear model underpredicted the observed mean drug effect ($\Delta\Delta\text{ETT}$) of the SR 500 mg q 12 h dose. The difference between observed mean and model predicted is smaller using the nonlinear model. Because there was a significant gender difference, the model predictions in Figure 23 are separated by gender. It is noted that the data contained 78 % males, and males had a greater drug effect than females. Predicted mean $\Delta\Delta\text{ETT}$ of males, as one would expect, are higher than the naïve average of observed $\Delta\Delta\text{ETT}$. Thus, combining the gender data into one mean would result in a model predicted line closer to the observed mean $\Delta\Delta\text{ETT}$.

Table 22. Reviewer's final model predicted peak and trough mean $\Delta\Delta\text{ETT}$ (seconds)

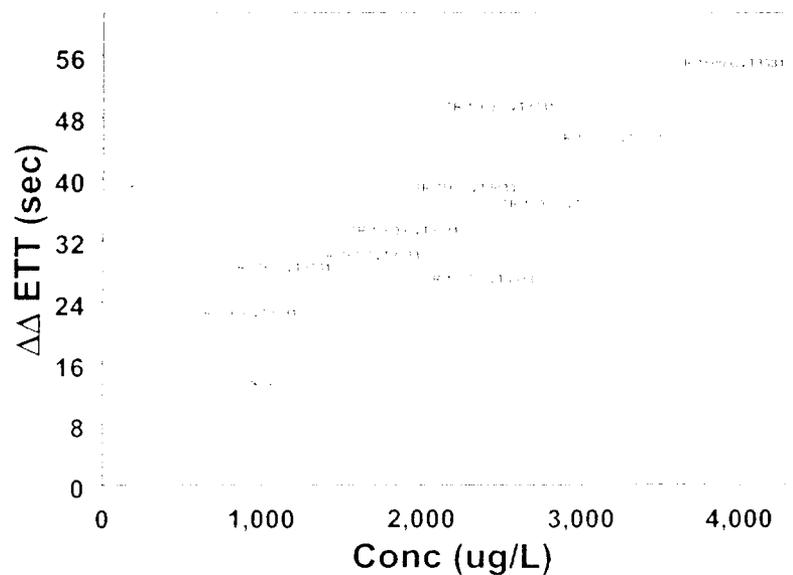
	Males		Females	
	Trough	Peak	Trough	Peak
500 mg SR q 12h – CVT 3031	23.8	28.9	6.6	8.4
750 mg SR q 12h – CVT 3033	35.8	42.5	11.4	14.7
1000 mg SR q 12h – CVT 3031	40.4	45.7	13.6	16.5
1000 mg SR q 12h – CVT 3033	43.6	48.3	15.3	18.2
1500 mg SR q 12h – CVT 3031	51.9	55.7	20.6	23.5

Figure 23. Reviewer's model predicted and observed mean $\Delta\Delta ETT$



The observed mean $\Delta\Delta ETT$ from the SR 1000 mg BID dose in study CVT 3033 (parallel study) was 24.0 and 26.1 seconds at trough and peak, respectively. However, the same dose in study CVT 3031 (cross-over study) had a mean $\Delta\Delta ETT$ of 33.7 and 50.1 seconds at trough and peak, respectively. Figure 24 shows that the 1000 mg dose in CVT 3033 does not follow the same trend as the rest of the data, yet the 750 mg dose, also used in study CVT 3033, follows the same trend as the doses used in CVT 3031. The reviewer cannot explain this.

Figure 24. Observed mean peak and trough concentration vs. observed mean $\Delta\Delta ETT$ in CVT 3031 and CVT 3033 – data shown by dose and study



82. Gender

At baseline, females walk for a shorter time on a treadmill than males. The typical value of the baseline treadmill duration in a 64 year old (median age in effectiveness analysis) patient in study CVT 3033 is 5.47 minutes if female and 6.27 minutes if male. Thus, at baseline, females walk 48 seconds less than males.

Females also have less of an effect from ranolazine compared to males. The concentration required to produce half the maximal response (EC₅₀) in females is 11,000 ug/L, while in males is it only 2500 ug/L. See Table 22 for a comparison of effectiveness at peak and trough.

The smaller baseline duration and higher concentrations required for effectiveness translate into a smaller proportional effect in females. For example, a 64 year old female given ranolazine SR 500 mg q 12 h in study CVT 3031 would have the following effect at trough relative to placebo.

$$\frac{\text{Drug Eff}}{\text{Pbo ETT duration}} \cdot 100 = \frac{\text{Drug Eff}}{TV_{BSL} + TV_{EMAX}} \cdot 100 = \frac{6.54 \text{ sec}}{5.47 \text{ min} + 3.19 \text{ min}} \cdot \frac{1 \text{ min}}{60 \text{ sec}} \cdot 100 = 1.26 \%$$

where TV_{BSL} is the typical baseline ETT value and TV_{EMAX} is the typical maximal learning value.

A 64 year old female receiving SR 500 mg q 12 h would typically have 1.3 % higher ETT duration than one receiving placebo.

A 64 year old male given ranolazine SR 500 mg q 12 h in study CVT 3033 would have the following effect at trough relative to placebo.

$$\frac{\text{Drug Eff}}{\text{Pbo ETT duration}} \cdot 100 = \frac{\text{Drug Eff}}{TV_{BSL} + TV_{EMAX}} \cdot 100 = \frac{23.76 \text{ sec}}{6.27 \text{ min} + 3.19 \text{ min}} \cdot \frac{1 \text{ min}}{60 \text{ sec}} \cdot 100 = 4.19 \%$$

A 64 year old male receiving SR 500 mg q 12 h would typically have 4.2 % higher ETT duration than one receiving placebo.

Thus, a lower baseline treadmill duration and a smaller drug effect in females translate into approximately 70 % $\left[\frac{1.26 - 4.19}{4.19} \right]$ less proportional benefit from ranolazine SR 500 mg q 12 h than males. The proportional benefit decreases with higher doses. For the 1000 mg dose and 1500 mg dose, females have approximately 60 % and 55 % less proportional benefit than males, respectively.

83. CHF

Patients with CHF have proportionally more benefit from ranolazine than patients without CHF.

The typical value of the maximal learning in a 64 year old male without CHF in study CVT 3033 is 3.19 minutes (SE: $\pm 6.6\%$). Patients with CHF have 25% less maximal learning capacity than patients without CHF, or 2.39 minutes (SE: $\pm 23.5\%$) vs. 3.19 minutes. However, the drug effect is independent of the presence or absence of CHF. Thus, a 64 year old male with CHF given ranolazine SR 500 mg q 12 h in study CVT 3031 would have the following effect relative to placebo.

$$\frac{\text{Drug Eff}}{\text{Pbo ETT duration}} \cdot 100 = \frac{\text{Drug Eff}}{TV_{BSL} + TV_{LMAX}} \cdot 100 = \frac{23.76 \text{ sec}}{6.27 \text{ min} + 2.39 \text{ min}} \cdot \frac{1 \text{ min}}{60 \text{ sec}} \cdot 100 = 4.6\%$$

A similar patient without CHF would have the following effect relative to placebo.

$$\frac{\text{Drug Eff}}{\text{Pbo ETT duration}} \cdot 100 = \frac{\text{Drug Eff}}{TV_{BSL} + TV_{LMAX}} \cdot 100 = \frac{23.76 \text{ sec}}{6.27 \text{ min} + 3.19 \text{ min}} \cdot \frac{1 \text{ min}}{60 \text{ sec}} \cdot 100 = 4.2\%$$

Therefore, a patient with CHF has approximately $10\% \left(\frac{4.6 - 4.2}{4.2} \right)$ more proportional benefit than a patient without CHF.

84. Test for carryover effect

The reviewer believes that a carryover effect in the cross-over study CVT 3031 is unlikely. Patients in study CVT 3031 received four treatments for one week each without an interim washout between treatments. There are two scenarios that can result in a carryover effect.

1. Long pharmacokinetic half-life of parent or active metabolite and/or
2. Persistent pharmacodynamic effect after active moiety is eliminated because of slow onset or offset.

Regarding the pharmacokinetics, the half-life of the parent drug is approximately 7 hours. Therefore, the parent drug is completely eliminated in less than 7 days. In the mass balance study, 83% of the total radioactivity was recovered by 48 hours post dose. By one week, 98% of total radioactivity was recovered. Thus, the parent drug and any metabolites are completely eliminated within one week. For these reasons, it is unlikely that pharmacokinetics would contribute to a carryover effect.

Regarding the pharmacodynamics, if there were a carryover effect, then the significance of the drug effect would not be maintained in a cross-over study. The reviewer separated data from the four studies used in the population PK/PD analysis by study design (cross-over or parallel). Studies RAN 080, RAN 1514 and CVT 3033 were all cross-over study designs with no interim washout and study CVT 3031 was a parallel study. Each data set was analyzed with and without drug effect. There was a significant drug effect, $p < 0.0001$, found in both the parallel and cross-over studies (see Table 23). Additionally, the parameter estimates of the analysis with drug effect for both the parallel and cross-over studies are similar to the final model (Table 21). This analysis supports no carryover effect due to persistent pharmacodynamics.

The parameter estimates, specifically the EC_{50} , between the parallel and cross-over studies cannot be directly compared because the final model is a nonlinear model, and the dose range in the cross-over studies was wider than that in the parallel study. Thus, the parameter estimates should be different between the two study designs, however they are similar to the final model.

Table 23. Change in OFV for drug effect for parallel and crossover studies

	Parallel study CVT 3033	Cross-over studies RAN 080, RAN 1514, CVT 3033
No drug effect	--	--
Drug effect	- 86.037	-158.672

85. Test if Russian center 710 is significantly different from all other centers

It is unlikely that Russian center 710 has more influence on the effectiveness than the other study centers.

Possible reasons for Russian center 710 to have more influence on the effectiveness include:

1. Higher concentrations.
2. Different patient characteristics.
 - 2a. Were the baseline ETTs lower in Russian, leading to proportionally more effect?
3. More pharmacodynamic effect.

Point 1 - concentrations

Concentrations in Russian center 710 seem higher than all other patients in the PK/PD analysis of effectiveness (studies CVT 3033, CVT 3031, RAN 080 and RAN 1514) (see Table 24). Yet patients at center 710 were equally (n=14) randomized to placebo, 750 mg and 1000 mg. The 1st quartile concentration is almost double, and the median concentration is higher than the rest of the world. Thus, if one ignores concentration data and only analyzes the effectiveness by dose, one may falsely conclude that there is more effect in center 710 when the reason why center 710 may seem to have more effectiveness may be because concentrations are higher. The reviewer's analyses of the

effectiveness uses concentration and not dose. Thus, the reviewer did not find center 710 to have more effectiveness.

Table 24. Concentrations (ug/L) in the Russian center 710 & the rest of the world

	Russian center 710	Rest of the world
1 st Quartile	1,118.00	636.23
Median	1,765.00	1,460.30
Mean	1,837.00	1,777.10
3 rd quartile	2,313.00	2,500.00

It is noted that all patients in study CVT 3033 received the same formulation, DSM sustained release tablet.

Point 2 -patient characteristics

Other than a higher percentage of patients with CHF and concomitant diltiazem in site 710, the baseline demographics were similar (See Table 25).

Table 25. Baseline characteristics of patients in center 710 and all sites in study CVT 3033

	Russian center 710	Study 3033
Males	75 %	78 %
CHF	97 %	29 %
Weight (kg)	80.5 ± 10.3	80.6 ± 12.9
Height (cm)	169.3 ± 6.3	170.0 ± 8.6
Age (years)	56.7 ± 6.1	64.4 ± 9.2
Baseline ETT time (min)	7.6 ± 2.0	7.3 ± 1.9
Concomitant diltiazem	36 %	21 %

Mean ± SD

Of the patients in Russian site 710, mean concentrations of those patients taking diltiazem were not different from those patients not taking diltiazem (see Table 26).

Table 26. Ranolazine concentrations in Russian center 710 by diltiazem treatment

	On diltiazem	No diltiazem
750 mg	1597 ± 307	1781 ± 647
1000 mg	2025 ± 708	1694 ± 562

Mean ± SD

To determine if there were differences at baseline, center 710 was first tested as a covariate on the baseline treadmill duration and then on maximal learning. The results indicated that patients in center 710 did not have different baseline treadmill durations or maximal learning ($p > 0.05$).

Point 3 - pharmacodynamics

To determine if there were differences in pharmacodynamics, the reviewer first tested if a significant drug effect was preserved when the Russian data were removed (+2 patients

removed). The drug effect was significant ($p < 0.05$). Thus, removing the Russian data still preserves a significant drug effect that was also found with the final model.

Second, the parameter estimates of the drug effect model without Russian center 710 data were similar to the final model. Specifically the EC_{50} s are similar between the final model and the drug effect model without Russian center 710 data. These data support that there are no differences in pharmacodynamics.

Table 27. EC_{50} of reviewer's final model and final model without Russian center 710

	Final model	Model without Russian center
EC_{50} male (ug/L)	2,400	2,690
EC_{50} female (ug/L)	10,980	11,000

Because of differences in concentrations, similar patient characteristics and pharmacodynamics, it is unlikely that Russian site 710 has more influence on the effectiveness.

86. Reviewer's Analysis of Safety

The probability of the occurrence of the following adverse events and its relationship to exposure were examined using logistic regression in SAS version 8.2:

- syncope, asthenia and dizziness.

Maximum concentration was used as a surrogate for overall exposure.

The following concomitant medications were included in the analysis:

- coumadin, diltiazem, ketoconazole, metformin and verapamil.

Additionally, these variables were included in the analysis:

- ranolazine (whether patients received drug or placebo),
- race (white, black, asian, hispanic, other),
- weight,
- height or ideal body weight,
- gender,
- CHF,
- age,
- diabetes

Data from 25 parallel studies (2,431 patients) were included in the analysis. These studies contain the longest exposure (12 weeks) and concentrations as high as 12,172 ug/L. The mean maximum concentration was 1,960 ug/L. Cross-over studies (39 studies, 1,366 patients) were excluded in case there was a carryover effect in toxicity. To create the data set for the logistic regression, one adverse event observation per patient (some patients had a specific adverse event occur more than once) was merged with the patient's C_{max} data. C_{max} was used as a measure of exposure. It should not be

interpreted that the adverse event occurred at the maximum concentration. It was also likely that the adverse event was related to accumulated exposure.

If the adverse event occurred before the start of the dose, the data were deleted. Patients who had an adverse event were designated a "one" and those who did not were designated a "zero". The probability of having an adverse event was determined from the results of the logistic regression.

87. Syncope

The entire safety data set had 51 reports of syncope. Only one patient (cross-over study CVT 3031, ID 1331019) had both syncope and hypotension. There were 23 patients with syncope in the parallel studies.

The adverse event terms that defined syncope are listed below.

- 1 BLACK OUT SPELL
- 2 COLLAPSE
- 3 COLLAPSE DURING ERECT B.P.
- 4 COLLAPSE DURING RECOVERY
- 5 FAINTED
- 6 FAINTING
- 7 LOSS OF CONSCIOUSNESS
- 8 MILD VASO VAGAL ATTACK
- 9 NEAR FAINTING EPISODE
- 10 NEAR SYNCOPAL EPISODE
- 11 ONE EPISODE OF BLACKING OUT
- 12 POSTURAL SYNCOPE
- 13 SECOND SYNCOPAL EPISODE
- 14 SYNCOPAL EPISODE
- 15 SYNCOPAL EPISODES
- 16 SYNCOPE
- 17 VASO-VAGAL REACTION
- 18 VASOVAGAL ATTACK
- 19 VASOVAGAL ATTACK ON STANDING
- 20 VASOVAGAL EPISODE
- 21 VASOVAGAL REACTION
- 22 VASOVAGAL REFLEX
- 23 VASOVAGAL RESPONSE
- 24 VASOVAGAL SYNCOPE

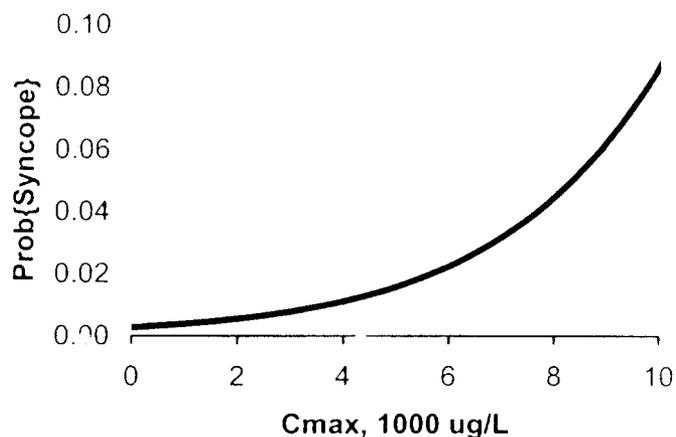
There was a significant concentration dependent effect on syncope (Table 28).

Table 28. Maximum likelihood estimates significant for syncope

	Estimate	Standard Error	P-value
Intercept	-5.9106	0.4834	< 0.0001
Cmax	0.3561	0.1044	0.0006

Figure 25 shows the probability of having syncope as maximum concentrations increase.

Figure 25. Probability of syncope



Concentrations as high as 9,000 ug/L observed with the SR 1000 mg bid dose translate into ~6% probability of syncope.

88. Asthenia

In the entire safety data set there were 760 reports of asthenia in 387 patients. There were 160 patients with asthenia in the parallel studies. We did not find a concentration dependent effect on asthenia.

89. Dizziness

In the entire safety data set there were 740 reports of dizziness. There were 209 patients with dizziness in the parallel studies. There was a significant concentration dependent effect on dizziness (Table 29).

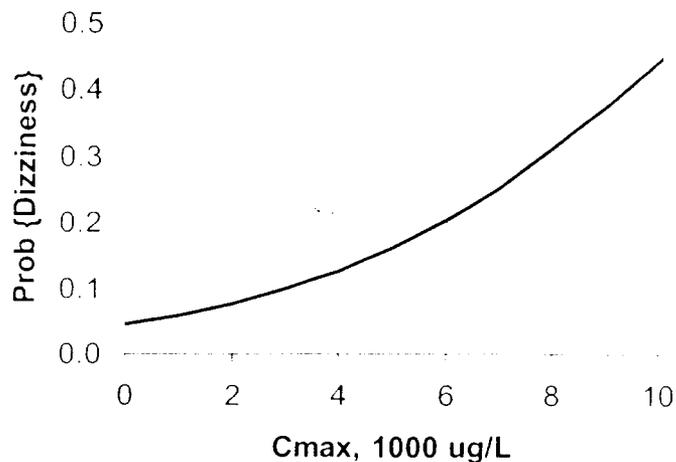


Table 29. Maximum likelihood estimates significant for dizziness

	Estimate	Standard Error	P-value
Intercept	-3.0683	0.1356	< 0.0001
Cmax	0.2850	0.0982	<0.0001

Figure 26 shows the probability of having dizziness as concentrations increase.

Figure 26. Probability of dizziness

Concentrations as high as 9,000 ug/L observed with the SR 1000 mg bid dose translates into ~35% probability of dizziness.

90. Notched T-waves

Fourteen studies with information on notched t-waves were available for analysis. This data set was the same one as that used in the population QTc analysis minus studies RAN069, RAN0114, RAN 2302, CVT 3016 and CVT 3018 because notched t-wave data were not reported. Thirty-one observations where the dose was zero and the concentration was greater than zero were removed by the reviewer. None of the removed observations contained notched T-waves. There were a total of 1271 patients with 458 of these patients continuing on to the open label studies. There were 283 reports of notched t-waves, 14,588 reports of no notched T-waves and 3 reported as unknown. Table 30 and Figure 27 show the concentrations of those with notched T-waves and those without. Overall, there seems to be a concentration dependent relationship, but the data are variable.

Table 30. Concentration (ug/L) of notched and no notched T-wave

Notch	Number pts	observations	Mean ± SD	Median
No	1,728	14,588	1,035 ± 1,532	180
Yes	118	283	3,758 ± 2,604	3,660

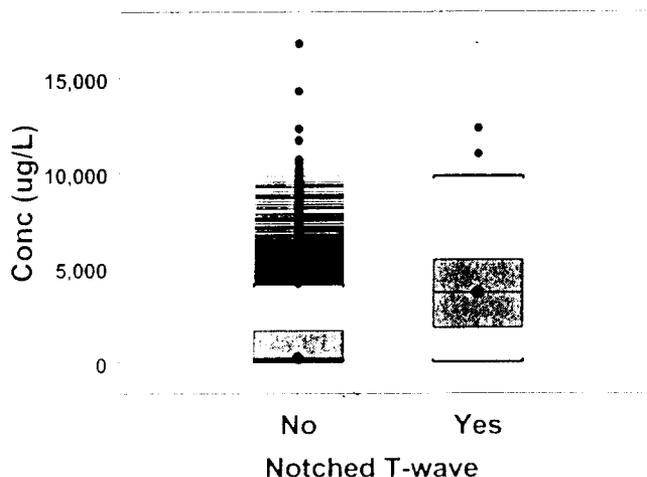


Figure 27. Concentration of notched and no notched T-waves

91. Appendix 1: NONMEM Control Streams

92. Sponsor's Base Model

:Model Desc: BASE MODEL with baseline effect BY STUDY (80,3033 & 3031 same)
for TAD & RAN 080 LINEAR TM effect=0 no ETA& EC50 BY STUDY

:Project Name: cvt2

:Project ID: NO PROJECT DESCRIPTION

SPROB RUN# 220

SINPUT C ID PTID=DROP SUBJ=DROP STDY=PER SCHD=DIFF=DROP
SD=DROP TDD=DROP DI=DROP FORM CONC OLDC=DROP DV ANG BDUR
BANG=DROP PDUR=DROP PANG=DROP SEX RACE AGE WT HT=DROP DBT
CHF

NYHA=DROP TERM=DROP REAS=DROP BET=DROP ATF=DROP

DIL=DROP AML=DROP CAL=DROP NIT=DROP EXE VER=DROP PLA CDUR

SDATA 104.csv IGNORE=C

SPRED

DUR=DV

IF(STDY.EQ.80.AND.PER.EQ.0)TM=1 ; CALCULATING DURATION ON STUDY
080

IF(STDY.EQ.80.AND.PER.EQ.1)TM=2

IF(STDY.EQ.80.AND.PER.EQ.2)TM=3

IF(STDY.EQ.80.AND.PER.EQ.3)TM=4

IF(STDY.EQ.1514.AND.PER.EQ.3)TM=1 ; CALCULATING DURATION ON
STUDY 1514

IF(STDY.EQ.1514.AND.PER.EQ.4)TM=2

IF(STDY.EQ.1514.AND.PER.EQ.5)TM=3

IF(STDY.EQ.1514.AND.PER.EQ.6)TM=4

IF(STDY.EQ.1514.AND.PER.EQ.7)TM=5

IF(STDY.EQ.1514.AND.PER.EQ.8)TM=6

IF(STDY.EQ.3031.AND.PER.EQ.2)TM=1 ; CALCULATING DURATION ON
STUDY 3031

IF(STDY.EQ.3031.AND.PER.EQ.3)TM=2

IF(STDY.EQ.3031.AND.PER.EQ.4)TM=3

IF(STDY.EQ.3031.AND.PER.EQ.5)TM=4

IF(STDY.EQ.3031.AND.PER.EQ.6)TM=5

IF(STDY.EQ.3033.AND.PER.EQ.2)TM=1 ; CALCULATING DURATION ON
STUDY 3033

IF(STDY.EQ.3033.AND.PER.EQ.3)TM=3

```

IF(STDY.EQ.3033.AND.PER.EQ.4)TM=7
IF(STDY.EQ.3033.AND.PER.EQ.5)TM=13
IF(STDY.EQ.3033.AND.PER.EQ.6)TM=13.3

SCHD1=0
SCHD2=0
SCHD3=0
SCHD4=0
IF(STDY.EQ.80.OR.STDY.EQ.3031.OR.STDY.EQ.3033)SCHD1=1
IF(STDY.EQ.1514)SCHD2=1
IF(STDY.EQ.3031)SCHD3=1
IF(STDY.EQ.3033)SCHD4=1

TBAS=THETA(1)*SCHD1+THETA(2)*SCHD2 ; BASELINE TIME AFTER DOS
BASE=TBAS+ETA(1)
IF(STDY.EQ.80)THEN
SLP=THETA(3)+ETA(2)
SDR=(TM*SLP) ; TIME ON STUDY EFFECT

ELSE

EMAX=THETA(4)+ETA(3)
TC50=THETA(5)*SCHD2+THETA(6)*SCHD3+THETA(7)*SCHD4
EC50=TC50+ETA(4)
SDR=(TM*EMAX)/(TM+EC50)

ENDIF

SDRE=BASE+SDR

DRSL=THETA(8)+ETA(5)
DRI=(CONC/1000)*DRSL
DRIE=DRI

F = SDRE - DRIE
Y = F + ERR(1)
IPRE = F

:INITIAL ESTIMATES

STHETA
(6) : 1 BASELINE Tad EFFECT 080 & 3031 & 3033
(6) : 2 BASELINE Tad EFFECT 1514
(0 FIX) : 3 TIME ON STUDY RAN 080
(4) : 4 EMAX TIME ON STUDY OTHER STUDIES
(3) : 5 EC50 TIME ON 1514

```

(3) : 6 EC50 TIME ON 3031
(3) : 7 EC50 TIME ON 3033
(0.2) : 8 DRUG EFFECT

SOMEGA

0.2 : [A] 1 BASELINE TAD
0 FIX : [A] 2 TIME ON STUDY RAN 080
0.4 : [A] 3 EMAX TIME ON STUDY OTHER STUDIES
0.4 : [A] 4 EC50 TIME ON STUDY OTHER STUDIES
0.4 : [A] 5 DRUG EFFECT

SSIGMA

1 : [A]

SEST MAXEVAL=9999 SIGD=3 PRINT=10 METHOD=1 NOABORT
MSFO=220.MSF

SCOV

\$TABLE FILE=220.TAB ID ETA1 ETA2 CONC DUR ANG SCHD PER BDUR TM
STDY

FORM SEX RACE AGE WT DRHE SDR SDRE BASE IPRE NOPRINT
ONEHEADER

;\$TABLE ID ETA1 ETA2 ETA3 NOPRINT ONEHEADER FILE=PATAB010

;\$TABLE ID PRED DV CONC WRES IPRE NOPRINT ONEHEADER
FILE=SDTAB010

;\$TABLE ID SD TDD BSHR BASE AGE WT NOPRINT ONEHEADER
FILE=COTAB010

;\$TABLE ID SEX RACE DBT CHF NYHA FORM PATI STDY
: NOPRINT ONEHEADER FILE=CATAB010

93. Sponsor's Final Model

Run 340

:Model Desc: FINAL MODEL - base sex+age, emax+chf, drsl+sex, using all data with Scov

:Project Name: cvt2

:Project ID: NO PROJECT DESCRIPTION

\$PROB RUN# 340

```
SINPUT C ID PTID=DROP SUBJ=DROP STDY PER SCHD DIFF=DROP
SD=DROP TDD=DROP DI=DROP FORM CONC OLDC=DROP DV ANG=DROP
BDUR=DROP
BANG=DROP PDUR=DROP PANG=DROP SEX RACE=DROP AGE WT
HT=DROP DBT CHF
NYHA=DROP TERM=DROP REAS=DROP BET ATE
DIL AML CAL NIT EXE=DROP VER PLA=DROP CDUR=DROP
```

\$DATA 107.csv IGNORE=C

\$PRED

```
IF(BET.GT.0.OR.ATE.GT.0.OR.DIL.GT.0.OR.AML.GT.0.OR.CAL.GT.0.OR.NIT.GT.
0)THEN
```

```
CNMD=1
```

```
ELSEIF(VER.GT.0)THEN ;CODING TO GET CONMED DATA IN CORRECT
FORMAT
```

```
CNMD=1 ;0=NO CONMED 1 = YES CONMED
```

```
ELSE
```

```
CNMD=0
```

```
ENDIF
```

```
IF(FORM.EQ.1.OR.FORM.EQ.2)THEN ; CODING TO SET FLAG FOR IR AND SR
DSG=1 ; 1 = SR & 0 = IR
```

```
ELSE
```

```
DSG=0
```

```
ENDIF
```

DUR=DV

```
IF(STDY.EQ.80.AND.PER.EQ.0)TM=1; CALCULATING DURATION ON STUDY
080
```

```
IF(STDY.EQ.80.AND.PER.EQ.1)TM=2
```

```
IF(STDY.EQ.80.AND.PER.EQ.2)TM=3
```

```
IF(STDY.EQ.80.AND.PER.EQ.3)TM=4
```

IF(STDY.EQ.1514.AND.PER.EQ.3)TM=1 ; CALCULATING DURATION ON
STUDY 1514

IF(STDY.EQ.1514.AND.PER.EQ.4)TM=2

IF(STDY.EQ.1514.AND.PER.EQ.5)TM=3

IF(STDY.EQ.1514.AND.PER.EQ.6)TM=4

IF(STDY.EQ.1514.AND.PER.EQ.7)TM=5

IF(STDY.EQ.1514.AND.PER.EQ.8)TM=6

IF(STDY.EQ.3031.AND.PER.EQ.2)TM=1 ; CALCULATING DURATION ON
STUDY 3031

IF(STDY.EQ.3031.AND.PER.EQ.3)TM=2

IF(STDY.EQ.3031.AND.PER.EQ.4)TM=3

IF(STDY.EQ.3031.AND.PER.EQ.5)TM=4

IF(STDY.EQ.3031.AND.PER.EQ.6)TM=5

IF(STDY.EQ.3033.AND.PER.EQ.2)TM=1 ; CALCULATING DURATION ON
STUDY 3033

IF(STDY.EQ.3033.AND.PER.EQ.3)TM=3

IF(STDY.EQ.3033.AND.PER.EQ.4)TM=7

IF(STDY.EQ.3033.AND.PER.EQ.5)TM=13

IF(STDY.EQ.3033.AND.PER.EQ.6)TM=13.3

SCHD1=0

SCHD2=0

SCHD3=0

SCHD4=0

IF(STDY.EQ.80.OR.STDY.EQ.3031.OR.STDY.EQ.3033)SCHD1=1

IF(STDY.EQ.1514)SCHD2=1

IF(STDY.EQ.3031)SCHD3=1

IF(STDY.EQ.3033)SCHD4=1

MAGE=64

TBAS=THETA(1)*SCHD1+THETA(2)*SCHD2 ; BASELINE TIME AFTER DOS

BASE=(TBAS+THETA(9)*SEX+THETA(10)*(AGE-MAGE))*ETA(1)

IF(STDY.EQ.80)THEN

SLP=THETA(3)+ETA(2)

SDR=(TM*SLP) ; TIME ON STUDY EFFECT

ELSE

EMAX=(THETA(4)+THETA(11)*CHF+THETA(12)*SEX)+ETA(3)

TC50=THETA(5)*SCHD2+THETA(6)*SCHD3+THETA(7)*SCHD4

EC50=(TC50+THETA(14)*SEX)*ETA(4)

SDR=(TM*EMAX)/(TM+EC50)

ENDIF

SDRE=BASE+SDR

DRSL=(THETA(8)+THETA(13)*SEX)*ETA(5)

DR1=(CONC/1000)*DRSL

DR1E=DR1

F = SDRE+DR1E

Y = F + ERR(1)

IPRE = F

:INITIAL ESTIMATES

\$THETA

(0.6) : 1 BASELINE TAD EFFECT 080 & 3031 & 3033

(0.9) : 2 BASELINE TAD EFFECT 1514

(0 FIX) : 3 TIME ON STUDY RAN 080

(0,2.5) : 4 EMAX TIME ON STUDY OTHER STUDIES

(0,1.83) : 5 EC50 TIME ON 1514

(0,2.5) : 6 EC50 TIME ON 3031

(0,2.5) : 7 EC50 TIME ON 3033

(0,0.2) : 8 DRUG EFFECT

(0.001) : 9 SEX ON BASE

(0.001) : 10 AGE ON BASE

(0.001) : 11 CHF ON EMAX

(0 FIX) : 12 SEX ON EMAX

(0.001) : 13 SEX ON DRSL

(0 FIX) : 14 SEX ON EC50

\$OMEGA

2 : [A] 1 BASELINE TAD

0 FIX : [A] 2 TIME ON STUDY RAN 080

5 : [A] 3 EMAX TIME ON STUDY OTHER STUDIES

0.5 : [A] 4 EC50 TIME ON STUDY OTHER STUDIES

0.04 : [A] 5 DRUG EFFECT

\$SIGMA

1 : [A]

SEST MAXEVAL=9999 SIGD=4 PRINT=10 METHOD=1

MSFO=340.MSF

\$COV

STABLE FILE=340.TAB ID BASE EMAX EC50 DRSL CONC TM STDY

FORM SEX AGE WT DR1E SDR SDRE BASE CNMD IPRE NOPRINT

ONEHEADER

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:$TABLE ID PRED DV WRES IPRE NO$PRINT ONE$HEADER FILE=SDTAB300
:$TABLE ID AGE WT NO$PRINT ONE$HEADER FILE=CGTAB300
:$TABLE ID SEX DBT CHF CNMD FORM DSG NO$PRINT ONE$HEADER
FILE=CATAB300
```

94. Reviewer's Final Model

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$PROB RUN# BASEMODEL DELMX_S_S80_TD.CTL
```

```
SINPUT C ID PTID=DROP SUBJ=DROP STDY PER SCHED DIFF=DROP
SD=DROP TDD=DROP DI=DROP FORM CONC OLDC=DROP DV ANG BDUR
BANG=DROP PDUR=DROP PANG=DROP SEX RACE AGE WT HT=DROP DBT
CHF
NYHA=DROP TERM=DROP REAS=DROP BET=DROP AFE=DROP
DIL=DROP AML=DROP CAL=DROP NIT=DROP EXE VER=DROP PLA CDUR
```

```
$DATA c:\data\nhf\fdan\da\ranolazine_reviewer\pd\data\nophocpdose.csv IGNORE=C
```

```
$PRED
```

```
DUR=DV
```

```
IF(STDY.EQ.80.AND.PER.EQ.0)TM=1 ; CALCULATING DURATION ON STUDY
080
```

```
IF(STDY.EQ.80.AND.PER.EQ.1)TM=2
```

```
IF(STDY.EQ.80.AND.PER.EQ.2)TM=3
```

```
IF(STDY.EQ.80.AND.PER.EQ.3)TM=4
```

```
IF(STDY.EQ.1514.AND.PER.EQ.3)TM=1 ; CALCULATING DURATION ON
STUDY 1514
```

```
IF(STDY.EQ.1514.AND.PER.EQ.4)TM=2
```

```
IF(STDY.EQ.1514.AND.PER.EQ.5)TM=3
```

```
IF(STDY.EQ.1514.AND.PER.EQ.6)TM=4
```

```
IF(STDY.EQ.1514.AND.PER.EQ.7)TM=5
```

```
IF(STDY.EQ.1514.AND.PER.EQ.8)TM=6
```

```
IF(STDY.EQ.3031.AND.PER.EQ.2)TM=1 ; CALCULATING DURATION ON
STUDY 3031
```

```
IF(STDY.EQ.3031.AND.PER.EQ.3)TM=2
```

```
IF(STDY.EQ.3031.AND.PER.EQ.4)TM=3
```

```
IF(STDY.EQ.3031.AND.PER.EQ.5)TM=4
```

```
IF(STDY.EQ.3031.AND.PER.EQ.6)TM=5
```

```
IF(STDY.EQ.3033.AND.PER.EQ.2)TM=1 ; CALCULATING DURATION ON
STUDY 3033
```

```
IF(STDY.EQ.3033.AND.PER.EQ.3)TM=3
```

IF(STDY.EQ.3033.AND.PER.EQ.4)TM=7
 IF(STDY.EQ.3033.AND.PER.EQ.5)TM=13
 IF(STDY.EQ.3033.AND.PER.EQ.6)TM=13.3

SCHD1=0
 SCHD2=0
 SCHD3=0
 SCHD4=0

IF(STDY.EQ.80.OR.STDY.EQ.3031.OR.STDY.EQ.3033)SCHD1=1
 IF(STDY.EQ.1514)SCHD2=1
 IF(STDY.EQ.3031)SCHD3=1
 IF(STDY.EQ.3033)SCHD4=1

IS80=0
 IF (STDY.EQ.80) IS80=1

CONCMG = CONC/1000
 MAGE = 64

TVBSL = THETA(1)*SCHD1 + THETA(7)*SCHD2 + THETA(8)*SEX +
 THETA(9)*(AGE-
 MAGE) :TV BSL

TREADMILL DUR (min)
 TVLMX = (THETA(2) + THETA(11)*CHF) :TV MAX

LEARN EFF (min)
 TVL50 = THETA(3)*SCHD2 + THETA(4)*SCHD3 + THETA(5)*SCHD4
 :TV TIME WKS REACH

1/2 MAX LEARNING
 TVEM = THETA(6)
 TVSL80 = THETA(12)
 TVEC = THETA(13)+ THETA(10)*SEX :TVDE GENDER ON
 DRUG EFFECT

ETBSL = ETA(1)
 ETLMX = ETA(2)
 ETL50 = ETA(3)
 ETEM = ETA(4)
 ETEC = ETA(5)

BSL = TVBSL + ETBSL
 LMX = TVLMX + ETLMX
 L50 = TVL50 + ETL50
 EMAX = TVEM + ETEM
 EC50 = TVEC * EXP(ETEC)

PEFF = (1-IS80)*(LMX * TM) (TM - L50) + TVSL80 * TM * IS80

EFF = EMAX * CONCMG/(CONCMG + EC50)
RESP = BSL + PEFF + EFF
Y = RESP + ERR(1)

:INITIAL ESTIMATES

\$THETA (0, 6) :1BSL803133
\$THETA (3) :2LMX
\$THETA (0, 1) :3L5014
\$THETA (0, 2) :4L5031
\$THETA (0, 1) :5L5033
\$THETA (1.5 FIX) :6EMAX
\$THETA (0, 8) :7BSL14
\$THETA (-1) :8BSLSEX
\$THETA (-0.01) :9BSLAGE
\$THETA (8) :10ECSEX
\$THETA (-1) :11LMXCHF
\$THETA (0.1) :12SL80
\$THETA (0.2,10) :13EC50

SOMEGA BLOCK(2)

2 :1WBSL
0.5 2 :2WLMX

SOMEGA 1 :3WL50
SOMEGA 0.2 :4Wemax
SOMEGA 0.2 :5Wec50

\$SIGMA 1

SEST MAXEVAL=9999 SIGD=3 PRINT=10 NOABORT
METH=1; FOCE

SCOV

STABLE ID ETBSL ETLMX ETL50 ETEM ETEC BSL LMX 1.50 EMAX EC50 STDY
TM
CONCMG DV Y NOPRINT ONEHEADER FILE=pemax2.fit

95. Appendix 2: SAS code for logistic regression – example

```
*****;
***   LOGISTIC REGRESSION   ***
*****;
proc logistic data=div1000 descending;
  model ae=cmax ageyr wtkg HTCM male black
        white hispanic asian other chf dx
        diltiazem verapamil ran
        metformin ketoconazole coumadin
        /selection=backward slstay=0.05;
TITLE 'syncope';
run;
```

96. Appendix 3: Formulations and Assays

Table 31. Formulation in study RAN 080

Strength	Formulation	Batch no
Ranolazine 400 mg HCL capsules		CT00 SC1082A
Atenolol 100 mg tablets	manufacturer: ICI plc. England	49361/91
glyceryl trinitate 0.5 mg	manufacturer: Hileross Pharmaceuticals	CT00 SC058AQ (GF289)
placebo	manufacturer: ICI plc. England	49182/91
	manufacturer: SRS	CT1025 SC272H

*267 mg ranolazine dihydrochloride (IR) capsule is equivalent to 226 mg of ranolazine free base

*400 mg ranolazine dihydrochloride (IR) capsule is equivalent to 342 mg of ranolazine free base

Ranolazine-
microcrystalline cellulose
povidone K-25
croscarmellose sodium
magnesium stearate
size 0 brilliant blue capsule shells

Plasma samples were determined by HPLC using fluorimetric detection following solid phase extraction.

Table 32. Formulation in study RAN 1514

Strength	Formulation	Batch no
267 mg IR capsule	F43285-010	43285-193-11767 43285-193-11889
400 mg IR capsule	F43285-011	43285-193-11768 43285-193-11890
placebo capsule	p43285-013	43285-193-11766

*267 mg ranolazine dihydrochloride (IR) capsule is equivalent to 226 mg of ranolazine free base

*400 mg ranolazine dihydrochloride (IR) capsule is equivalent to 342 mg of ranolazine free base

No information is provided on the assay.

Table 33. Formulation in study CVT 3031

Strength	Lot no.	Batch no.
500 mg SR tablet	791751	GUS00278

	791771	00010
placebo tablet	6995 and 8007 7314 and 7492	00010 GUS00278

Ranolazine SR was formulated with a film-coated tablet containing 500 mg of ranolazine base as the active ingredient. Each tablet also contained the following inactive ingredients: microcrystalline cellulose, methacrylate copolymer (Type C), hydroxypropyl methyl cellulose, magnesium stearate, sodium hydroxide, titanium dioxide, polysorbate 80, polyethylene glycol, carnauba wax and FD&C Blue No.2

The placebo tablet contained lactose monohydrate, microcrystalline cellulose, titanium dioxide, polysorbate 80, polyethylene glycol, carnauba wax, and FD&C Blue No. 2.

Review

NDA: **21526**

Compound: Ranolazine
Submission Dates: 12.27.02
04.15.03
06.25.03

Sponsor: CV Therapeutics
Pharmacometrics Reviewer: Venkatesh Atul Bhattaram
Team Leader: Joga Gobburu

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QUESTION BASED REVIEW

The aim of the analysis was to study the relationship of plasma ranolazine concentrations and QTc prolongation. An understanding of the role of various factors such as age, gender, concomitant medications, disease condition can be achieved by administering the drug to various groups of patients. To quantify the effect of such factors on ranolazine QTc prolongation mixed effects modeling techniques were used. A few important questions that may lead to better appreciation of the impact of the concentration-QTc relationship are considered below. In the text below,

$\Delta QTc = \text{Drug or Placebo Effect} - \text{Baseline QTc}$.

$\Delta\Delta QTc = \text{Drug Effect} - \text{Placebo Effect} - \text{Baseline QTc}$.

Concentration dependent QTc prolongation

(a) Is there an effect of ranolazine on heart rate?

Figure 1 shows that on average, RR interval decreased by 5 ms for every 1000 ng/ml increase in ranolazine plasma levels although the changes were very variable between different subjects on active treatment. Overall a minimal effect of ranolazine on RR interval is observed. The slope of linear regression of ranolazine plasma levels and ΔRR , msec is shown below:

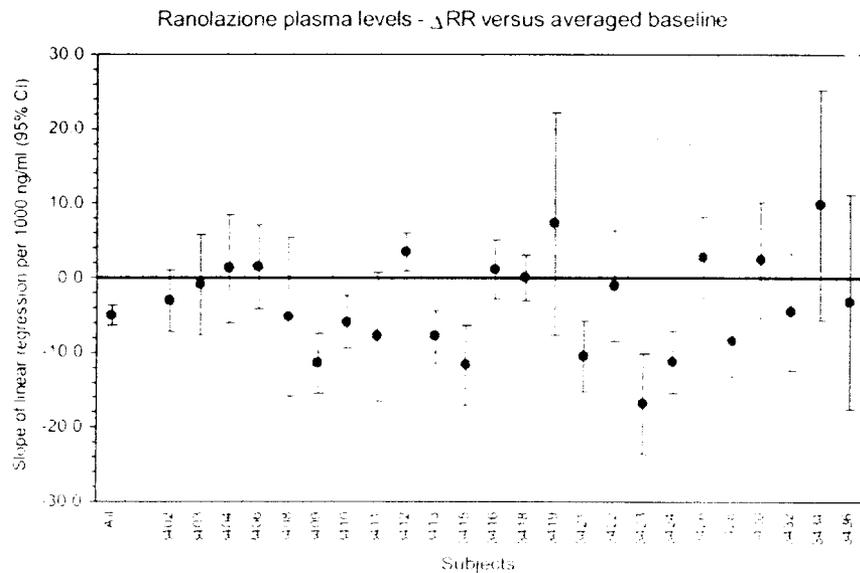


Figure 1. Relationship of averaged and individual changes in RR interval to ranolazine plasma levels in patients on active treatment (Study CVT 311).

(b) What is the best approach for correcting QT for RR, for ranolazine?

The best approach for correcting QT for RR would be the Individual Correction Method. Figure 15 shows the good performance of individual correction method for all occasions in representative patients in each study.

(c) What is the time course of ΔQTC in relation to ranolazine and its major metabolites (RS-88390, RS-88640, RS-94287)?

The time course of ΔQTC (Study CVT 3111) as calculated by Fridericia's correction formula is shown in Figure 2. Ranolazine was administered as prolonged infusion to achieve steady state for the ranolazine and its metabolites since the metabolites of ranolazine (RS-88390, RS-88640) have a long half-life of 10-20 h. The ΔQTC is not significantly different between 32-48h and 56-72 h indicating that the steady state for ΔQTC has been probably attained. Upon cessation of the infusion at 72 h the ΔQTC decreases and is comparable to the placebo. The time course of ranolazine and its metabolites is shown in Figure 3 and 4.

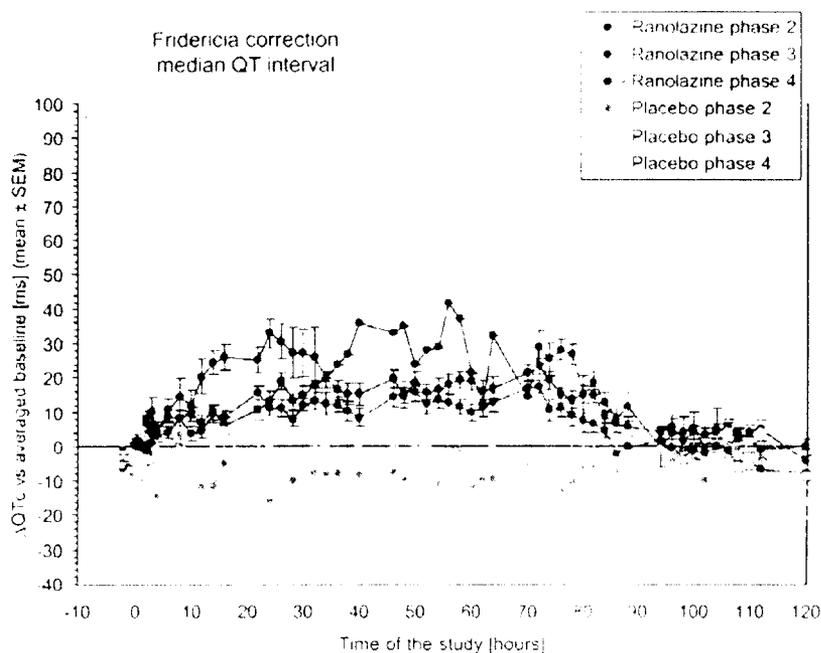


Figure 2. Development of changes in the Fridericia corrected QTc interval during different phases of the study.

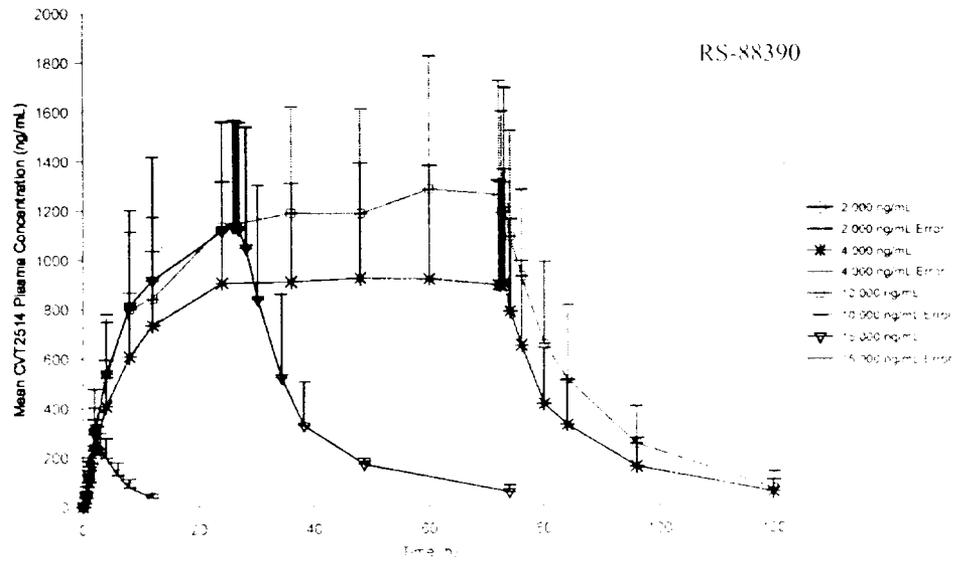
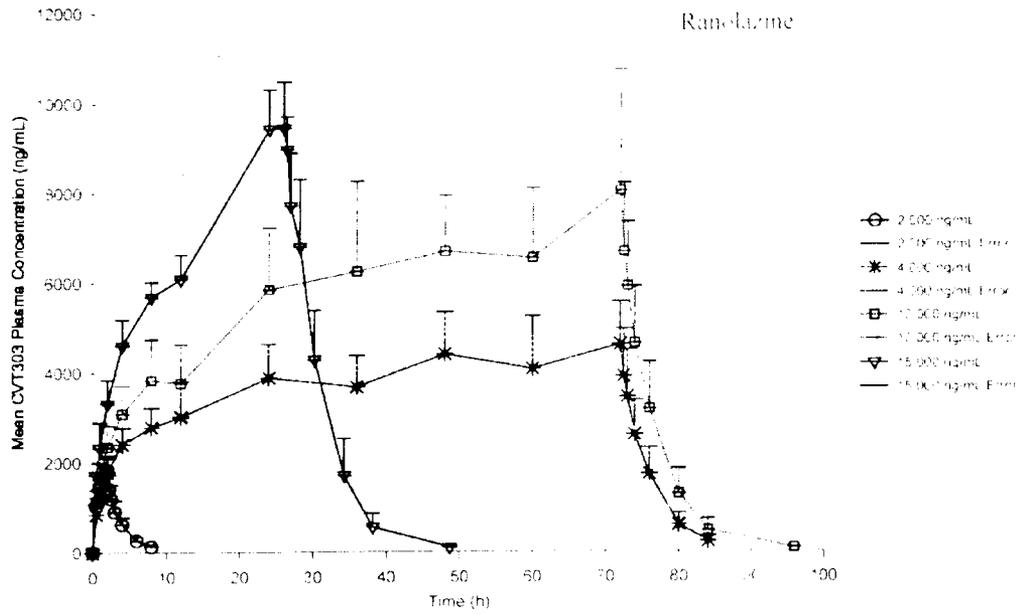


Figure 3. Plasma Concentration of Ranolazine and its metabolites after infusion of Ranolazine to target treatment.

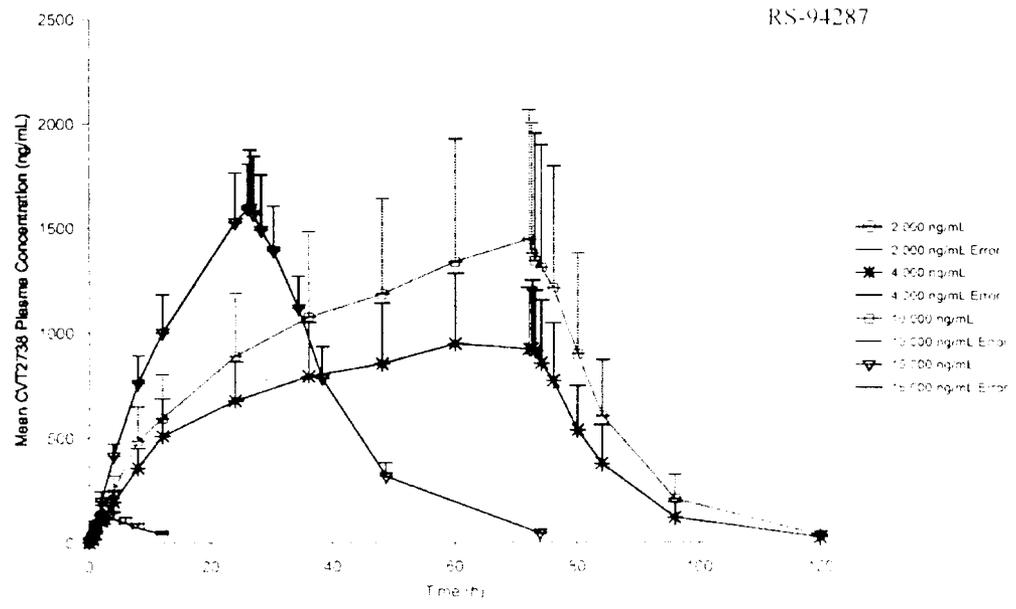
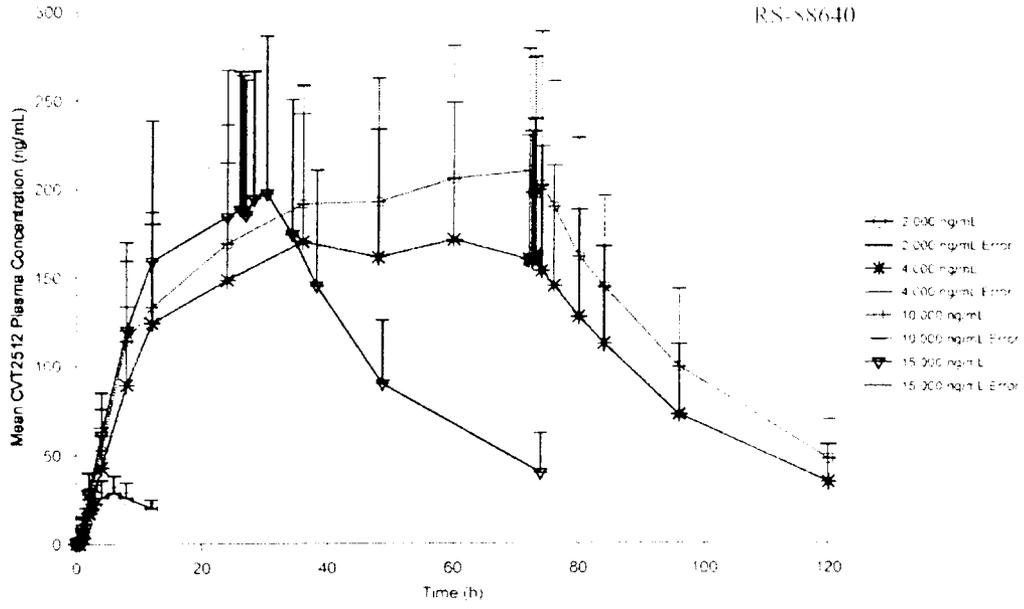


Figure 4. Plasma Concentration of Ranolazine and its metabolites after infusion of Ranolazine to target treatment.

3. Intrinsic Factors Affecting Ranolazine QTc prolongation

(a) What is the mean $\Delta\Delta$ QTc - time course at different doses in a typical subject?

The linear model predicted mean of $\Delta\Delta$ QTc at steady state after 500, 750, 1000 and 1500 mg is shown in Figure 5. The time course of the average ranolazine concentrations at steady state were available in young, healthy male volunteers (Study RAN 0114 and RAN 0201). The concentrations were multiplied by the slope of the concentration- Δ QTc relationship (2.56 msec per 1000 ng/mL) to calculate $\Delta\Delta$ QTc. The model was used to predict the $\Delta\Delta$ QTc because (a) Time course of Δ QTc and ranolazine were observed to be similar after intravenous infusion of ranolazine in Study CVT 3111(Figure 2, 3) (b) Good performance of the linear model to explain the Δ QTc-concentration relationship.

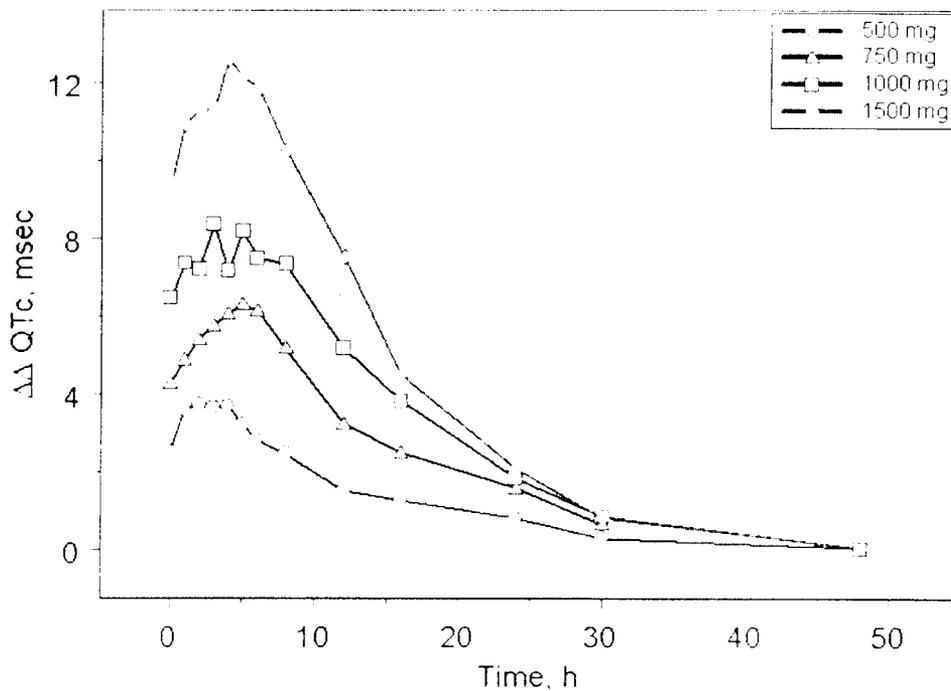


Figure 5. $\Delta\Delta$ QTc at various dose levels at steady state in a typical subject.

(b) Are females at higher risk of QTc prolongation from ranolazine than males?

No. There is no significant gender effect on slope of the concentration-QTc prolongation relationship.

(c) Do identical concentrations in normals and patients with different diseases such as renal or hepatic impairment, CHF or diabetes result in different effects on QTc prolongation?

- Except in patients with hepatic impairment, a mean increase of 2.56 msec in QTc is observed per 1000 ng/mL of ranolazine.
- A mean increase in QTc of 7.10 msec is observed per 1000 ng/mL in patients with mild or moderate hepatic impairment.
- Congestive heart failure, diabetes and renal impairment did not show any significant effect on slope of concentration-QTc relationship.
- The simulated $\Delta\Delta$ QTc in normal, hepatic and renal impairment patients is shown in Table 2.

(d) Can ranolazine be administered to patients with hepatic impairment?

In light of the current information ranolazine may not be administered to patients with mild or moderate hepatic impairment.

Our analysis shows that subjects with mild and moderate hepatic impairment are equally sensitive to QTc prolongation, compared to normals. Hence ranolazine should not be given to patients with any hepatic impairment.

Further, mild and moderate hepatic impairment increase the C_{max} by factor of 1.3 and 1.7 respectively resulting in exaggerated QTc prolongation in the dose range of 500-1000 mg ranolazine bid. Use of lower doses (375 mg bid) in patients with mild hepatic impairment might jeopardize efficacy. In patients with moderate hepatic impairment a reduced dose of ranolazine evokes still unacceptably prolonged QTc intervals.

1. Drug Interactions

(a) What is the QTc prolongation if ranolazine is administered with CYP3A4, CYP2D6 inhibitors and P-glycoprotein modulators?

Increases in average steady-state concentrations of ranolazine are observed in drug interaction studies (Refer to Dr Peter Hinderling reports). The mean C_{max} values after 375 mg dose was obtained from control group in Study CVT301-10

(Ketoconazole Interaction Study). The mean C_{max} values after 500 and 1000 mg dose were obtained from Study CVT 3031. The C_{max} value after 750 mg dose was calculated by multiplying the concentrations after 500 mg dose by a factor of 1.68.

The C_{max} values after 375, 500, 750 and 1000 mg were multiplied by the factor corresponding to the increase in C_{max} value observed in drug interaction studies. Simulations were performed using the calculated C_{max} values in various scenarios (drug interactions, hepatic, renal impairment) using SAS[®] to determine the percentage of patients with $\Delta\Delta$ QTc intervals of 0-5, 5-10 and \Rightarrow 10 msec. The results are shown in Table 1 and 2. Since the mean difference in C_{max} in healthy subjects and patients is 22% (Refer to Dr Hinderling's Report) the results in Table 1 and 2 can also be interpreted for a patient with the target disease.

Table 1. Calculated $\Delta\Delta$ QTc, msec for different ranolazine dose levels and drug interactions in a typical patient.

	Dose*	Cmax Mean (SD)	$\Delta\Delta$ QTc (msec)				
			Mean	% < 5 msec	% > 5 msec	% 5-10 msec	% >=10 msec
Ranolazine (R)	375	739(440)	1.9	94	6	4	2
	500	1136(682)	2.9	85	15	12	3
	750	1925(1145)	4.9	67	33	23	10
	1000	2473(1461)	6.3	56	44	29	15
R+Diltiazem (SR) (Day 4)	375+180	1405(836)	3.6	79	21	16	5
	500+180	2159(1296)	5.5	60	40	27	13
	750+180	3659(2177)	9.4	36	64	33	31
	1000+180	4701(2777)	12.0	26	74	32	42
	375+240	1772(1054)	4.4	70	30	22	8
	500+240	2724(1635)	7.0	50	50	30	20
	750+240	4616(2747)	11.8	27	73	33	40
	1000+240	5930(3503)	15.2	18	82	30	52
	375+360	2077(1236)	5.3	62	38	26	12
	500+360	3192(1916)	8.2	42	58	33	25
	750+360	5409(3218)	13.8	21	79	30	49
	1000+360	6941(4104)	17.8	14	86	26	60
R+Diltiazem (SR) (Day 8)	375+180	1106(658)	2.8	86	14	12	2
	500+180	1699(1020)	4.4	72	28	21	7
	750+180	2880(1713)	7.4	48	52	31	21
	1000+180	3669(185)	9.5	36	64	33	31
	375+240	1394(829)	3.6	79	21	17	4
	500+240	2142(286)	5.5	62	38	25	13
	750+240	3631(2160)	9.3	36	64	34	30
	1000+240	4664(2755)	11.9	26	74	32	42
	375+360	1700(1012)	4.4	72	28	20	8
	500+360	2613(1569)	6.7	52	48	30	18
	750+360	4429(2635)	11.3	28	72	33	39
	1000+360	5690(3361)	14.6	20	80	30	50
R+Diltiazem (IR) Day 4	375+180	1107(659)	2.8	86	14	12	2
	500+180	1701(1021)	4.4	71	29	21	8
	750+180	2884(1716)	7.4	48	52	31	21
	1000+180	3704(2188)	9.5	37	63	33	30
R+Diltiazem (IR) Day 8	375+180	1331(792)	3.4	80	20	16	4
	500+180	2045(1228)	5.2	64	36	25	11
	750+180	3467(2063)	8.9	39	61	33	28
	1000+180	4453(2631)	11.4	28	72	33	39
R+Verapamil	375+120	1421(846)	3.6	79	21	16	5
	500+120	2184(1311)	5.6	60	40	27	13
	750+120	3702(2202)	9.5	37	63	33	30

	1000+120	4755(2809)	12.2	26	74	33	41
R+Cimetidine	375+400	829(493)	2.1	92	8	7	1
	500+400	1274(765)	3.3	82	18	15	3
	750+400	2160(1285)	5.5	61	39	26	13
	1000+400	2774(1639)	7.1	49	51	32	19
R+Paroxetine	375+20	866(515)	2.2	91	9	8	1
	500+20	1331(799)	3.4	80	20	16	4
	750+20	2256(1342)	5.8	60	40	26	14
	1000+20	2898(1712)	7.4	48	52	31	21
R+Digoxin (CHF)	375+0.125	873(519)	2.2	91	9	8	1
	500+0.125	1331(805)	3.4	80	20	16	4
	750+0.125	2256(1353)	5.8	60	40	26	14
	1000+0.125	2899(1725)	7.5	48	52	31	21
R+Simvastatin	375+80	842(501)	2.2	92	8	7	1
	500+80	1293(777)	3.3	81	19	15	4
	750+80	2193(1305)	5.6	60	40	26	14
	1000+80	2816(1664)	7.2	49	51	31	20
R+Ketoconazole	375+200	1900(1130)	4.9	67	33	23	10
	500+200	3589(2155)	9.2	37	63	33	30
	750+200	6083(3619)	15.6	17	83	29	54
	1000+200	7814(4616)	20.0	10	90	25	65

* Doses were administered as follows: Ranolazine (bid); Cimetidine (tid); Diltiazem SR (QD); Diltiazem IR (tid); Digoxin (QD); Ketoconazole (bid); Paroxetine (QD); Simvastatin (QD); Verapamil (tid);

Table 2. Calculated $\Delta\Delta$ QTc, msec for different ranolazine dose levels in renal or hepatically impaired patients.

	Dose	Cmax Mean (SD)	$\Delta\Delta$ QTc (msec)				
			Mean	% <5 msec	% > 5 msec	% 5-10 msec	% >=10 msec
Renal Impairment							
Mild (>50- 80mL/min)	375	1134(675)	2.9	85	15	13	2
	500	1743(1047)	4.5	70	30	22	8
	750	2955(1758)	7.6	46	54	32	22
	1000	3796(2242)	9.7	36	64	33	31
Moderate (30-50mL/min)	375	1012(602)	2.6	88	12	10	2
	500	1556(934)	4.0	74	26	20	6
	750	2637(1569)	6.8	52	48	29	19
	1000	3388(2001)	8.7	41	59	32	27
Severe (<30 mL/min)	375	1088(647)	2.8	87	13	11	2
	500	1672(1004)	4.3	72	28	20	8
	750	2834(1686)	7.3	48	52	32	20
	1000	3640(2150)	9.3	38	62	32	30
Hepatic Impairment*							
Mild	375	945(562)	6.7	42	58	32	16
	500	1452(872)	10.3	17	83	42	41
	750	2462(1465)	17.5	3	97	24	73
	1000	3162(1868)	22.5	1	99	15	84
Moderate	375	1292(769)	9.2	24	76	43	33
	500	1985(1192)	14.1	7	93	33	60
	750	3365(2002)	23.9	1	99	13	86
	1000	4322(2553)	30.7	1	99	6	93

***- Slope factor of 7.10 msec per 1000 ng/mL was used for calculating $\Delta\Delta$ QTc in hepatically impaired patients.**

INTRODUCTION

Ranolazine is a novel compound that has been evaluated in clinical trials as a potential treatment for angina. Ranolazine is a member of a new class of drugs whose anti-anginal effects are believed to result from partial inhibition of fatty acid oxidation (pFOX inhibition). Ranolazine inhibits enoyl-CoA hydratase and carnitine acyl translocase, enzymes that mediate the beta-oxidation of fatty acids. Ranolazine is pharmacologically unrelated to calcium channel blockers, beta blockers, and nitrates. Ranolazine is a film-coated, extended-release tablet for oral administration containing 375 mg or 500 mg of ranolazine.

The sponsor submitted a total of 4 reports dealing with modeling PK and/or PD of ranolazine, as follows:

1. Population pharmacokinetics of ranolazine in healthy subjects and in patients with angina.
2. A study to investigate the relationship between plasma ranolazine concentration following intravenous administration and the QTc interval recorded electrocardiographically in healthy volunteers (Study CVT 3111).
3. Assessment of QT interval changes in electrocardiograms of ranolazine study CVT-3111 (by Marek Malik).
4. Modeling the relationship between observed ranolazine concentrations and the effect on the QTc intervals as documented in healthy subjects and patients with cardiac angina.

The QT analysis conducted by the sponsor did not include two important clinical pharmacology studies such as the studies in which the impact of hepatic impairment and renal impairment were assessed. For this reason, the reviewer appended the data from these 2 studies to the data set employed by the sponsor to evaluate the concentration-QTc prolongation relationship.

The focus of this review is:

1. To evaluate sponsor's population pharmacokinetic analysis. The sponsor did not utilize the PK model developed for any purpose other than identifying important covariates.
2. To develop a concentration-QTc relationship with all relevant studies included.

SPONSOR'S METHODS

Design/Data

Intravenous Infusion Study

This was a randomized, placebo-controlled, repeat intravenous infusion, dose escalation, 4 period study involving 30 subjects.

Period 1: Target Concentration: 2000 ng/mL, Infusion duration: 2h.
Period 2: Target Concentration: 4000 ng/mL, Infusion duration: 72h.

Period 3: Target Concentration: 10000 ng/mL, Infusion duration: 72h.
 Period 4: Target Concentration: 15000 ng/mL, Infusion duration: 72h.

Individual pharmacokinetic parameters determined from period I were to be used to calculate the doses required in the subsequent periods for each subject. In each period the infusion of ranolazine/placebo was preceded by a 24 hour placebo infusion. The infusion duration of 72h was to achieve plasma levels of the key metabolites at steady-state and to investigate the relationship between the plasma concentrations of three major metabolites and the QTc interval to elucidate any possible delay in effect (with respect to the parent profile) that may be attributable to these metabolites.

Pharmacokinetic studies of the SR tablets

In total, eleven separate studies (seven Phase I and four Phase II or III) were included in this analysis (Table 3).

Table 3. Description of the Eleven Studies Included in the Population PK analysis

Study	Description
RAN0112	A single ascending dose study in healthy male volunteers to assess the Pharmacokinetics and safety profile of Ranolazine SR. <i>Subjects were divided into three groups with Group 1 receiving 500, 750 and 1000 mg ranolazine SR, Group 2 receiving 1250 and 1750 mg ranolazine SR and Group 3 receiving 1500 and 2000 mg ranolazine SR.</i>
RAN0114	An ascending multiple dose study to assess the pharmacokinetics and tolerability of Ranolazine SR in healthy male volunteers. <i>Each subject received 500, 750 and 1000 mg ranolazine SR bid.</i>
RAN0117	An ascending multiple dosing study to assess the safety, tolerability and pharmacokinetics of Ranolazine SR administered three times daily in healthy male subjects. <i>Each subject received 500, 750 and 1000 mg ranolazine SR tid.</i>
RAN0201	A study to investigate the pharmacokinetics, safety and tolerability of Ranolazine SR 1500 and 2000 mg administered twice daily in young, healthy male subjects.
CVT 3013	A Phase I, open-label, single-dose, pharmacokinetic bioequivalence study comparing two 500 mg Ranolazine SR tablets (reference) to two 500 mg Ranolazine SR tablets (test), and comparing one 750 mg Ranolazine SR tablet (reference) to two 375 mg ranolazine SR tablets (test) in normal, healthy, male subjects.
CVT 3014	A study to assess the effect of food on the single dose pharmacokinetics of ranolazine SR at dose of 1000 mg in healthy volunteers.
CVT 3015	A three-way crossover study to determine the single dose and steady state pharmacokinetics of Ranolazine SR at doses of 500 mg, 1000 mg and 1500 mg in healthy volunteers.

RAN2302	A double-blind, placebo-controlled, parallel design, pilot study of the safety and efficacy at peak of Ranolazine SR 1000 mg bid in the treatment of intermittent claudication.
CVT 3021	A double-blind, randomized, parallel, pharmacokinetic and safety study of Ranolazine SR 750 mg twice a day administered alone and in combination with digoxin 0.125 mg once a day in patients with congestive heart failure.
CVT 3031	Cross-over, multiple-dose study of Ranolazine SR as monotherapy for chronic stable angina pectoris at doses of 500 mg bid, 1000 mg bid and 1500 mg bid (MARISA).
CVT 3033	A double-blind, randomized, stratified, placebo-controlled, parallel study of Ranolazine SR at doses of 750 mg twice a day and 1000 mg twice a day in combination with anti-anginal medications in patients with chronic stable angina pectoris (CARISA).

Pharmacokinetics

The sponsor analyzed the data using non-compartmental and compartmental methods.

Non-compartmental analysis

The plasma concentration-time profiles of ranolazine and metabolites in periods 1 to 4 (Study CVT 3111) were analyzed by non-compartmental methods using WinNonlin (Version 3.2). The following pharmacokinetic parameters were estimated: C_{max} , t_{max} , $C_{initial}$, $t_{initial}$, AUC_{0-t} , $AUC_{0-\infty}$, $\%AUC_{extrapolated}$, $t_{1/2}$, λ_z , CL, V_{ss} and MRT.

Compartmental Analysis

The sponsor explored various compartmental models for analyzing the data. The compartmental models included linear and/or saturable elimination pathways with first order distribution kinetics. Population pharmacokinetic models were built using a non-linear mixed-effect population modeling approach with the NONMEM software (double precision, Version V, Level 1.1) and NMTRAN pre-processor 1. Models were run using the Digital Visual Fortran Compiler (Version 5.0D) on a personal computer under the Microsoft Windows NT 4.0 operating system. The NONMEM interface software, PDx-Pop 2, was used to run NONMEM. Goodness-of-fit diagnostic plots were prepared within S-Plus 2000 Professional Release 3. Screening of potential covariates was conducted using the General Additive Modeling (GAM) feature of Xpose 3 version 3.

Covariate Models

The sponsor explored for influential prognostic factors from demographic data (age, weight, height, sex, race), the presence of other disease conditions (diabetes, congestive heart failure (CHF), the corresponding New York Heart Association (NYHA)

classification of the CHF and concomitant medications (diltiazem, atenolol, amlodipine and digoxin).

The sponsor performed an initial screening of potential covariates using the GAM feature of Xpose (A population model building aid for NONMEM using SPLUS) using the POSTHOC parameter estimates.

After initial screening the covariate model building was carried out using stepwise forward selection and backward elimination techniques. Significance was defined as a change in objective function of at least 20 points from inclusion-exclusion of covariate when using the First-Order (FO) estimation procedure in NONMEM.

Random Effects Models

The sponsor used exponential error models to describe the inter-individual errors on all parameters. The residual error model was initially described by a combined additive and proportional (constant coefficient of variation) error model.

Model Qualification

The final model was evaluated using a predictive check procedure. Dosing histories, demographic and covariate information from Studies CVT 3031 and CVT 3033 were used to simulate ranolazine concentrations at the actual sampling times using the final model estimates of the fixed and random effect parameters. Thirty simulations were performed and the 90% prediction intervals computed. The number of observations contained within the corresponding prediction intervals was computed. According to the Data Analysis Plan, the model was considered suitable for predictive purposes if 80% of the observations were within the corresponding prediction intervals.

Plasma Concentration-Effect Relationship (QTc)

The sponsor submitted several reports for the QT analysis. In one of the reports the sponsor analyzed the data from study CVT 3111 using Bazett's correction formula and individually optimized correction formulae.

The sponsor did a comprehensive analysis of the concentration-QTc data by including the data from 17 studies (Table 4). The overall objective of this analysis was to describe the relationship between observed ranolazine plasma concentrations, covariates and the effect on the QTc interval. Only plasma records that were taken within 20 minutes of the start of the ECG were included in the analysis.

Table 4. Description of the studies used in QT analysis by the sponsor

Study	Description
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RAN069	A pharmacokinetic study to examine the effects of 4 weeks of dosing with 400 mg tid of ranolazine in healthy volunteers on adrenocortical function, plasma lipid, glucose and ranolazine concentrations.
RAN0114	An ascending multiple dose study to assess the pharmacokinetics and tolerability of sustained release ranolazine in healthy male volunteers.
RAN0117	An ascending multiple dosing study to assess the safety, tolerability and pharmacokinetics of sustained release ranolazine administered three times daily in healthy male subjects.
RAN0121	A pharmacokinetic study to investigate the potential PK and/or PD interaction between ranolazine and diltiazem following multiple doses of both drugs.
RAN0201	A study to investigate the pharmacokinetics, safety and tolerability of ranolazine SR 1500 and 2000 mg administered twice daily in young, healthy male subjects.
RAN2302	A double-blind placebo controlled parallel designed pilot study to investigate the safety and efficacy of ranolazine SR 1000 mg bid in subjects being treated for intermittent claudication.
CVT 3012	A study to investigate the potential PK and/or PD interaction between ranolazine SR 1000 mg bid and once daily modified release diltiazem at doses of 180 mg, 240 mg or 360 mg in healthy males.
CVT 3015	A pharmacokinetic study to determine the single dose and steady state pharmacokinetics of SR ranolazine administered at doses of 500 mg, 1000 mg or 1500 mg for 4.5 days to healthy volunteers.
CVT 3017	A pharmacokinetic study to investigate the potential PK interaction between ranolazine and simvastatin following multiple doses of both drugs in healthy volunteers.
CVT 3021	A pharmacokinetic and safety study of ranolazine SR 750 mg bid administered with digoxin 0.125 mg QD in patients with congestive heart failure.
CVT 3031	A double-blind randomized, placebo-controlled efficacy and safety study in patients with chronic stable angina pectoris administered ranolazine SR 500 mg, 750 mg or 1000 mg bid administered as monotherapy.
CVT 3032	A long-term safety study in patients with chronic stable angina pectoris administered ranolazine SR 500 mg, 750 mg or 1000 mg bid.
CVT 3033	A double-blind randomized, placebo-controlled efficacy and safety study in patients with chronic stable angina pectoris administered ranolazine SR 750 mg or 1000 mg bid administered in combination with background antianginal therapy.
CVT 3034	A long-term safety study in patients with chronic stable angina pectoris administered ranolazine SR 750 mg or 1000 mg bid administered in combination with background antianginal therapy.
CVT 301-10	A pharmacokinetic study to investigate the effect of ketoconazole on the pharmacokinetics, safety and tolerability of ranolazine in healthy subjects
CVT 301-13	A multiple-dose pharmacokinetic study with paroxetine at steady-state to investigate the effect of paroxetine on the PK of ranolazine.

CVT 3111	A dose-escalation study to characterize the relationship between the plasma ranolazine concentrations following intravenous administration of ranolazine and the QTc interval recorded electrocardiographically in healthy volunteers.
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Structural Models

The observed concentrations from the pharmacokinetic studies that used the IR or SR formulations were employed to drive the QT model. Equation 1 describes the relationship between RR interval and QT. The sponsor evaluated QTc intervals (msec) after Fridericia's (QTcF) correction (0.33) as it was almost equal to the population specific correction factor (0.32) was determined using off-drug data from each study (i.e. all baseline, run-in, placebo and data from active treatment arms, other than Ranolazine).

$$QT_{ij} = \alpha_i * RR_{ij}^{\beta_i} \quad (1)$$

In equation 1, QT_{ij} is the j^{th} QT interval of the i^{th} patient, similarly α_i is the corrected QT normalized to an RR of 1 min and RR is the RR interval (min) and β is the exponent coefficient of the i^{th} patient.

The drug effect is added to the above equation assuming linear or nonlinear (E_{max}) relationship between concentration and QTc prolongation. The linear relationship is shown below:

$$QT_{ij} = \alpha_i * RR_{ij}^{\beta_i} + C_{ij} * \text{Slope}_i \quad (2)$$

In equation 2, Slope_i is the slope of the concentration-QTc relationship in the i^{th} patient.

Covariate Models

The sponsor explored for influential prognostic factors from demographic data (age, weight, height, sex, race, healthy or patient volunteer), creatinine clearance (CrCL, derived from serum creatinine data using the Cockcroft-Gault formula), the presence of other disease conditions (diabetes, congestive heart failure with NYHA Class I-IV classification).

For all continuous covariates, the covariate parameter estimates were centered on the median of the covariate divided by the standard deviation in the study population.

The sponsor performed an initial screening of potential covariates using the GAM feature of Xpose (A population model building aid for NONMEM using SPLUS) using the POSTHOC parameter estimates.

After initial screening the covariate model building was carried out using stepwise forward selection and backward elimination techniques. Significance was defined as a change in objective function of at least 20 points when using the First-Order (FO) estimation procedure in NONMEM.

Random Effects Models

The inter-individual variability error models on the structural model parameters were additive (e.g. Emax or slope) or exponential (e.g. EC50), as appropriate, and the initial random residual variability model had combined proportional and additive components. The random effects on alpha, beta and slope are referred to as ETAL, ETAB and ETAS respectively.

Model Qualification

A posterior predictive check was performed by simulating the observed ECG measures using the final model parameter estimates, dosing history, sampling/ measurement times and covariate information. Fifty data sets were simulated. For each observed effect, a prediction interval (10 to 90%) was generated from the simulated values.

SPONSOR'S RESULTS

Pharmacokinetics

Intravenous Infusion Study

The mean pharmacokinetic parameters of ranolazine and its three major metabolites (RS-88390, RS-88640, RS-94287) are shown in Tables 5, 6, 7 and 8. The mean plasma clearance of ranolazine was reduced by approximately 35% in the other three treatments (4000, 10000 and 15000 ng/mL). There was a 33% decrease in the metabolic ratio ($AUC_{\text{metabolite}}/AUC_{\text{ranolazine}}$) of RS-88390 from the 2,000 ng/mL target treatment to the 15,000 ng/mL target treatment. The metabolite ratio of RS-88640 and RS-94287 however remained constant across target treatments. The terminal half-lives of the metabolites are longer than that of the parent drug.

Table 5. Mean (SD) Pharmacokinetic Parameter Estimates for Ranolazine Following Administration of the Four Treatments

Target Treatment (ng/mL)	C _{initial} (ng/mL)	AUC _{0-∞} (ng·h/mL)	t _{1/2,z} (h)	CL (L/h)	V _{ss} (L)
2,000	1813 (353)	6235 (1312)	1.82 (0.36)	40.1 (8.2)	83.6 (15.9)
4,000	4606 (958)	285217 (50048)	2.84 (0.64)	28.1 (4.9)	180.6 (61.4)
10,000	8027 (2696)	447414 (82594)	3.17 (0.54)	23.8 (4.3)	186.7 (62.3)
15,000	9196 (1046)	215502 (25808)	3.01 (0.47)	24.1 (3.2)	142.4 (19.1)

Table 6. Mean (SD) Pharmacokinetic Parameter Estimates for RS-88390 Following Administration of the Four Treatments

Target Treatment (ng/mL)	C _{initial} (ng/mL)	AUC _{0-∞} (ng·h/mL)	t _{1/2,z} (h)	Metabolic Ratio
2,000	229.5(91.4)	1603(611)	3.34(0.60)	0.27(0.11)
4,000	890(425)	71917(34342)	10.72(2.87)	0.25(0.12)
10,000	1257(464)	96377 (37512)	11.12(2.81)	0.22(0.10)
15,000	1158(382)	38314(12738)	12.93(2.54)	0.18(0.06)

Table 7. Mean (SD) Pharmacokinetic Parameter Estimates for RS-88640 Following Administration of the Four Treatments

Target Treatment (ng/mL)	C _{initial} (ng/mL)	AUC _{0-∞} (ng·h/mL)	t _{1/2,z} (h)	Metabolic Ratio
2,000	17.7(10.6)	—	—	—
4,000	159(69.8)	15250(7153)	19.77(4.59)	0.054(0.028)
10,000	209(69)	18732(7073)	20.51(5.21)	0.043(0.018)
15,000	192(69)	9617(3782)	20.37(3.31)	0.045(0.018)

Table 8. Mean (SD) Pharmacokinetic Parameter Estimates for RS-94287 Following Administration of the Four Treatments

Target Treatment (ng/mL)	C _{initial} (ng/mL)	AUC _{0-∞} (ng·h/mL)	t _{1/2,z} (h)	Metabolic Ratio
2,000	113(30.4)	1278(361)	5.81(1.51)	0.21(0.05)
4,000	917(293)	63363(19689)	7.57(1.22)	0.23(0.07)
10,000	1441(620)	90483(34672)	7.86(0.91)	0.20(0.06)
15,000	1522(239)	47531(8130)	8.43(0.98)	0.22(0.04)

Population Pharmacokinetic Analysis

Intravenous Infusion Study

The models were developed on the findings (decreased clearance of ranolazine and the metabolite ratios) reported in the noncompartmental analysis. A two-compartment open model with zero-order input, first-order distribution and with 2 parallel metabolic pathways, one linear and another saturable, was fitted to ranolazine plasma profiles (Figure 6).

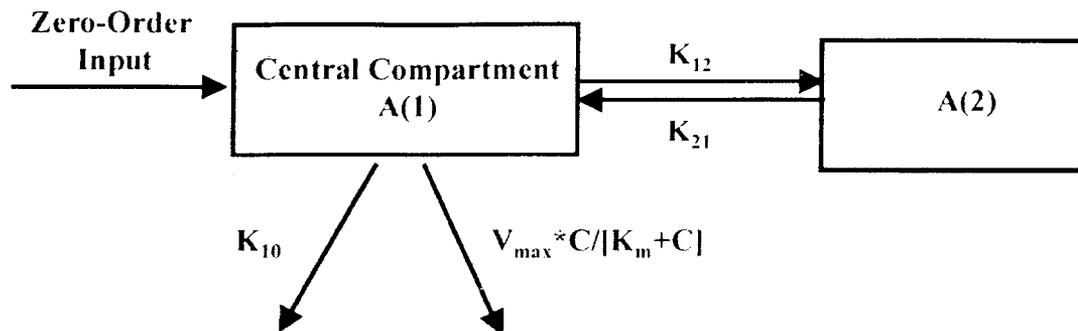


Figure 6. Non-linear Pharmacokinetic Model for Ranolazine (Intravenous Infusion).

The pharmacokinetic parameters used to characterize the model were: central compartment volume of distribution (V_c), maximum velocity (V_{max}) and Michaelis-Menten constant (K_m) for the saturable metabolic pathway, first-order elimination rate constant (K_{10}) for the linear metabolic pathway and K_{12} and K_{21} as the distribution coefficients between the central and peripheral compartment. The estimates of the parameters are shown in table 9.

Table 9. Final estimates of population pharmacokinetic parameters of ranolazine in healthy subjects from a pharmacokinetic model with parallel linear and saturable metabolic pathways.

Parameter	Estimate [95% CI]	Precision (%CV) ^s
V_{max} (mg/h)	55.4 [25.2-85.6]	27.8
K_m (ng/mL)	1660 [580-2740]	33.2
V (L)	44.5 [40.4-48.6]	4.7
K_{10} (h^{-1})	0.307 [0.220-0.393]	14.4
K_{12} (h^{-1})	1.04 [0.79-1.29]	12.1
K_{21} (h^{-1})	0.558 [0.506-0.670]	7.1
Inter-patient variability in V_{max} (%CV)*	27.3 [16.1-35.0]	33.2
Inter-patient variability in V (%CV) *	10.3 [2.2-14.5]	48.8
Inter-patient variability in K_{10} (%CV)	15.4 [6.5-20.8]	41.9
Inter-patient variability in K_{12} (%CV)	16.2 [8.2-21.3]	37.7
Inter-patient variability in K_{21} (%CV)*	8.0 ^a	115.7
Proportional residual variability (%CV)*	17.8	9.1
Additive residual variability (μ g/mL)	0.05	29.0

^a 95% confidence interval was non calculable because of large

standard error	
§ Precision was calculated as the standard error divided by the parameter estimate x 100.	
* The % CV for both inter-patient and residual variability is an approximation taken as the square root of the variance x 100.	

Oral Pharmacokinetic Studies

A one-compartment model with parallel linear and saturable elimination was used to explain the data as a two-compartment model with parallel linear and saturable elimination nor a one-compartment model with linear or saturable elimination provided a better description of the data. The final population parameter estimates were used to derive the individual predicted values for Vc, Vmax, K10, K12 and K21, by invoking the POSTHOC subroutine in NONMEM. Individual Km values were not obtainable because the variance for the population estimate was not estimable (Table10).

Table 10. Ranolazine SR Base Population Pharmacokinetic Parameter Estimates

Parameter	Typical Value (%RSE*)	Inter-individual (%RSE*)
Ka (h ⁻¹)	0.0746 (5.71%)	25.3 (20.2%)
Vmax (mg/h)	55 FIXED	NE
Km (ng/mL)	2310 (9.48%)	141 (28.8%)
K10 (h ⁻¹)	0.215 (6.56%)	45.2 (19.2%)
V (L)	100 (6.16%)	41.1 (14.4%)
	Intra-individual, Residual Error	
Parameter	Estimate (%RSE*)	
σ^{21} prop	%CV=42.9 (10.7%)	
σ^{22} prop	%CV=27.6 (25.9%)	
σ^{21} add	SD=219 (76.6%)	
σ^{22} add	SD=186 (53.6%)	
* %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100 Abbreviations: FO = first order, Ka = absorption rate constant, Vm = maximum rate of process, Km = Michaelis-Menten, constant, K10 = elimination rate constant, V = volume of distribution, σ^{21} prop = proportional component of the residual error, model for Phase II studies, σ^{22} prop = proportional component of the residual error model for Phase I studies, σ^{21} add = additive, component of the residual error model for Phase II studies, σ^{22} add = additive component of the residual error model for, Phase I studies, NE = Not Estimated.		

In order to explore the sensitivity of the model and parameter estimates to the fixed typical value parameters for Vm, models with fixed value of this parameter altered by ±

10% were explored. The resulting minimum objective function values and Km estimates (typical value) were not significantly affected by the choice of the fixed Vmax value.

Covariate Model building

The covariate information is shown in table 11. Different covariates were tested on the linear clearance and volume of distribution. For the nonlinear pathway, Vmax could not be accurately estimated from the data due to a low proportion of high concentrations. Influence of covariates on Km was not tested as the overall departure from dose proportionality was minor, indicating a small change in the nonlinear pathway at the observed plasma concentration range.

Table 11: Summary of Covariates In Oral Pharmacokinetic Studies

	FEMALE (N=174)	MALE (N=725) (N=725)
Age (years)	64.0 (37-86)	62.0 (18-92)
Weight (kg)	72.0 (45-124.3)	82.0 (51.9-152)
CrCL (mL/min)	79.0 (31.6-181.9)	90.8 (28.4-256.9)
Race		
Caucasian	162	680
Black	8	26
Asian	1	7
Hispanic	3	5
Other	0	7
Diabetes	47	149
CHF	67	171

The covariate models are expressed as:

$$TVV = 110 \cdot \left(\frac{\text{Age, years}}{51} \right)^{0.635} \cdot \left(\frac{\text{Weight, kg}}{78} \right)^{0.936}$$

$$TVCL = 22.4 \cdot \left(\frac{\text{Age, years}}{51} \right)^{-0.326} \cdot \left(\frac{\text{Weight, kg}}{78} \right)^{1.07}$$

where TVV and TVCL represent typical value of volume of distribution and linear clearance respectively.

For a patient of 78 kg the clearance decreased by approximately 0.1 L/h or 0.5% for every year above/below the median value of 51 years (Table 12). The volume increased by approximately 1.3 L or 1.2% for each year of age. For a patient of 51 years (i.e., median value), clearance of the linear pathway changed by approximately 0.3 L/h or 1.3% for every kg that they differed from the median of 78 kg. Similarly,

volume changed by approximately 1.3 L or 1.2% for every kg. The clearance of ranolazine decreased by 40% upon coadministration with diltiazem. The absorption rate constant was shown to be 1.30 times faster from the DSM SR product compared to the Syntex SR product. The population and individual predictions versus observed concentrations are shown in Figure 7.

Table 12. Ranolazine SR Final Model Population Pharmacokinetic Parameter Estimates

Parameter	Typical Value (%RSE*)	Inter-individual %CV (%RSE*)
Ka (h ⁻¹)	0.0631 (8.46%)	33.8 (21.0%)
Vm (mg/hr)	55 FIXED	NE
Km (ng/mL)	2050 (9.71%)	135 (23.1%)
CL (L/h)	22.4 (3.16%)	48.5 (11.6%)
V (L)	110 (7.33%)	67.7 (19.9%)
Effect of Age on CL	-0.326 (29.3%)	
Effect of Weight on CL	1.07 (15.9%)	
Effect of Age on V	0.635 (20.8%)	
Effect of Weight on V	0.936 (14.3%)	
Change in CL with diltiazem	0.628 (7.74%)	
Change in ka with DSM SR tablet	1.30 (7.21%)	
Intra-individual, Residual Error		
Parameter	Estimate (%RSE*)	
σ^{21}_{prop}	%CV= 41.6 (7.40%)	
σ^{22}_{prop}	%CV= 32.2 (19.5%)	
σ^2_{add}	SD= 136 ng/mL	
* %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100		
Abbreviations: FO = first order, Ka = absorption rate constant, Vm = maximum rate of process, Km = Michaelis-Menten constant, CL = clearance of linear pathway, V = volume of distribution, σ^2_{prop} Phase II = proportional component of the residual error model associated with Phase II studies, σ^2_{prop} Phase I = proportional component of the residual error model associated with Phase I studies σ^2_{add} = additive component of the residual error model, NE = Not Estimated.		

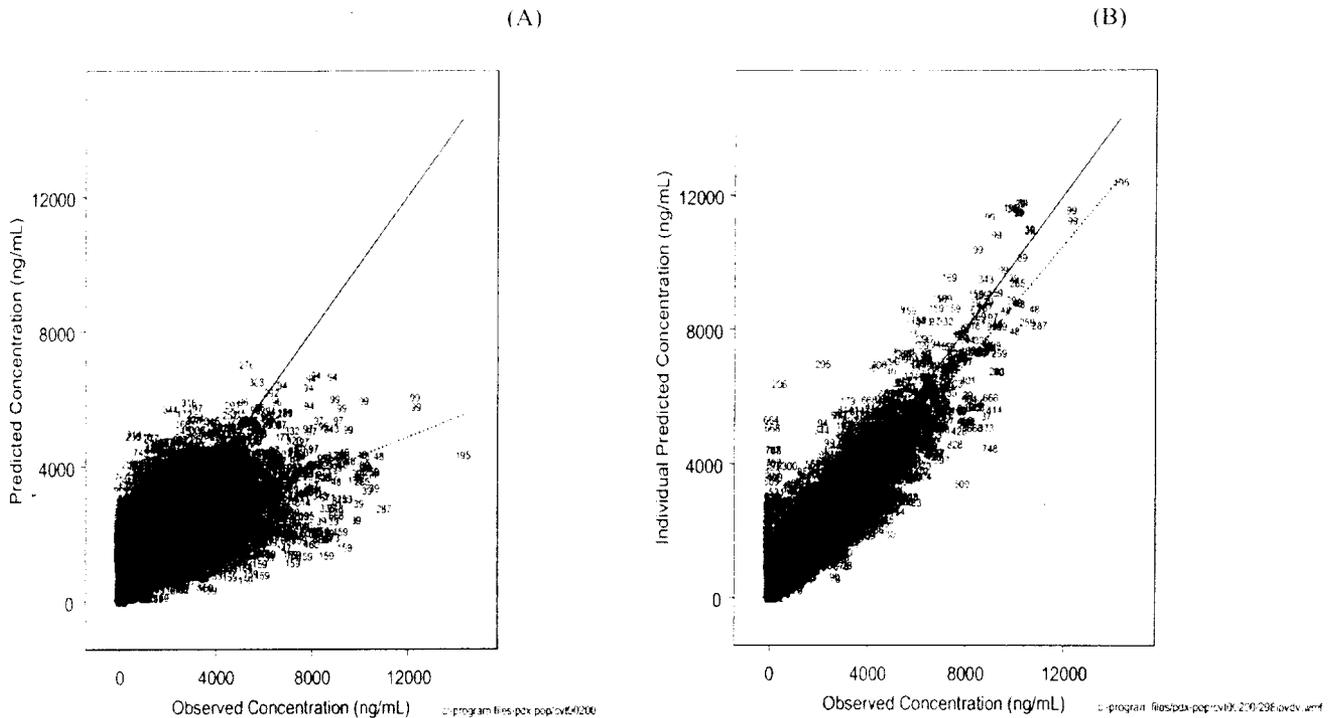


Figure 7 (A) Population mean (B) Individual prediction versus observed Plasma Ranolazine Concentration (ng/mL) after oral administration of ranolazine.

Plasma Concentration-Effect Relationship (QTc)
Intravenous Infusion Study

Bazett’s correction method overcompensated for the correlation between QT and RR in all subjects. Additional PKPD analysis was performed using the individually optimized correction formulae. The data were pooled by subject (off drug) and the best correction formula, using a library of regression models, was sought for each subject. The QTc data generated with these individually optimized correction formulae were unbiased and the PK/ PD evaluation resulted in an average slope of 2.29 msec per 1,000 ng/mL ranolazine concentration (range 0.87 to 4.61 msec/1000 ng/mL). The overall variability in QTc values also decreased and no subject had an increase in QTc from baseline by more than 60 msec in any of the recorded ECGs, based on the median QT interval for each ECG.

Combined Studies Analysis

Population Correction Factor

The sponsor determined the correction factor (β) by including all QT and RR values that were taken while the patient was not on ranolazine treatment. A linear mixed-effect regression of the log transformed QT and RR values was used to estimate the population factor β (Figure 8).

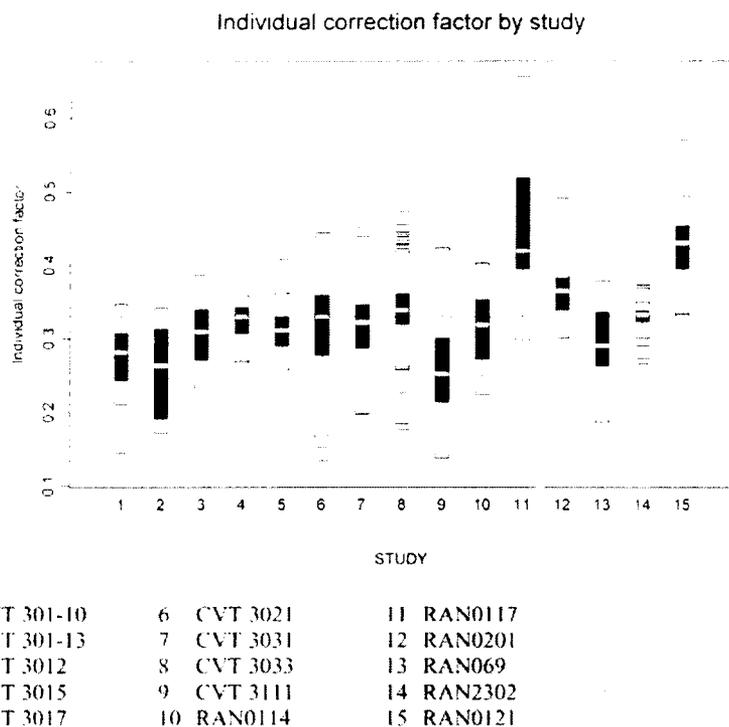


FIGURE 8. INDIVIDUAL CORRECTION FACTOR BY STUDY

The population correction factor was determined to be 0.3299 i.e., equal to Fridericia's Correction factor. Thus, Fridericia's correction factor was used throughout the analysis.

Δ QTc-Concentration Relationship

A total of 1766 individuals from 16 studies contributed 15,819 QTcF observations for this analysis. The sponsor examined for the relationship between the changes in QTcF from baseline and model- predicted ranolazine plasma concentrations using Emax model. Parameter estimates from the linear model were more consistent and had lower variability and objective function than the Emax models. Thus an empirical linear pharmacodynamic model was fitted to the data.

The relationship between ranolazine concentrations and change in QTc based on Fridericia's correction factor was found to be most suitable. The slope of the relationship is approximately 2.4 msec per 1000 ng/mL of ranolazine (Figure 9).

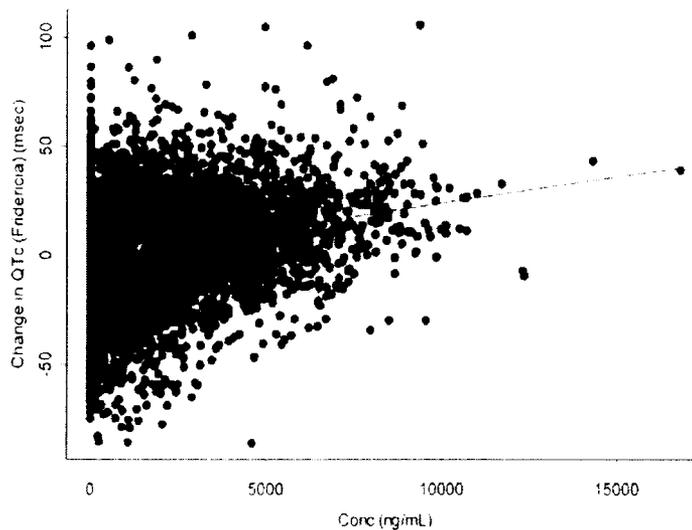


Figure 9. Observed change from baseline of QTc interval (Fridericia's Correction) versus Ranolazine Concentration.

Covariate Model Building

The covariates tested in the model are shown in table 13.

Table 13. Summary of Covariates in Concentration-QTc analysis

	Study	N (Number of Subjects/Patients)
Number of Subjects/Patients by Syntex-Sponsored Study		
	RAN069	29
	RAN0114	8
	RAN0117	11
	RAN0121	14
	RAN0201	8
Number of Subjects/Patients by CVT-Sponsored Study		
	CVT 3012	34
	CVT 3015	14
	CVT 3017	18
	CVT 3021	78
	CVT 3031	191
	CVT 3032	126
	CVT 3033	814
	CVT 3034	332
	CVT 3111	31
	CVT 301-10	43
	CVT 301-13	15
Formulation	SR [REDACTED]	266
	SR [REDACTED]	1440
	IV	31
	IR [REDACTED]	29
Patient Status (Healthy/Patients)		303/1463
Gender (Male/Female)		1364/402
Race (Caucasian/Black/Asian/Hispanic/Other)		1653/52/17/26/18
Diabetes (Yes/No)		398/1368
CHF (Yes/No)		447/1319
NYHA (0/1/2/3/4)		1319/133/236/76/2

No significant patient factors were found to influence the change in QTc for patients on ranolazine, including age, weight, gender, NYHA classification, diabetes, race and drug formulation. Important factors in determining the change in QTc were NYHA classification and baseline QTc for the placebo effect (intercept) term. The final covariate model parameters are shown in table 14.

Table 14. Final Model Parameter Estimates of the sponsor's concentration-QTc model

$$COV1=(\text{Baseline QTc}-418)/24.5$$

$$COV4=(\text{Baseline Heart Rate}-68)/12.1$$

IND1=0, for NYHA Classification less than 2.5

IND1=1, for NYHA Classification greater than 2.5.

Parameter	Typical Value (%RSE*)	Inter-individual (%RSE*)
$INT0 = COV1 * THETA(3) * ((1 - IND1) + THETA(7) * IND1)$ $INT2 = COV4 * (THETA(5) * (1 - IND1) + THETA(6) * IND1)$ $INTC = THETA(1) * (1 - IND1) + THETA(4) * IND1 + INT0 + INT2 + ETA(1)$		
INT (msec)		SD=11.7 (5.75%)
θ_3	-9.91 (6.16%)	
θ_7	0.303 (40.6%)	
θ_5	0 FIXED	
θ_6	0 FIXED	
θ_1	-1.81 (17.3%)	
θ_4	0 FIXED	
$SLP0 = THETA(2) + COV4 * THETA(8) * ((1 - IND1) + THETA(9) * IND1)$ $SLP = SLP0 * EXP(ETA(2))$		
SLP (msec/ng/mL)		61.1% (17.1%)
θ_2	0.00243 (4.16%)	
θ_8	0 FIXED	
θ_9	0 FIXED	
Intra-individual, Residual Error		
Parameter	Estimate (%RSE*)	
σ_{add}^2	SD=11.2 (2.87%)	

* %RSE, percent relative standard error of the estimate = SE/parameter estimate * 100

Abbreviations. FOCEI = first order conditional estimation with interaction, INT = intercept, SLP = slope, σ_{add}^2 = additive residual error model

Model Evaluation (Pharmacokinetic, Pharmacodynamic)

Formal model evaluation was performed by simulations using the final model that included covariates. The predictions are shown in Figure 10 and 11.

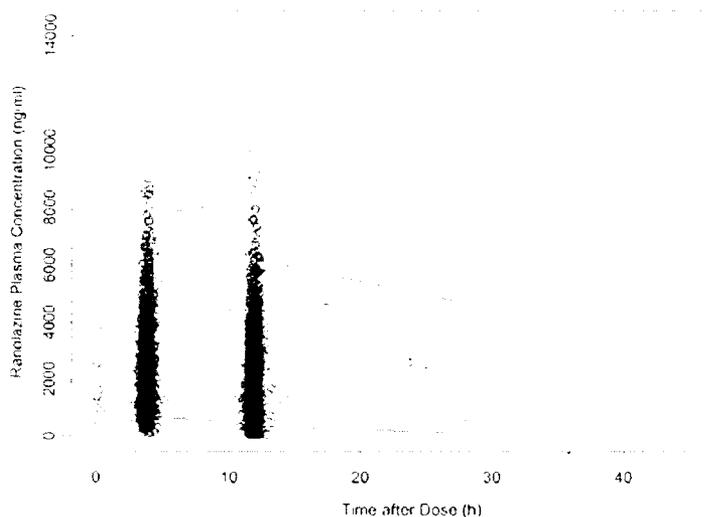


Figure 10. Evaluation of the Final Population Pharmacokinetic Model. Observations were grouped according to time taken after dose to reflect sampling scheme in studies CVT 3031 and CVT 3033.

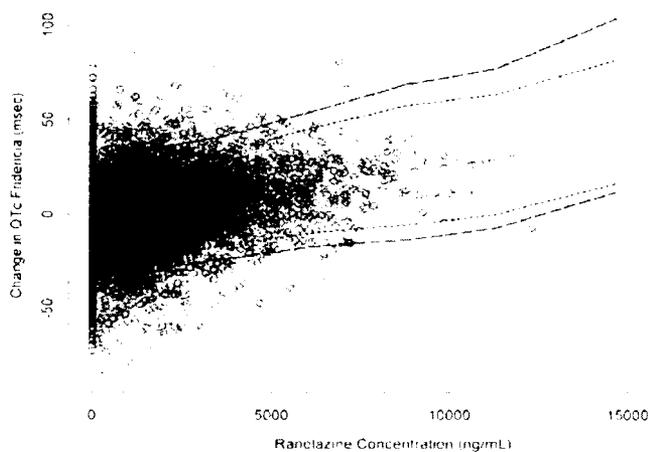


Figure 11. Pharmacodynamic Model Evaluation (The solid line represents the 50th percentile, the short dashed lines represent the 20th and 80th percentile, and the long dashed lines represent the 10th and 90th percentile).

Special Population Analysis (Hepatic)

The sponsor evaluated the effect of ranolazine on the QTc interval in patients with hepatic impairment. A polynomial function was fit to the data and estimates of slope were derived (Figure 12).

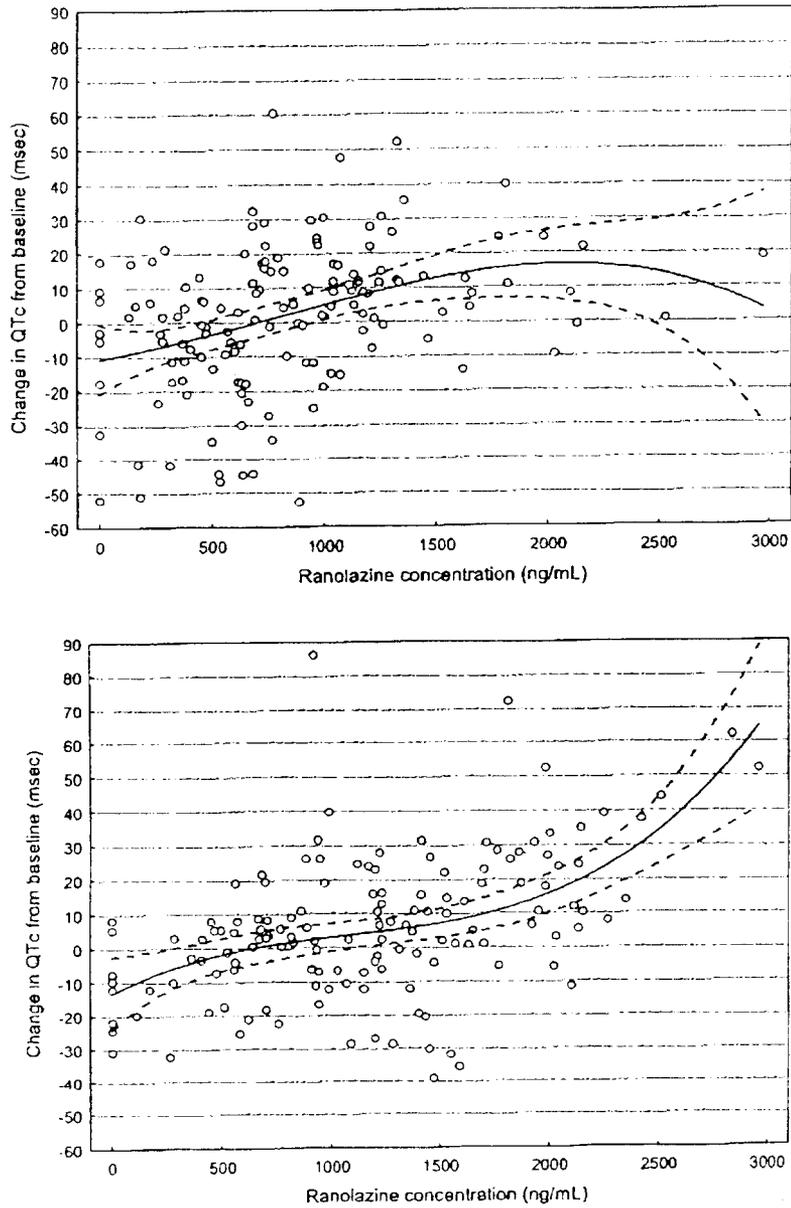


Figure 12. Concentration-Response Relationship for Change in QTc from baseline in subjects with (A) Mild and (B) Moderate hepatic impairment.

A linear regression function showed that subjects with moderate hepatic impairment had an increase of on average 15.2 msec per 1000 ng/mL ranolazine concentration. However, the relationship was rather nonlinear with a steeper slope at concentrations above approximately 1500 ng/mL and a more shallow slope at lower concentrations. Subjects with mild hepatic impairment showed no sign of a greater response but rather a plateau.

REVIEWER COMMENTS

Pharmacokinetics

1. The pharmacokinetic model developed by sponsor was based on the results of intravenous infusions studies to different target concentrations. The proposed model was based on the prior knowledge of the metabolic pathways and the observed changes in the metabolite ratios. The model building procedure was found to be rational.
2. The pharmacokinetics of ranolazine were found to be influenced by renal impairment. The study CVT 3016 (Study in patients with renal impairment) showed a reduction in ranolazine clearance in parallel with a reduction in CrCL. In the population pharmacokinetic analysis, however, data from study CVT 3016 was not included.
3. The population pharmacokinetic model is reported to under-predict the peak concentrations of ranolazine (Figure 1A). This was attributed by the sponsor to the fact that a simple first-order absorption rate constant was used for absorption. Simulations performed by the reviewer also observed under-predictions of the peak concentrations. (Example: 500 mg dose b.i.d at steady state in study RAN 0114: $C_{\max(\text{Observed})}=1440$ ng/mL, $C_{\max(\text{Predicted})}=892$ ng/mL; $C_{\text{trough}(\text{Observed})}=988$ ng/mL, $C_{\text{trough}(\text{Predicted})}=511$ ng/mL).
4. The sponsor performed model evaluation by posterior predictive check by computing the prediction intervals and calculating the percentage of observations in the interval at corresponding sampling time. (Please refer to "Comments to be forwarded to sponsor").
5. The PK model used rate constants for the linear elimination pathway. One would expect that the random effects of these rate constants and the volume would be correlated. It is not clear whether the sponsor has tested such a hypothesis. Nevertheless, this might not improve the model predictive capability.
6. The sponsor in the "Software" section of the report state the use of Digital Visual Fortran Compiler (Version 5.0D). However, the output files of NONMEM state that the compiler used was "Visual Fortran 6.1 (Update A)". There is no mention of the version of compiler used in the population QTc analysis. The compilers should be consistently stated in the report.

7. Ideally, having a reliable population PK model serves several purposes, such as predicting concentrations where only pharmacodynamic observations are available. Nevertheless, the sponsor proposed model provides reasonable knowledge about the influence of covariates such as body weight and age on systemic clearance and degree of unexplained variability. Further improvement of the sponsor's model is not undertaken for the following reasons:
 - The time course of ranolazine concentrations follows a complex pattern. This is primarily due to the complex absorption process and high within- and between- patient variability, as evidence from the raw concentration data.
 - According to Dr. Hinderling, a possibility of diurnal variation in the PK was suggested.
 - As presented earlier, PK data from all the studies employed in the ΔQ_{Tc} analysis were not modeled. Inclusion of the 8 additional studies would be extremely time consuming, with little benefit in the understanding of the PK of ranolazine. PK data was collected in all clinical trials used in the pharmacodynamic analysis (effectiveness and toxicity).

Plasma-Concentration Effect Relationship (QTc)

1. Thirty two observations (from a total of 26 patients in studies in CVT 3033, 3021 and 3111) contained measurable concentrations for patients receiving placebo. Inclusion of erroneous concentrations for placebo group can influence the slope of the concentration-QTc relationship.
2. The sponsor analyzed the concentration-QTc relationship in patients with hepatic impairment using a polynomial equation. The sponsor also comments on nonlinearity in slope. A similar finding can also be seen in concentration-QTc relationship in intravenous study (CVT 3111) where there appears to be a threshold concentration (Figure 16). The sponsor does not explain why the slope is steeper in moderate hepatic impairment.
3. The sponsor should use 'one model' for explaining the data or provide physiological reasoning for using different mathematical models for different studies. A much better analysis could be performed by including the data from hepatic impairment into the sponsor's population analysis and explaining the trend in the data.
4. The model evaluation by the sponsor indicates that the majority of the model simulated QTc values fall within 10 and 90% prediction intervals. However, this finding is not surprising in view of the high variability observed in the slope and intercept. It is recommended that the sponsor perform posterior predictive check

by matching the individual and sampling times along with any covariate information and estimating the prediction error.

5. The sponsor in the "Software" section of the report did not state the compiler used for the analysis. The compilers should be consistently stated in the report.
6. In the covariate analysis, the sponsor reports that baseline QTc is an important covariate. The objective function value decreases by 964 units. However, the overall variability in the intercept did not decrease. The sponsor also comments that this could be due to interaction of NYHA Classification and Baseline QTc. This finding is rather due to an artifact which the sponsor did not consider.

For example:

X- Baseline QTc
Y- QTc in Placebo Group
 $\Delta QTc_{\text{placebo}} = X - Y$

Model for Placebo Group: $\Delta QTc_{\text{placebo}} = \text{Intercept}$

Now if we plot Intercept versus Baseline QTc (X) it will obviously be correlated which is not a surprising finding.

It is because of this artifact correlation, there is no significant impact on the overall variability in the intercept (13.6 vs 11 msec), inspite of a big change in objective function.

COMMENTS TO BE FORWARDED TO SPONSOR

1. The use of compilers should be consistently stated in the reports. This would help in checking reproducibility of the results. These should be a part of good modeling practices by the sponsor.
2. It is recommended to perform posterior predictive check (PPC) by matching individuals, sampling times and estimating prediction error. PPC as applied by the sponsor is not a sensitive test for the predictive ability of the model because:
(a) The proposed model parameters use covariates. Comparison of ΔQTc without consideration of these covariates might not ensure rejection of poor models
(b) The unexplained variability/patient-to-patient variability is high. Hence, the 10th and 90th percentiles would be unacceptably high to reject poor models.
3. The sponsor is recommended to use 'one model' for explaining the concentration- ΔQTc relationship and provide physiological reasoning to use different models. Use of different mathematical models reduces the applicability of the models in various clinical settings.

REVIEWER'S METHODS

The sponsor's analysis of the concentration-QTc prolongation data was well performed. The reviewer, for the reasons stated below, re-analyzed these data:

1. Data from the hepatic impairment study were not included in the analysis. There could be important labeling implications of the results from this study. Particularly, if the sensitivity to QTc prolongation is higher in hepatic impaired, then a meta-analysis is necessary.
2. The reviewer found that data from some subjects could be erroneous. The concentrations were more than zero in few subjects who appear to have received placebo. Since the reason for this is not clear, such data should have been removed from the analysis.

Design/Data

The QT analysis conducted by the sponsor did not include few important clinical pharmacology studies such as the studies in which the impact of hepatic impairment, renal impairment were assessed. For this reason, the reviewer appended the data from these 2 studies to the data set employed by the sponsor to evaluate the concentration-QTc prolongation (Δ QTc) relationship.

Data formatting was performed using SAS[®]. The study design for the two studies included are as follows:

CVT 3016: This study evaluated the multiple dose pharmacokinetics of ranolazine and the metabolites RS-88390, RS-88640 and RS-94287 in subjects with mild, moderate or severe renal impairment and in matched healthy volunteers. The dosing regimen comprised a loading dose of 875 mg ranolazine SR and maintenance doses of 500 mg, leading to predicted steady state ranolazine plasma concentrations. (See Dr Hinderling's individual reviews for further details).

CVT3018: This study evaluated the multiple dose pharmacokinetics of ranolazine and the metabolites RS-88390, RS-88640 and RS-94287 in subjects with mild or moderate hepatic impairment and in matched healthy volunteers. The dosing regimen comprised a loading dose of 875 mg ranolazine SR and maintenance doses of 500 mg, leading to predicted steady state ranolazine plasma concentrations. (See Dr Hinderling's individual reviews for further details).

The number of missing plasma ranolazine concentrations were 115 although corresponding QT intervals were available. Since hepatic and renal impairment could alter the pharmacokinetics of ranolazine thereby influencing the elimination of ranolazine, the missing ranolazine concentration data were imputed by log-linear regression of the terminal portion (minimum of 4-5 points) of the pharmacokinetic profile

in the studies CVT 3016 and 3018. The predicted concentrations of the regression line were merged into the database.

Pharmacokinetics

Pharmacokinetic models were not developed for use in the PK modeling as rich data was available. Instead observed concentrations were used to model the QTc prolongation.

Plasma Concentration-Effect Relationship (QTc)

Structural Models

A two-stage (1) Estimation of Correction factor followed by (2) Estimation of Concentration-QTc prolongation relation was used for describing the Δ QTc (Change in QTc from baseline) and ranolazine concentration relationship.

(1) Estimation of Correction Factor: The QT data from drug free phase (run-in, placebo) were analyzed using the following relationship:

$$QT_{ij} = \alpha_i * RR_{ij}^{\beta_i}$$

Where QT_{ij} is the j th QT interval of the i th patient, similarly α_i is the corrected QT and RR is the RR interval and β_i is the exponent coefficient of the i th patient.

(2) Estimation of Concentration-QTc relationship: The individual specific β -values derived from Stage-I were merged using SAS into the full database (run-in, placebo, treatment). For individuals with missing drug-free data, the median beta value for the specific study was substituted.

Model Building

A careful exploration of the data was first performed using graphical techniques before analysis in NONMEM using SPLUS. Based on the findings from exploratory analysis, several models as shown below were tested to define an ideal base model (no covariates) for Δ QTc-concentration relationship. In the models below INT, SLP and CONC refer to intercept, slope and ranolazine plasma concentration respectively.

Model 1: Includes only intercept. No effect of drug is added in the model.

$$\Delta QTc = INT$$

Model 2: Includes the effect of drug using linear model with intercept.

$$\Delta QT_c = INT + SLP \cdot CONC$$

Model 3: Includes the effect of placebo (PLBEFF).

$$\Delta QT_c = INT + SLP \cdot CONC + PLBEFF \cdot ON$$

Where ON is a binary variable for placebo effect (0 if time=0, 1 if time > 0).

Model 4: Expands Model 3 by including the concept of threshold concentrations.

$$\Delta QT_c = INT + SLP \cdot (THRESHOLD - CONC) + PLBEFF \cdot ON$$

Model selection was based on Objective function for nested models 1, 2, 3 and 4. A log-likelihood profiling method was implemented, if necessary, to determine the threshold concentration. According to this method, model parameters were estimated at various fixed values of the threshold concentration. The threshold concentration yielding the minimum objective function value would serve as the final estimate. This process can be viewed as 'Sensitivity Analysis' and is a reasonable method when faced with estimation difficulties, such as unsuccessful convergence.

Covariate Models

The covariates evaluated included demographic data (age, weight, height, sex, race) and creatinine clearance (CrCL) (Table 15). The database used by the sponsor for the population pharmacokinetic analysis contained the CrCL information which was calculated by Cockcroft-Gault formula. In the renal impairment study, the estimated creatinine clearance from urine data was included. The CrCL from these two sources was included into the QT data base using SAS[®]. For missing CrCL values a value of 100 mL/min was imputed, while CrCL greater than 140 mL/min were set to 140 mL/min. The effect of the presence of other disease conditions (diabetes, hepatic, renal impairment congestive heart failure (CHF) and the corresponding New York Heart Association (NYHA) classification of the CHF on different model parameters were also tested. The POSTHOC estimates of individual realization of variability were plotted against covariates. The covariate model building was carried out using stepwise forward selection and backward elimination techniques.

All continuous covariates entered the model according to the following function centered at the median value. For example:

$$TVINT = \theta_1 \cdot \left(\frac{Age}{Median} \right)^{\theta_2}$$

Where TVINT= Typical value of INTERCEPT for individual i and θ_1 is the population mean for an individual of median age and θ_2 is the exponent.

For categorical variables, typical values were determined using:

$$TVINT = \theta_1 \cdot SEX + \theta_2 \cdot (1 - SEX)$$

Where θ_1 is the typical value for SEX=1 (Female) and θ_2 is the typical value for SEX=0 (Male).

The influence of covariates were examined on slope and intercept. Significance was defined as a change in objective function of at least 20 points for 1 additional parameter when using the First-Order (FO) estimation procedure in NONMEM.

Table 15. Summary of Covariate Information

Demographics	
Age (Yrs)	62 (18-92)
Height (Cm)	172 (147-203)
Weight (Kg)	80 (40-152)
Creatinine Clearance (mL/min)	100 (5-126)
Baseline QTc (msec)	419 (351-548)
Baseline Heart Rate (min)	68 (43-120)
Gender	

Male	1407
Female	420
Race	
Caucasian	1714
Black	52
Asian	17
Hispanic	26
Others	18
Disease Condition	
Diabetes	
Yes	403
No	1424
Congestive Heart Failure	
Yes	447
No	1380
NYHA Classification	
0	1380
1	133
2	236
3	76
4	2
Hepatic Impairment	
NO	1811
	8
	8
Mild	
Moderate	

Random Effects Models

The inter-individual variability error models on the structural model parameters were additive (e.g. Slope, Placebo) or exponential (e.g. Intercept, Threshold), as appropriate, and the initial random residual variability model had an additive component. The random effects (differences between the individual and typical parameter values) on slope, placebo, intercept, threshold are referred to as ETSL, ETPL, ETIN and ETTH respectively.

REVIEWER'S RESULTS

Pharmacokinetics

No population pharmacokinetic model was developed by the reviewer.

Plasma Concentration-Effect Relationship (QTc)

Structural Models

A total of 17858 observations from 1827 individuals were used. The relationship between ΔQTc and concentrations is shown in Figure 13. A two stage analysis technique was used to describe the data.

In Stage-I, individual correction factors (β_i) were estimated. The population mean correction factor (β) was 0.334 (CV=25.13%). The estimates of individual correction factor by study is shown in Figure 14. Representative plots of few individuals in different studies are shown in Figure 15.

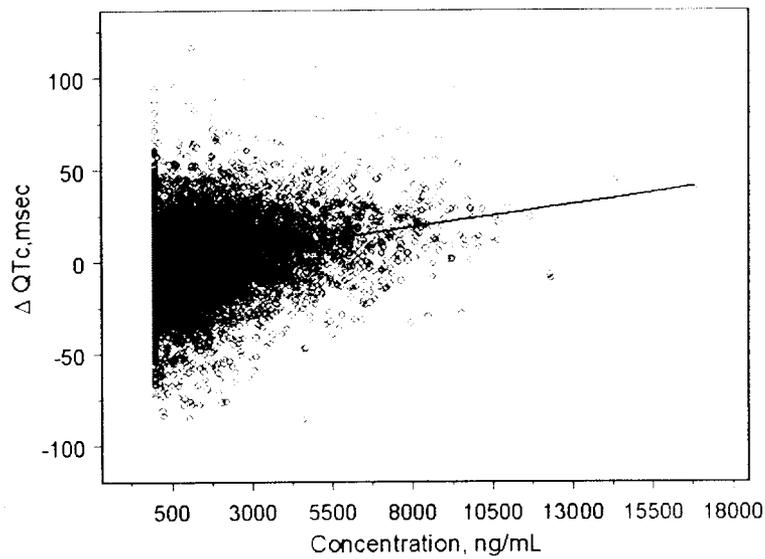


Figure 13. ΔQTc vs Ranolazine Concentrations

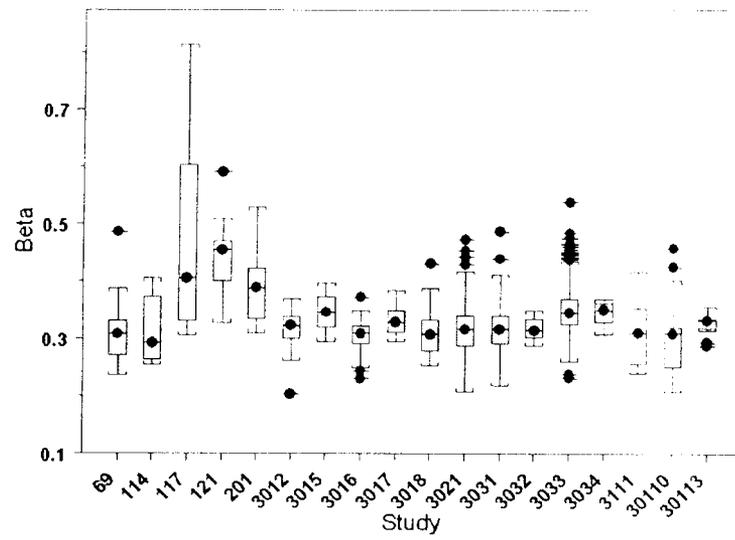


Figure 14. Individual Correction Factor (β) by Study

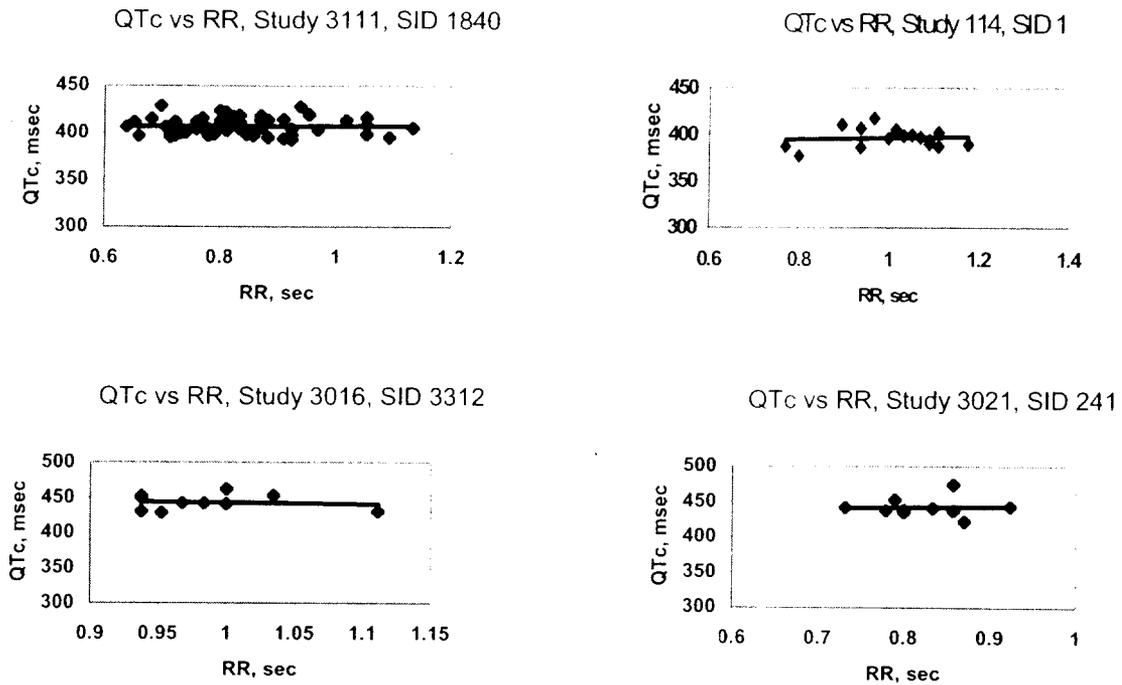


Figure 15. QTc vs RR in representative subjects using individual correction method (SID is a unique ID associated with a patient in the database).

In Stage-2 of the analysis, the data was explored using graphical techniques and analyzed by various models as mentioned earlier. Figure 16 shows the plot of Δ QTc vs concentrations in the intravenous infusion study (CVT 3111). Visual examination of the graph suggests that at concentrations below about 1000 ng/mL, there is no clear signal of QTc prolongation. At higher concentrations a clear upward trend is seen.

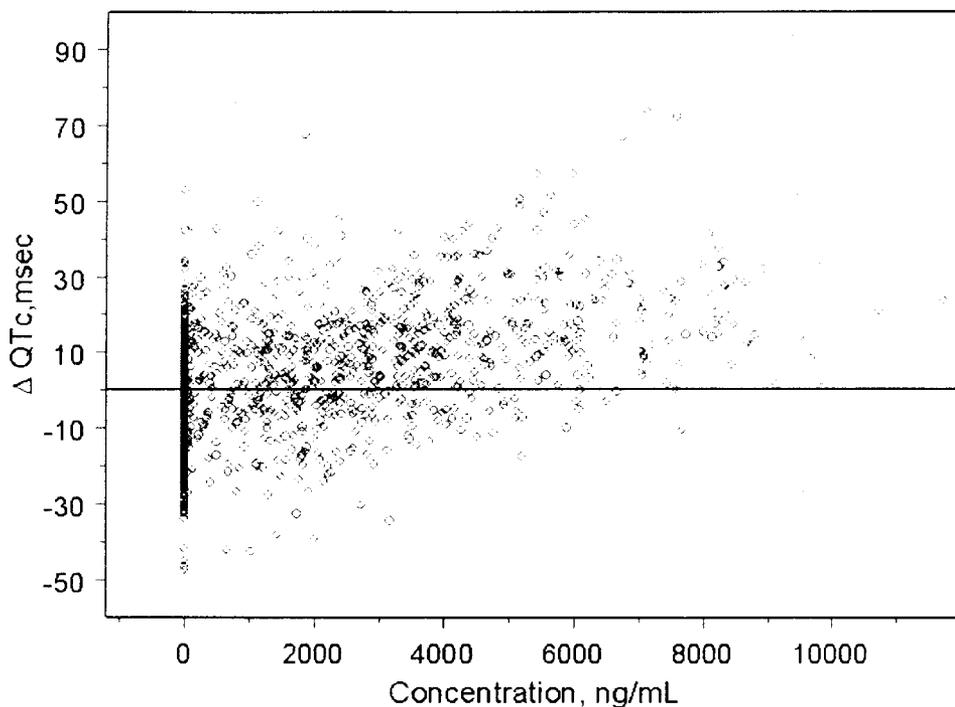


Figure 16. ΔQT_c vs Concentration in intravenous infusion study (CVT3111) (One concentration of 18000 ng/mL was removed for clarity).

Initial analysis of the data using the threshold model was faced with difficulties in estimating the threshold concentrations. Hence a log-likelihood profiling method was used. The model with threshold concentrations of 300 ng/mL (CV: 250%) was found to better describe the trend in the data when compared to linear model (Figure 17). The mean threshold concentrations are much lower than the trough concentrations of ranolazine after oral dose of 500 mg (988 ng/mL). The slope of ΔQT_c vs ranolazine concentration relationship was not different between the linear (2.56 msec per 1000 ng/mL) and threshold model (2.70 msec per 1000 ng/mL). Hence it was inferred that a simple linear model (Model 3) provided a good description of the observed data and was considered as base model for further covariate analysis (Table 16).

Table 16. Summary of Models for Δ QTc-Concentration analysis.

Model	Objective Function	Δ OBJ*	Significance**
1. Intercept	109307		
2. Intercept, Slope	107660	1702	p<0.001
3. Intercept, Slope, Placebo Effect	107605	55	p<0.001
4. Threshold Model	107530	130	p<0.001

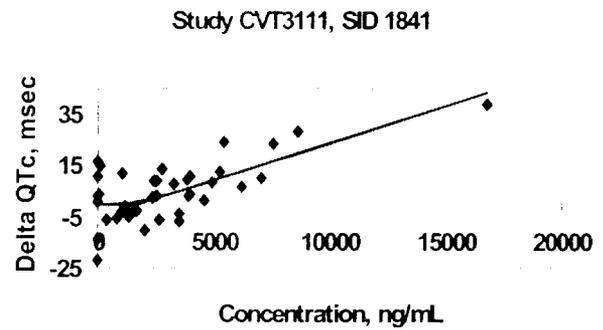
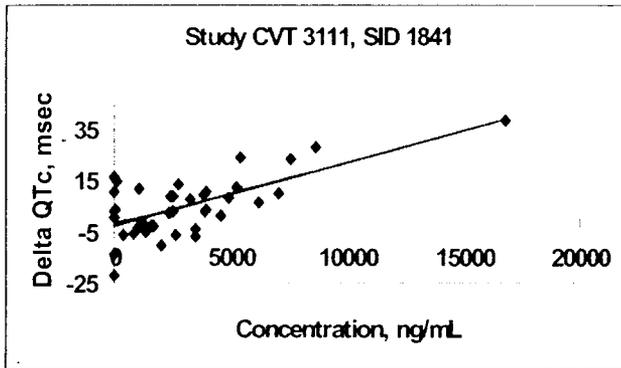


Figure 17. Δ QTc vs Concentration (A) Linear Model (B) Threshold Concentration Model (Observed data (\blacklozenge) with the individual prediction line is shown: SID is a unique ID associated with a patient in the database)

Covariate Model Building

Covariate models were developed using stepwise forward and backward selection methods. The plots of slope and intercept vs various covariates is shown in Figure 18 and 19.

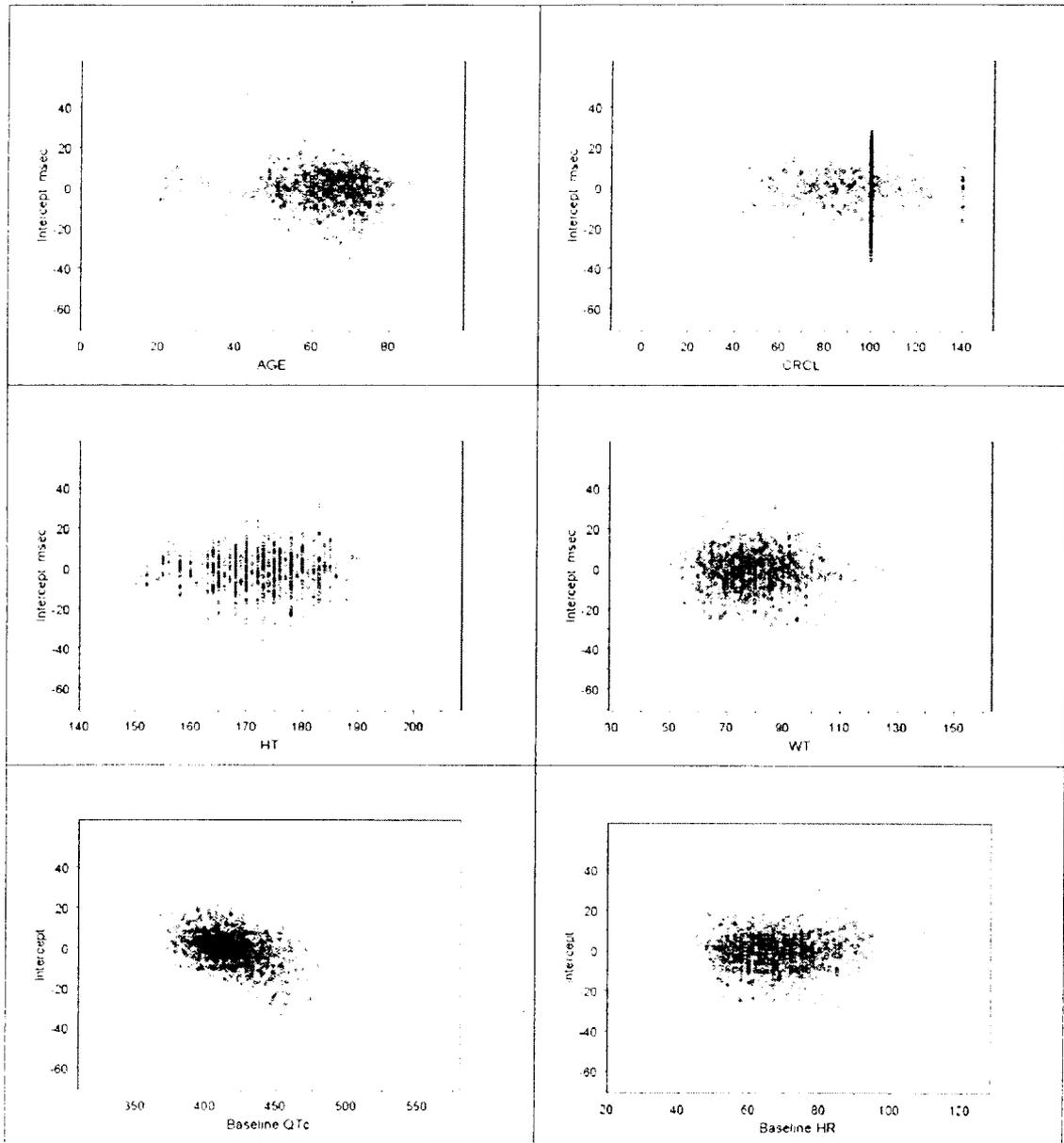


Figure 18 (A). Diagnostic Plots of Intercept versus Covariates (Age, Creatinine Clearance (CrCL), Weight (WT), Height (HT))

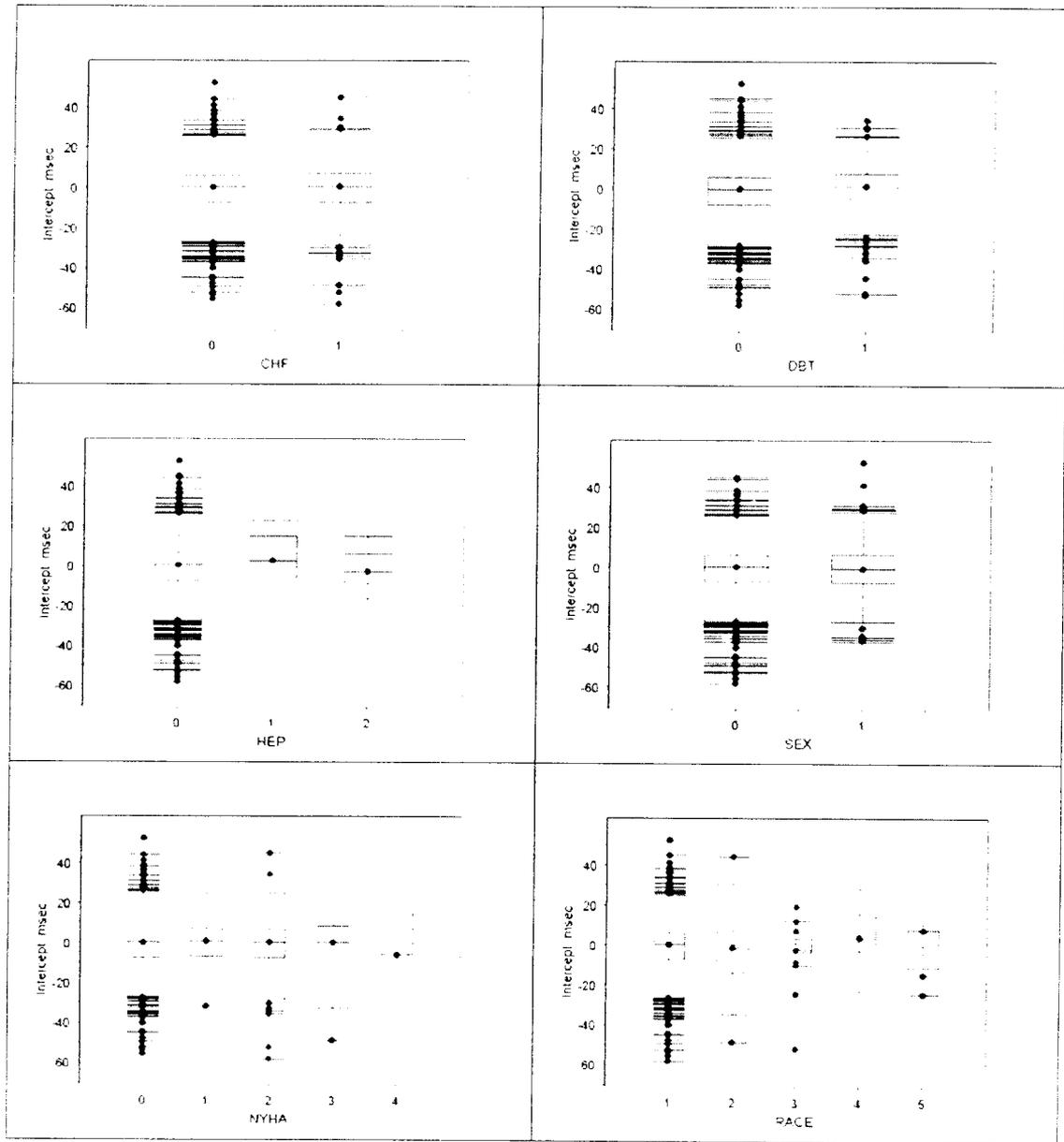


Figure 18 (B). Diagnostic Plots of Intercept versus Categorical Covariates (CHF, DBT, Hep, NYHA, RACE, SEX)

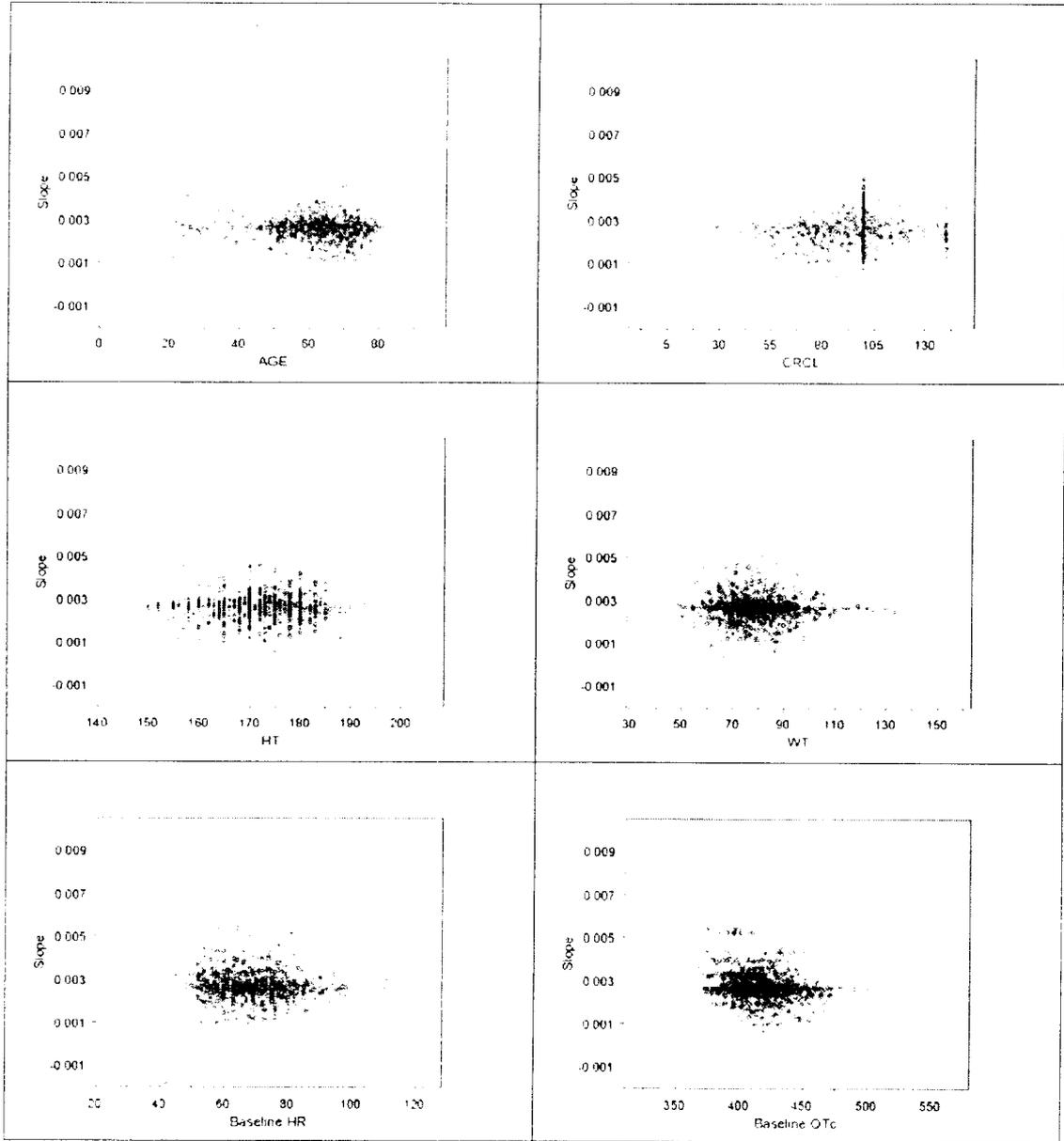


Figure 19 (A). Diagnostic Plots of Slope versus Covariates (Age, Creatinine Clearance (CrCL), Weight (WT), Height (HT))

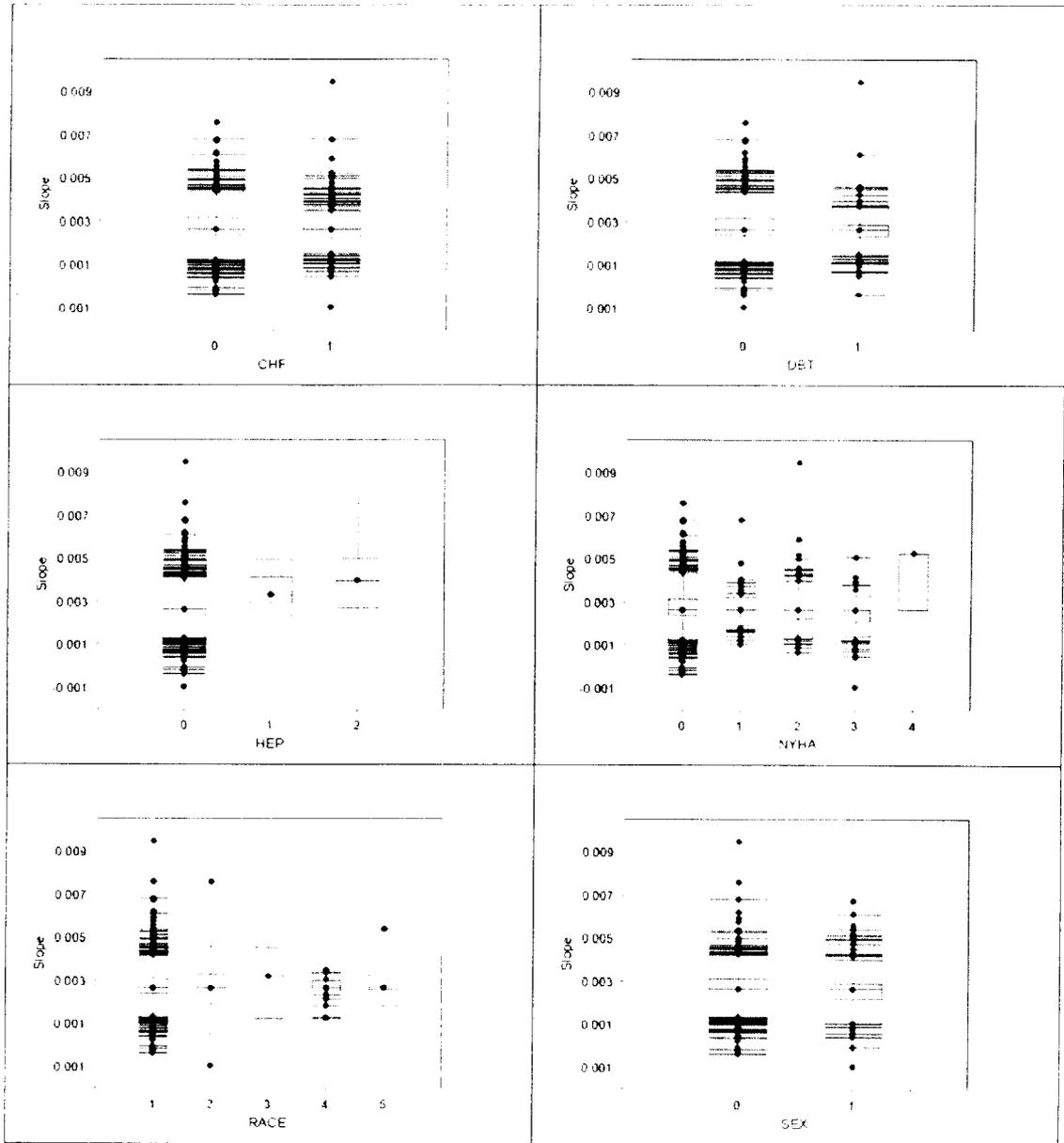


Figure 19 (B). Diagnostic Plots of Slope versus Categorical Covariates (CHF, DBT, Hep, NYHA, RACE, SEX)

Table 17 shows the results of stepwise forward selection procedure and full model. Statistical significance for a covariate was defined as a change in objective function of at least 20 units per degree of freedom.

Table 17. Stepwise Forward Selection of Covariates, Intermediate and Final Model

Model	OBJ	Δ OBJ	Significance
Base (No Covariates)	107605.25		
Intercept			
PL~AGE	107608.77	3.52	No
PL~WT	107606.60	1.35	No
PL~HT	107605.24	-0.01	No
PL~CRCL	107605.06	-0.19	No
PL~GENDER	107600.22	-5.03	No
PL~DIABETES	107603.63	-1.62	No
PL~HEPATIC	107602.73	-2.52	No
PL~NYHA	107597.24	-8.01	No
PL~RACE	107602.56	-2.69	No
PL~CHF	107605.02	-0.23	No
PL~BSHR*	107584.53	-20.72	No
PL~BSQTC*	107050.62	-554.63	No
Slope			
SLP~AGE	107587.30	-17.95	No
SLP~WT	107603.92	-1.33	No
SLP~HT	107602.70	-2.55	No
SLP~CRCL	107605.08	-0.17	No
SLP~GENDER	107601.75	-3.50	No
SLP~DIABETES	107601.15	-4.10	No
SLP~HEPATIC (Healthy vs Mild+Moderate)	107579.00	-26.25	Yes
SLP~HEPATIC (Healthy vs Mild vs Moderate)	107579.56	-25.69	Yes
SLP~NYHA	107594.54	-10.71	No
SLP~RACE	107620.94	15.68	No
SLP~CHF	107602.80	-2.45	No
SLP~BSHR*	107685.11	79.86	No
SLP~BSQTC*	107418.64	-186.61	Yes
Intermediate Model			
INT~1 SLP~HEPATIC	107579.00	-26.25	Yes
INT~1 SLP~HEPATIC+BSQTC*	107626.19	47.19	No
Full Model			

INT~1 SLP~HEPATIC	107579	-26.44	Yes
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Note: * BSQTC- Baseline QTc, HEP- Hepatic Status, BSHR- Baseline Heart Rate.

The estimates of the final covariate model and 95% confidence intervals is shown in Table 18. In spite of a significant drop in objective function after including a baseline QTc, it was not included in further analysis as the correlation was due to artifact. No covariates were significant for the placebo effect. Only hepatic status was a significant covariate on the slope. The estimate of slope in patients with hepatic impairment was two fold lower than reported by the sponsor. This is because the sponsor uses a polynomial function to explain the trend in the data while in the reviewer's analysis a simple linear equation was used to describe the data from all the studies which included the hepatic studies. The goodness of fit for the final covariate model is shown in Figure 15.

The final covariate equation can be expressed as:

$$\Delta QTc = -1.27 - 1.46 \bullet \text{PlaceboEffect} + \text{Slope} \bullet \text{Concentration}$$

Slope : 2.56 msec per 1000 ng/mL ranolazine (Healthy)
 7.10 msec per 1000 ng/mL ranolazine (Mild, Moderate Hepatic
 Impairment)

Table 18. Base model and Final Parameter Estimates For Concentration- Δ QTc Relationship.

Parameter	Base Model		Final Model	
	Mean	SE ^a (%CV)	Mean	SE ^a (%CV)
OBJF	107605		107579	
No. of Parameters	7		10	
Intercept, msec [95% CI]	-1.31 [-0.43, -2.19]	33.9	-1.27 [-0.39, -2.15]	35
Placebo, msec [95% CI]	-1.44 [-0.77, -2.10]	23.0	-1.46 [-0.79, -2.12]	22.7
Slope, msec per ng/mL [95% CI]	0.0026 [0.0023, 0.0028]	3.9		

Hepatic Status on Slope [95% CI]				
Absent			0.0026 [0.0024, 0.0028]	3.9
Mild Moderate			0.0071 ^b [0.0039, 0.010]	16.3
$\omega_{\text{Intercept}}$ (SD, msec)	13.03	5.9	13.03	5.9
ω_{Slope} (SD, msec/ng/mL)	0.0018	23.2	0.0017	23.6
ω_{placebo} (SD, msec)	3.31	25.8	3.31	25.8
σ (SD, msec)	10.81	3.0	10.81	3.0

a- SE represents Standard Error, b- One typical value was computed for mild and moderate hepatic status.

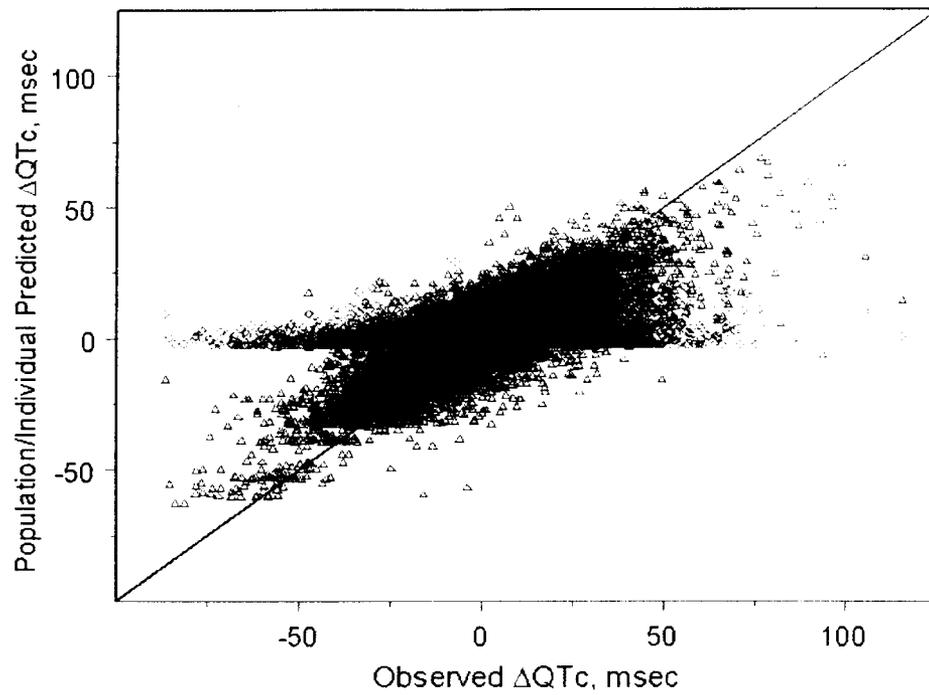


Figure 20. Population (O), Individual Predicted (Δ) vs Observed ΔQT_c (Final Covariate Model using Simple Linear Equation).

Appendix III

<i>Office of Clinical Pharmacology and Biopharmaceutics</i>				
<i>New Drug Application Filing and Review Form</i>				
General Information About the Submission				
	Information		Information	
NDA Number	21-526	Brand Name	Ranexa	
OCPB Division (I, II, III)	I	Generic Name	Ranolazine	
Medical Division	HFD 110	Drug Class	Antianginal	
OCPB Reviewer	Peter Hinderling	Indication(s)	Angina pectoris	
OCPB Team Leader	Patrick Marroum, Joga Gobburu	Dosage Form	SR tablets, 375 mg, 500 mg	
		Dosing Regimen	500 mg, 750 mg, 1000 mg bid	
Date of Submission	12/27/02	Route of Administration	Oral	
Estimated Due Date of OCPB Review		Sponsor	CV Therapeutics	
PDUFA Due Date	10/27/03	Priority Classification	Standard	
Division Due Date	9/11/03			
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			
I. Clinical Pharmacology				
Mass balance:	X	2	1	
Isozyme characterization:	X	6	6	
Blood/plasma ratio:	X	1	1	
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	24	5	
multiple dose:	X	10	6	
<i>Patients-</i>				
single dose:	X	4	0	
multiple dose:	X	5	4	
Dose proportionality -				
fasting / non-fasting single dose:	X	9	3	
fasting / non-fasting multiple dose:	X	4	3	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	9	8	
In-vivo effects of primary drug:	X	7	7	
In-vitro:	X			
Subpopulation studies -				
ethnicity:				
gender:	X	1	1	
pediatrics:				
geriatrics:				
renal impairment:	X	1	1	
hepatic impairment:	X	2	2	
PD:				
Phase 2:	X	3	2	
Phase 3:	X	2	2	
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:	X	2	2	
Population Analyses -				
Data rich:	X	4	3	

Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	X	1	1	
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2	2	
replicate design; single / multi dose:	X	1	1	
Food-drug interaction studies:	X	3	1	
Dissolution:	X	1	1	
(IVIVC):	X	1	1	
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	X	1	1	
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		57	37	
<i>Filability and QBR comments</i>				
	"X" if yes	Comments		
Application filable ?	X			
Comments sent to firm ?	X			
QBR questions (key issues to be considered)	1. Relationship between ranolazine concentration and effect on exercise duration or QTc interval and derivation of effective and safe concentration-and dose range 2. Identification of clinically relevant covariates and implications for labeling			
Other comments or information not included above				
Primary reviewer Signature and Date	Peter Hinderling , 9/ 2/03			
Secondary reviewer Signature and Date	Patrick Marroum, Joga Gobburu			

CC: NDA 21-256, HFD-850(Lee), HFD-110 (Targum, Gordon), HFD-860 (Hinderling, Marroum, Mehta, Sahajwalla), CDR