CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-526

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21526 **SUBMISSION DATE: 7/26/05**

IND: 43735

TYPE: 2 Resubmission

BRAND NAME: Ranexa™

GENERIC NAME: Ranolazine

DOSAGE STRENGTH: 500 mg Sustained Release Tablets

SPONSOR: CV Therapeutics

DIVISION OF PHARMACEUTICAL EVALUATION: DPE 1

REVIEWER: Peter H. Hinderling, MD

PHARMACOMETRIC REVIEWER: Atul Bhattaram, Ph.D.

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RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Type 2 resubmission of NDA 21526 and finds the clinical pharmacology and biopharmaceutics sections acceptable provided the labeling comments are adequately addressed.

The sponsor is requested to keep the FDA dissolution specifications as recommended earlier by the FDA:

Condition	FDA Recommendation
Dissolution Medium	[ ]
Paddle Speed	[ ] rpm
USP Apparatus II	
Volume	[ ] mL
Specifications	0.5 h: [ ]
	4.0 h: [ ]
	12.0 h: [ ]
	20.0 h: NLT [ ]

COMMENTS

The following are issues to be addressed by the sponsor:

1. The sponsor intends to market Ranexa in one strength only, the non-scored 500 mg tablet, thereby limiting critically the capability of adjusting the dose of ranolazine.

2. Deletion of the 12 hour value ([ ] dissolved) in the dissolution specifications proposed by the sponsor would result in accepting formulations with [ ] dissolution at 5 hours. Drug delivery by such a formulation would profoundly alter the plasma concentration profile of ranolazine. Thus, the dissolution specifications recommended earlier by the Agency should be maintained.

3. The results of study 301-16 do not definitively delineate the mechanism responsible for the elevation of serum creatinine in the presence of ranolazine. The study did not demonstrate that the ranolazine associated serum creatinine concentrations are rapidly reversible. Also, in study 301-16 ranolazine had no impact on the serum concentrations of BUN, in contrast to previous studies.

The final decision about the clinical relevance of the observed elevations of the serum concentrations of creatinine and BUN should be made by the Medical Reviewer depending on whether the elevations in the longer term studies were rapidly reversible or not.

4. The sponsor's reanalysis of the RR and QT data of study 3018 in report 303-10C concludes that patients with mild hepatic impairment and healthy subjects display similar QTc prolongations following administration of ranolazine, whereas subjects with moderate hepatic impairment show a significantly increased sensitivity to the QT prolonging effects of ranolazine. In contrast, the population PK-PD analysis conducted by the Agency using the QTc data from patients, special populations and healthy volunteers shows that both patients with mild and moderate hepatic impairment share an increased sensitivity of ranolazine's QT prolonging effect. The sponsor's reanalysis used the median QT interval from all leads and considered only the 16 healthy subjects and 16 patients with mild or moderate hepatic impairment participating in study 3018. In contrast, the Agency's analysis used the maximum QT interval of all leads and data from 324 healthy volunteers and 16 patients with and 1484 patients without overt hepatic impairment. For theses reasons the results obtained by the Agency's analysis ought to be considered decisive.

From the OCPB point of view the resubmission is acceptable.

Peter H. Hinderling, MD

Division of Pharmaceutical Evaluation 1

RD/FT Initialed by Patrick J. Marroum, PhD Cc HFD-110 NDA 21526 HFD 860 (Mehta, Hinderling)

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EXECUTIVE SUMMARY

The salient points of the approvable letter of October 23, 2003, included that the studies conducted provide evidence that ranolazine is an effective anti-anginal drug in an undifferentiated population of patients, including patients receiving sub-maximal treatment with other anti-anginals. The performed trials in angina, however, do not adequately characterize the relationship between dose and therapeutic effect sufficiently to provide labeling instructions. It will be necessary to obtain additional dose-response information. In addition there are three important safety concerns: 1) Potential testicular toxicity, manifest as impaired fertility in rats, 2) Prolongation of QT interval in humans, given that ranolazine treats a symptom (angina) and other anti-anginals do not prolong QT, there needs to be a clear reason to approve a therapy with a possibly life threatening risk 3) Adequate safety exposure. The submitted database has information on fewer than 1000 patients given relevant doses of ranolazine for at least one month.

To address these concerns additional animal data are needed to resolve the issues of potential testicular toxicity. To resolve the QT prolongation issue data could be provided demonstrating that ranolazine has benefits that offset the concern arising from the effects on QT. In patients with angina, this additional benefit could include showing efficacy in populations not adequately treated with maximally tolerated or labeled doses of more than one class of approved anti-anginals. Such data should be obtained from randomized, prospectively designed trials, exploring a broad-range of doses of ranolazine, to be conducted following discussions with the Agency. Demonstration of a benefit on fixed clinical endpoints, such as myocardial infarction or death, also would obviously overcome concerns about effects on the QT interval. The available data suggest a smaller effect of ranolazine in women with angina. Future clinical studies should further characterize this apparent gender difference. Finally such a trial could satisfy the need for a larger safety database. However, in later meetings with the company the Agency stated that further characterization of the dose-response relationship for Ranexa would not be necessary if one dose has demonstrated efficacy in patients with resistant angina (CVT study 3037).

In the following the main elements of the resubmission as well as changes relative to the original submission are described.

Contents of the Resubmission

Clinical Study CVT 3037

This study was to address the safety concerns expressed in the approvable letter, including the QTc prolongation at higher ranolazine plasma concentrations and the insufficient exposure to ranolazine in terms of treatment duration and number of subjects.

Study 3037 was a placebo controlled, double-blind, parallel group study in 565 patients with chronic stable angina, receiving the maximum labeled dose of amlodipine (10 mg qd) and

reporting ≥3 angina attacks per week at baseline. Intake of diltiazem, verapamil and grapefruit juice was not permitted.

The patients were enrolled and randomized to a 1 week regimen of 500 mg bid followed by a 5 week regimen of ranolazine ER (1000 mg bid). In addition to amlodipine and nitroglycerin, approximately 45% of the patients were on stable doses of long acting nitrates. The patients maintained a diary on data and time of angina attacks and nitroglycerin consumption during the double-blind phase of the trial. In addition, quality of life measures (QOL) were assessed through the Seattle Angina Questionnaire (SAQ) three times during the study (at screening, randomization and study completion). The SAQ assesses five different dimensions of an angina event, namely frequency, physical limitation, angina stability, disease perception, and treatment satisfaction. The primary efficacy variable was the average weekly rate of angina attacks during the 6 week double-blind treatment phase. Secondary efficacy endpoints included the average weekly rate of nitroglycerin consumption and LOQ assessments by Seattle Angina Questionnaire (SAQ).

The enrollees were mostly Caucasian males of mean age of 61.7 years from East European centers.

The results of the study showed a statistically significant decrease in mean (SEM) weekly angina attacks (placebo: 4.30 (0.64), ranolazine: 3.29 (0.26) and mean weekly doses of nitroglycerin (placebo: 3.57 (0.54), ranolazine: 2.72 (0.38) in the patients on ranolazine compared to placebo. The QOL results showed a statistically significant improvement only for the angina frequency dimension.

Males on amlodipine 10 mg qd receiving 1000 mg ranolazine bid showed a statistically significant decrease of weekly anginal attacks and dose of nitroglycerin. Females displayed a smaller decrease of weekly anginal attacks than males. However, because of the lower number of female subjects, the between treatment difference was not statistically significant. The weekly nitroglycerine consumption in females was not impacted by ranolazine. Earlier studies using walking time on a treadmill as endpoint indicated that ranolazine's efficacy is only about 30% of that in males. The efficacy in females has not been demonstrated and the risk-benefit relationship in females is still not adequately defined.

The study added a 5 week ranolazine exposure of 1000 mg bid in 277 patients to the safety database of the drug. However, the dose range was not extended beyond ranolazine 1000 mg bid. The co-administration of diltiazem, verapamil and grapefruit juice with ranolazine that would have led to importantly increased ranolazine concentrations was not permitted by the protocol of study CVT 3037. The sponsor has not performed a thorough QTc study. Hence, the prolongation of the QTc interval by ranolazine relative to that by moxifloxacin is not known. The risk- benefit relationship of ranolazine, particularly in females, remains to be defined.

Clinical Pharmacology and Biopharmaceutics

The part contains 5 reports reporting on 2 in vitro studies and 3 in vivo studies. The two in vitro studies investigated the plasma protein binding of the ranolazine metabolites. The three clinical pharmacology reports related to specific safety issues previously identified which included ranolazine's QTc prolongation in patients with hepatic impairment, safety of the drug in subjects on diltiazem or verapamil that are subsequently exposed to high ranolazine plasma concentrations, and the mechanism(s) by which ranolazine elevates serum creatinine.

The in vitro binding **CVT Studies 303-040-N and 303-045-N** showed that the ranolazine metabolites CVT-2514, CVT-4786 and CVT-2537 are between 70% and 75% plasma bound in the presence of each other and additional metabolites. The metabolite CVT-2538 showed a much lower mean binding of about 14%. CVT-2514 and CVT-4786 represent two of the major circulating metabolites of ranolazine. For all the metabolites tested the binding was concentration independent. The tested concentration range for the metabolites CVT-2514, CVT-4786 and CVT 2537 included and exceeded the range encountered under clinical conditions. The binding of the metabolites in plasma was not investigated in the presence of ranolazine.

CVT Study 301-16 investigated the effect of ranolazine 1000 mg bid administered for 5 days on the serum concentrations of creatinine and on other volume and renal function parameters in healthy male volunteers. In previous studies ranolazine administration was associated with an elevation of serum creatinine and BUN concentrations. The results of the study confirmed a rapid and sustained, approximately 15 % increase of the serum concentrations of creatinine observed in previous studies. At the same time the creatinine clearance, the daily amounts of creatinine excreted in urine and the sinistrin clearance-as a measure of GFR- did not statistically significantly differ between ranolazine and placebo treatments. The ranolazine treatment did not have a consistent, statistically significant effect on any of the studied volume or renal tubular variables. The serum concentrations of BUN were not increased in the presence of ranolazine. Unfortunately, the study was not designed to demonstrate that the creatinine elevation associated with ranolazine is reversible. Thus, this short term study did not definitively delineate the mechanism responsible for the observed increase in serum creatinine by ranolazine nor demonstrate the reversibility of the phenomenon.

Report CVT 303-010C using the RR and QT interval data reported in CVT Study 3018 of the original NDA, recomputed the QTc intervals. The goal of CVT Study 3018 was to investigate the pharmacokinetics and QTc prolongation of ranolazine in patients with mild or moderate hepatic impairment in comparison to healthy volunteers. The subjects, after an initial loading dose of 875 mg, received four 500 mg doses of ranolazine SR bid. In contrast to the original study report the reanalysis utilized the median QT interval of all available leads and, using the baseline values, individually corrected the QT interval for changes in the RR interval by determining the regression function of QT on RR with the smallest residual. The prolongation of QTc by ranolazine was then obtained from the difference in QTc measured at corresponding time points after and prior to drug administration. The exposure-response relationship was expressed as mean change in QTc per 1000 ng/mL ranolazine. The results of the reanalysis by the sponsor confirmed that the prolongation of QTc in the patients with moderate hepatic impairment was

significantly greater than in patients with mild hepatic impairment and matched healthy volunteers in that order. Also, the individual and mean values of the maximum observed QTc intervals of the reanalysis were comparable to those in the original analysis. In conclusion, the results of the reanalysis of the QT and RR interval data confirmed the results obtained previously by the sponsor, but were at variance with the results by the population PK-PD analysis of the Agency.

The Agency's analysis determined that both patients with mild and moderate hepatic impairment display an increased sensitivity towards the QT prolonging activity of ranolazine. The sponsor's reanalysis used the median QT interval from all leads and considered only the 16 healthy subjects and 16 patients with mild or moderate hepatic impairment participating in study 3018. In contrast, the Agency's analysis used the maximum QT interval of all leads and data from 324 healthy volunteers and 16 patients with and 1484 patients without overt hepatic impairment. For theses reasons the results obtained by the Agency's analysis ought to be considered decisive.

The goal of **CVT Study CVT 3112**, using a partial cross-over design in Phase 1 of the trial, was to investigate the impact of the calcium antagonists, diltiazem or verapamil, administered orally on the pharmacokinetics and the QTc prolongation of intravenously administered ranolazine in 24 healthy male subjects. Ranolazine was given as a loading infusion (250 mg/h for 1 h) and by maintenance infusions (65 mg/h for 23 hours) on Day 1 with the goal to reach steady-state concentrations of between 1500-3000 ng/mL. The subjects were randomized prior to Day 1 to receive either a treatment with 180 mg diltiazem SR bid (Treatment A) or 240 mg verapamil SR bid (Treatment B). On Day 6 the subjects received a loading infusion (250 mg/h for 1 h) and maintenance infusions (65mg/h for 6 h and 40 mg/h for 17 h). In Phase 2 of the trial, performed several weeks after Phase 1, the subjects received a single dose of 400 mg moxifloxacin. QT corrected for heart rate was obtained from the baseline QT and RR intervals using the Fridericia and Bazett formulae.

In the presence of diltiazem the steady state concentrations of ranolazine were increased by 49.3% during the faster maintenance infusion and 34.0 % during the slower maintenance infusion of ranolazine. In the presence of verapamil the steady-state plasma concentrations of ranolazine were increased by 36.3 % and 19.8% during the faster and slower maintenance infusions, respectively. An increase in QTcF of generally < 10 msec was found after ranolazine administration in the presence or absence of the two calcium antagonists. There was no clear relationship between plasma concentrations and QTc within the studied concentration range. After moxifloxacin administration QTF was increased by 10-20 msec for 4-6 hours after administration.

Diltiazem and verapamil are known CYP 3A and P-glycoprotein inhibitors and are likely to be co-administered with orally administered ranolazine, a CYP 3A and P-glycoprotein substrate, in subjects with chronic stable angina. Previous Studies (CVT 3012, CVT 301-11) submitted in the original NDA had investigated the effect of co-administered diltiazem or verapamil, on the pharmacokinetics and QTc prolongation of ranolazine after oral administration. QT corrected for heart rate was obtained using the Bazett formula and baseline values.

In study CVT 3012 slow release diltiazem 360 mg qd co-administered with 1000 mg ranolazine bid increased Cmax and AUC0-τ 2.8 fold. In study CVT 301-11 verapamil 120 mg tid co-administered with ranolazine SR 750 mg bid increased Cmax 1.9 fold and AUC0-τ 2.2 fold.

In the absence of diltiazem the average plasma concentrations of ranolazine in CVT Study 3112 after intravenous administration were approximately 2.6 to 3.1 times greater than in the earlier performed CVT Study 3012 with oral administration of ranolazine. The highest daily dose of diltiazem, 360 mg, used in CVT Study 3012 was the same as the daily dose of diltiazem in CVT Study 3112. However, the steady-state ranolazine concentrations after intravenous administration increased only 1.5 fold, compared to 2.8 fold after oral administration of ranolazine.

The dose of verapamil used in CVT Study 3112 with intravenous ranolazine administration was twice the dose used in CVT Study 301-11 with oral administration of ranolazine. In the presence of verapamil the ranolazine concentrations increased 2.2 fold after oral administration but only 1.4 fold after intravenous administration of ranolazine. After oral administration of ranolazine, diltiazem and verapamil exerted a 2.8 and 2.2 fold increase of the ranolazine plasma concentrations, respectively, compared to a 1.5 and 1.4 fold increase, respectively after intravenous administration of ranolazine.

These results indicate that both calcium antagonists inhibit the CYP3A and P-glycoprotein substrate ranolazine whether the drug is given intravenously or orally. However, when ranolazine is given orally, the inhibitory impact of the calcium antagonists is significantly greater than after intravenous administration of ranolazine. These findings suggest that there is a pre-systemic part to the drug-interaction between ranolazine and the two calcium antagonists that is more important than the systemic part. It can be estimated that the pre-systemic interaction by diltiazem and verapamil is responsible for a 1.9 fold and a 1.6 fold increase, respectively, of the plasma concentrations of ranolazine.

Because this interaction study used an intravenous administration of ranolazine it does not provide any additional information that could be extrapolated to the oral co-administration of ranolazine and verapamil or diltiazem.

Changes in the Resubmission Relative to the Original NDA Submission

Labeling

In the resubmission CV Therapeutic, Inc., is seeking approval for ranolazine for the treatment of chronic angina in patients who have not achieved an adequate response with other anti-anginal drugs. Ranexa should be used in combination with calcium channel blockers and/or nitrates.

In the original NDA submission ranolazine was indicated for the treatment of chronic angina in patients with severe coronary artery disease, [redacted]

Mechanism of Action

In the resubmission a new mechanism of action of ranolazine, inhibition of the late sodium current, is proposed, whereas in the original NDA partial inhibition of fatty acid uptake and oxidation by ranolazine's interference with enoyl-CoA hydratase and carnitin translocase was thought to be responsible for the drug's efficacy. Ranolazine selectively inhibits the late sodium current. During ischemic conditions, the late sodium current is increased, leading to intracellular sodium dependent calcium overload. Ranolazine by inhibiting the sodium-dependent calcium over-load, is believed to exert its anti-anginal and anti-ischemic effects by improving myocardial relaxation, decreasing diastolic contractile tension, and decreasing extra-vascular compression. This reduction in cellular calcium overload is expected to reduce myocardial stiffness, oxygen consumption and ATP utilization.

Dosage strength

The 500 mg ER tablet is the only strength proposed in the resubmission. In the original submission two tablets of ranolazine of strength 375 mg and 500 mg were proposed. The 500 mg tablet is not scored.

Based on dissolution results obtained with additional batches the sponsor proposes modifications of the dissolution specifications for the 500 mg ER tablets as follows:

Time (h)	Current Acceptance Criteria	Proposed Acceptance Criteria
0.5	[redacted]	same as current
4.0	[redacted]	[redacted]
12.0	[redacted]	delete
20.0	NLT [redacted]	same as current

APPENDIX I: PROPOSED PACKAGE INSERT

24 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

APPENDIX II: REVIEW OF SUBMITTED INDIVIDUAL STUDIES

IN VITRO STUDIES

STUDY CVT 303.040-N BINDING OF RANOLAZINE METABOLITES CVT-2514, CVT-4786, AND CVT-2537 TO HUMAN PLASMA IN VITRO

STUDY ID: CVT 303.040-N
Volume: 3, ITEM **5**

OBJECTIVES

To determine extent of binding of three metabolites of ranolazine, CVT-2514, CVT-4786, and CVT-2537 to plasma from male human subjects *in vitro.*

METHODS

Human blood was collected in the afternoon before the study by [redacted] from four healthy males using sodium or lithium heparin as anticoagulant. After separation of the red cells, the plasma samples were kept at 4 ° C during shipment to CV Therapeutics. The plasma samples were used within 24 hours after collection. None of the subjects were exposed to any medication for at least one week prior to the study.

CVT-2514 (Lot No. SAR-103-41-2), CVT-4786 (Lot No. SAR-114-20), CVT- 2738), Lot No. Ran 2-01-D) and CVT-2512 (Lot No. SAR-103-46-1) standards were synthesized at [redacted] CVT-2738 was synthesized by [redacted] All metabolite standards were at least [redacted] % pure as determined by HPLC-UV assay.

Various amounts of the metabolites CVT -2514, CVT-4786, CVT-2537, CVT-2512 and CVT-2538 in methanol were added together to tubes. The contents were then evaporated to dryness. Human plasma was then added and the below concentrations of the metabolites generated:

Concentration ID	CVT-2514 (ng/mL)	CVT-4786 (ng/mL)	CVT-2738 (ng/mL)	CVT-2512 (ng/mL)	CVT-2537 (ng/mL)
1	2000	7500	3000	500	500
2	1000	2000	1500	250	250
3	500	500	500	125	125
4	200	300	200	50	50

The spiked plasma samples were incubated in a thermostatically controlled water bath at 37° C for 0.5 hour. After equilibration to room temperature, triplicate aliquots (0.350 mL) of each incubated plasma sample were transferred to [ ] ultrafiltration devices [ ] in 96-well plates and centrifuged in a tabletop centrifuge kept at 37° C at approximately 1950 x g for one hour. The molecular cut-off for the [ ] device was 10 0000 Daltons. One hour of centrifugation was found to be sufficient to produce 0.050 to 0.075 mL of ultrafiltrate. Plasma from each subject was studied in triplicate at each concentration level. In a pilot study ultrafiltrate was spiked with the metabolites and then ultrafiltered and the recovery measured. This was to test whether CVT-2514, CVT-4786 or CVT-2537 bound to the ultrafiltration device used.

ASSAY

Concentrations of the CVT-2514 in plasma were determined using a validated LC-MS/MS method using D_3-ranolazine as internal standard. Concentrations of CVT-4786 and CVT-2537 were also determined by a validated LC-MS/MS method using phenyllactic acid as internal standard. QC samples in filtrate were determined by the same method using standards prepared in blank filtrate. The concentrations of the metabolites in ultrafiltrate were measured by the same assay methods and using standards prepared in blank ultrafiltrate. QC samples prepared in plasma and filtrate were analyzed with each batch of plasma and filtrate samples. The respective concentrations in plasma and filtrate for the metabolites CVT-2512 and CVT-2538 were not determined.

The stability of the analytes in the samples before and after incubations of 30 minutes and 1.5 hours was determined.

Plasma protein binding was determined from

% drug bound = [(Cp- Cf)/Cp]

where Cp corresponds to the concentration of the metabolite in plasma (concentration after incubation was used) and Cf is the concentration of the metabolite in the filtrate representing the unbound concentration.

RESULTS

The concentrations of CVT-2738 before and after incubation at 37° C were equivalent indicating stability of the analyte during the experiment.

The recovery of CVT-2514 in ultrafiltrates of filtrates spiked with the metabolite was about 890% suggesting some non-specific binding. The corresponding values for CVT-4786 and CVT 2537 were close to 100 % indicating no important binding to the ultrafiltration devices.

The mean (SD) plasma protein binding of CVT-2514, CVT-4786, and CVT-2537 in plasma of 4 healthy male human subjects is shown in the table below:

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TABLE 4

Summary Results of Binding of CVT-2514, CVT-4786, and CVT-2537 to Human Plasma

CVT-2514		CVT-4786		CVT-2537	
Conc. in Plasma (ng/mL)	%Bound (Mean ± SD)[a]	Conc. in Plasma (ng/mL)	%Bound (Mean ± SD)[a]	Conc. in Plasma (ng/mL)	%Bound (Mean ± SD)[a]
200	74.3 ± 1.20	300	72.7 ± 2.47	50	75.4 ± 2.92
500	73.1 ± 1.69	500	72.7 ± 2.50	125	76.0 ± 1.57
1000	72.7 ± 2.77	2000	73.4 ± 2.09	250	76.5 ± 1.53
2000	73.1 ± 2.43	7500	78.8 ± 2.12	500	75.8 ± 1.57

[a]Mean ± SD of results from 4 male subjects.

The mean plasma protein binding of CVT-2514, CVT-4786 and CVT-2537 ranged between 70 to 75% over the concentration range investigated. These results appeared to indicate that the plasma protein binding of the three ranolazine metabolites is concentration independent and is not affected by the presence of the other metabolites. The plasma protein binding of the ranolazine metabolites in the presence of ranolazine was not investigated.

CONCLUSIONS

The plasma protein binding of the ranolazine metabolites CVT -2514, CVT-4786 and CVT-2537 is 70 to 75 % and appears not to be concentration dependent or affected by varying concentration of other ranolazine metabolites. The plasma protein binding of the ranolazine metabolites in the presence of ranolazine was not determined in this study.

COMMENTS

1. The plasma protein binding of drugs is known to be pH dependent. The plasma samples were filtered for 1 hour. The report does not indicate how the pH was kept at 7.4 during the filtration process.

2. The plasma protein binding of the ranolazine metabolites in the presence of ranolazine was not investigated.

3. The report does not discuss whether the concentrations of the metabolites tested in this in vitro study cover the clinically relevant concentration range.

4. Of the major circulating metabolites of ranolazine CVT-2738, CVT-4786, CVT 2514 and CVT-2512), only CVT-2514 was investigated in this study. It is not clear what priority criteria the sponsor applied in choosing the compounds to be tested

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STUDY CVT 303.045-N BINDING OF RANOLAZINE METABOLITE CVT-2738 TO HUMAN PLASMA IN VITRO

STUDY ID: CVT 303.045-N
Volume: 3, ITEM 5

OBJECTIVES

To determine the plasma protein binding of ranolazine metabolite CVT-2538 in male human plasma *in vitro*

METHODS

Human blood was collected in the afternoon before the study by [ ] from four healthy males using sodium or lithium heparin as anticoagulant. After separation of the red blood cells, the plasma samples were kept at 4 ° C during shipment to CV Therapeutics. The plasma samples were used within 24 hours after collection. None of the subjects were exposed to any medication for at least one week prior to study.

CVT-2738 (Lot No. Ran 2-01-D, purity —) was synthesized by [ ]

Various amounts of CVT-2738 in methanol were added to test tubes. The content was evaporated to dryness. Human plasma was then added to achieve final concentrations of CVT-2738 of 200, 500, 1500 and 3000 ng/mL. The samples containing CVT-2738 were incubated in a thermostatically-controlled water-bath at 37 ° C for 0.5 hours. After equilibration to room temperature , triplicate aliquots (0.350 mL) of each incubated plasma sample were transferred to [ ] ultrafiltration devices [ ] in 96-well plates and centrifuged at 37° C in a tabletop centrifuge at approximately 1950 x g for one hour. The molecular weight cutoff of the [ ] device was 10 000 Daltons. One hour of centrifugation was found to be sufficient to produce 0.050 to 0.075mL of ultrafiltrate. Protein binding of CVT-2738 in plasma from each human subject was studied in triplicate at each concentration level. In a pilot study ultrafiltrate was spiked with CVT-2738 and then ultrafiltered and so the binding of the metabolite to the ultrafiltration device tested.

ASSAY

The concentrations of CVT-2738 in plasma were determined using a validated LC-MS/MS method using [ ] HPLC system [ ]. Ranolazine-d3 was used as internal standard. The concentrations of CVT-2738 in the ultrafiltrate and buffer were determined by a similar method using standards prepared in blank filtrate and buffer, respectively. QC samples for the determination of CVT-2738 in plasma and plasma filtrate were prepared in the respective blank matrices with each batch of plasma or filtrate sample.

The stability of CVT-2738 in human plasma during the experiments was determined comparing the concentrations before and after incubation at 37° C for 3 hours.

Plasma protein binding was determined from

% drug bound = [(Cp- Cf)/Cp]

where Cp corresponds to the concentration of the metabolite in plasma (concentration after incubation was used) and Cf is the concentration of the metabolite in the filtrate representing the unbound concentration.

RESULTS

The concentrations of CVT-2738 before and after incubation at 37° C were equivalent indicating stability of the analyte during the experiment.

The recovery of CVT-2738 in ultrafiltrates of filtrates spiked with the metabolite was close to 100 % indicating no important binding of CVT-2738 to the ultrafiltration devices.

The mean (SD) plasma protein binding of CVT-2738 in plasma of 4 healthy male human subjects is shown in the table below:

Table 2

Summary of Protein Binding of CVT-2738 in Human Plasma

Nominal Concentration in Plasma (ng/mL)	Measured Concentration in Plasma (ng/mL)	%Protein Bound
200	211 ± 9.64[a]	13.2 ± 3.40[a, b]
500	543 ± 25.4	16.1 ± 0.821
1500	1610 ± 26.5	13.2 ± 2.31
3000	3180 ± 110	12.7 ± 5.86

[a] Mean ± SD (n=4). Values were rounded to 3 significant figures

[b] Ultrafiltration was carried out in triplicate at each concentration for each subject.

The results on the plasma protein binding of CVT-2738 in plasma of healthy male subjects indicate the metabolite's binding is about 14 % and concentration independent. The plasma protein binding of CVT-2738 is considerably smaller than that of the other ranolazine metabolites and ranolazine tested in other in vitro studies. The impact of the presence of ranolazine and the other main metabolites of ranolazine on the binding of CVT-2738 has not been determined in this study.

CONCLUSION

The plasma protein binding of CVT-2738 is about 14 % and concentration independent. The plasma protein binding of CVT-2738 is considerably smaller than that of the tested other ranolazine metabolites and ranolazine.

COMMENTS

2. The plasma protein binding of drugs is known to be pH dependent. The plasma samples were filtered for 1 hour. The report does not indicate how the pH was kept at 7.4 during the filtration process.

3. The size of the volume that is filtered during the ultrafiltration process is known to impact the extent of binding. The filtered volume amounted to up to about 20 % of the plasma volume. The impact of the filtrate volume on the measured plasma protein binding ought to have been tested as part of the validation process of the method.

2. The plasma protein binding of CVT-2738 in the presence of ranolazine and the major other ranolazine metabolites was not investigated.

5. The report does not discuss whether the concentrations of the CVT-2738 tested in this in vitro study cover the clinically relevant concentration range.

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APPENDIX II: IN VIVO STUDIES

STUDY CVT 301-16- A STUDY TO INVESTIGATE THE RENAL EFFECTS OF RANOLAZINE IN HEALTHY MALE SUBJECTS

Previous studies have shown that ranolazine administration causes a slight, but rapid and sustained increase in serum creatinine, BUN and albumin. These changes are largely independent of dose, occur to a plateau, and are observed to the same extent in patients with congestive heart failure, as well as those on ACE-inhibitors and diuretics. There has been no evidence of nephrotoxicity and the changes are rapidly reversible after withdrawal of drug administration.

OBJECTIVES

1. To investigate the effects of ranolazine on glomerular filtration rate, following single and multiple oral dose administration to steady-state in healthy male subjects

2. To investigate the effects of ranolazine on markers of proximal and distal tubular renal function following single oral dose administration and multiple oral dose administration to steady-state in healthy male subjects

3. To investigate the effects of ranolazine on the plasma levels of atrial natriuretic peptide, arginine vasopressin and the renin/angiotensin/aldosterone axis, following single oral dose administration and multiple oral dose administration to steady-state in healthy male subjects

FORMULATIONS

Ranolazine SR film coated tablets debossed with the initials CVT containing 500 mg ranolazine (Batch No. IK2754A were supplied by CV Therapeutics. Placebo ranolazine SR tablets (excipients) without debossing (Batch No. 0G2747A) were also provided by CV Therapeutics. Inutest ® 25% was supplied in 20 mL ampoules (Batch Nos. 209625, 213063), each containing 5000 mg of sinistrin. This was diluted with 0.9% sodium chloride. Inutest® 25% and sodium chloride 0.9% was provided by [redacted]

DESIGN

This is a randomized, single blind, placebo controlled, two way cross-over, multiple dose study in 18 healthy male subjects. Two oral treatments were investigated. Treatment A consisted of a loading dose of 1500 mg SR ranolazine on the morning of Day 1 followed by an evening dose of 1000 mg ranolazine 12 hours later. On Days 2 to 4 1000 mg SR ranolazine was administered

daily 12 hours apart, with the last dose administered on the morning of Day 5. Treatment B consisted of placebo administered every 12 hours) on Days 1 through 5, inclusive with the last dose administered in the morning of Day 5. The subjects were institutionalized for two sessions consisting of 10 study days (Day-4 to Day 6). There was an interval of at least 7 days between Day 6 of Session 1 and Day -4 of Session 2. Subjects remained resident in the Clinical Unit just 24 hours after receiving the last dose on the morning of Day 5. A discharge medical examination was performed on Day 6 of the second study session. A 14-day follow up contact concluded each subject's participation in the study. Diet, posture or level of activity was controlled as much as possible. The level of sodium and water intake was fixed at approximately 1000 mmol/day and 2000 mL/day, respectively. There was a fixed regimen of fluid intake at regular intervals throughout the day. The protein content of the meals was constantly controlled.

Subjects were not permitted to take any regular or prescribed or over-the counter medication (including multivitamins or herbal remedies) in the two weeks prior to study start and until the end of the study. The occasional use of paracetamol (maximum 2 g/day) was permitted. Ingestion of alcohol and caffeine from 48 hours prior to start and during the residential sessions of the study was not permitted. Between the residential sessions alcohol intake was restricted to two units per day (one unit corresponds to ½ pint of beer, one shot of spirits, or a small glass of wine). Ingestion of grapefruit juice or grapefruit containing products including Sevilla oranges and marmalade from 2 weeks prior to admission to the end of the study was also not permitted. Subjects were required to refrain from strenuous exercise.

The study population consisted of healthy male subjects in the age between 18 and 65 years with a BMI between 19 and 29 kg/m2. Subjects had a QTc interval at inclusion no greater than 440 msec and a creatinine clearance > 80 mL/min computed from the Cockroft-Gault formula based on serum creatinine age, and body weight.

The scheduled study activities are listed in the below scheme:

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Table 2: Study Assessments Flow Chart

Procedure	Screening	Day –4	Day –3	Day –2	Day –1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Interview and Medical History	✓										
Physical Examination	✓		✓								✓
Height	✓										
Weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital Signs[1]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood and Urine Safety Laboratory Tests	✓		✓								✓
Virology	✓										
Drugs of Abuse Test	✓	✓									
Alcohol Breath Test	✓	✓									
ECG[2]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
GP Letter	✓										
Adverse Events		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant Medications	✓	✓									
Continued Eligibility Assessments		✓	✓								
Fluid Intake[3]			✓	✓	✓	✓	✓	✓	✓	✓	✓
Renal Biochemistry/Hematology			✓	✓	✓	✓	✓	✓	✓	✓	
Erythropoietin			✓								✓
AVP/ANP			✓	✓	✓	✓	✓	✓	✓	✓	✓
Urine Collection			✓	✓	✓	✓	✓	✓	✓	✓	✓
Renin/Angiotensin/Aldosterone					✓	✓				✓	
Inutest®					✓	✓				✓	
Ranolazine PK[4]						✓		✓		✓	
Dosing[5]						✓	✓	✓	✓	✓	
Discharge Medical Examination											✓

[1] Vital signs were measured at approx. 0800, 1200, 1700 and 2200 on Days -3 to 5, except for Day 6 which was 0900. Additionally, standing blood pressure was measured at approx. 0800 and 2200, on Days -3 to 5, and at 0900 on Day 6.

[2] ECGs were recorded at approx. 0800, 1200, 1700 and 2200 on Days -3 to -1, 0800 and 1200 on Days 1 to 5 and 0900 on Day 6.

[3] 250 ml of water was to be given at approx. 0700, 0900, 1200, 1430, 1700, 1900, 2100 and 2300 on Day -3 to Day 6, with the exception of Days -1, 1, and 5 when fluid intake followed the Inutest® protocol.

[4] Ranolazine PK samples were taken at approx. 0900 and 1300 on Days 1, 3 and 5.

[5] Dosing was at approx. 0900 and 2100 on Days 1 to 4 and 0900 on Day 5.

ASSAY

The plasma concentrations of ranolazine were measured at the Department of Preclinical Development, CV Therapeutics, Inc. A validated LC-MS/MS method [redacted] was used. The internal standard was d3-ranolazine and the quantification range was 50- 10 000 ng/mL using 0.1 mL plasma.

The assay used to measure sinistrin could not be located in the report.

PK PROFILING

Blood Sample Collection

Blood samples for the determination of plasma concentrations of ranolazine were collected at approximately 0900 and 1300 on Days 1, 3 and 5. Dosing occurred at approximately 0900 and 2100 on Days 1 to 4 and 0900 on Day 5 of the sessions.

Measurement of Glomerular Function

Inutest® is a polysaccharide very similar to inulin. It is freely filtered by the glomerulus with little or no tubular reabsorption or secretion. The polysaccharide is not metabolized and only a negligible fraction is excreted in the bile. The measurement of glomerular filtration rate (GFR) using the Inutest® was performed on Days -1, 1 and 5 prior to the first blood sample of the day (0900).

After an infusion cannula was placed into the antecubital vein of the upper limb contralateral to the PK sampling cannula, the volunteers received a bolus of sinistrin (100 mL Inutest® 5g/100 mL in 10 minutes) followed by a continuous infusion for 6 hours (1440 mL Inutest® 10 mg/mL). The aim was to reach steady-state concentrations of sinistrin of 0.1-0.3 mg/mL by 2 hours of the start of the infusion. On the days of determining GFR the subjects received a low protein lunch approximately 1 hour after the commencement of the sinistrin infusion.

Blood samples for the determination of sinistrin were taken at 0, 2, 4 and 6 hours after start of the sinistrin admnistration, and a urine collection for the recording urine flow rate and sinistrin concentrations was made over the period 2-6 hours.

Estimates for GFR were obtained by the below 2 methods:

1. GFR at 6 hours was computed from:

$$GFR\ (mL/min) = C_{Infusion}\ (mg/mL) \cdot Rate_{Infusion}\ (mL/min)\}/\ C_{Serum}\ (mL/min)$$

2. The mean GFR over a period of 2-6 hours was computed from:

GFR mL/min) = Ae (mg)/ AUC2-6 (mg min/mL)

The second method of computing GFR was considered the more robust method.

The bioanalyses of sinistrin were performed by [redacted]

PD PROFILING

Markers in Plasma and Serum

Blood urea nitrogen (BUN), serum creatinine, serum sodium, osmolality, albumin, hemoglobin (and red cell parameters), arginin vasopressin (AVP) and atrial natiuretic protein (ANP) were evaluated daily from Day -3 to Day 5. Subjects were rested quietly on their beds for a period of at least 30 minutes prior to blood sampling.

Erythropoietin was measured on Day -3 and Day 6. The renin/angiotensin/aldosterone axis was determined on Days -1, 1 and 5. Subjects were required to be supine on their beds for a period of at least 1 hour prior to collecting a first blood sample. Then the subjects were requested to stand up for a period of at least 5 minutes before a second blood sample was taken.

Markers of Volume Status and Renal Glomerular Proximal and Distal Tubular Function

Urine volume and urinary excretion of water, sodium, creatinine, urea, glucose and amino acids were measured in the collections of urine that commenced on Day-3 and ended at Day 6. Each day was divided into 4 collection periods, each lasting 6 hours. Urine aliquots taken from the morning collections on Day -3, 1 and 5 were used to measure β-N-acetyl-D-glucosamine (NAG) and β2 microglobuline

Daily creatinine clearance was computed from:

$$CLcr\ (mL/min) = (Ae(0\text{-}24)\ cr\ (mmol) \cdot 10^6) / (Ccr\ (\mu mol/L) \cdot 1440\ min)$$

Daily sodium clearance was calculated from:

$$CL_{Na}\ (mL/min) = Ae(0\text{-}24)\ Na\ (mmol) \cdot 10^3 / C_{Na}\ (mmol/L) \cdot 1440\ (min)$$

Markers of volume status, as well as renal proximal and distal tubular function including erythropoietin, serum osmolality, arginin vasopressin (AVP), atrial natriuretic protein (ANP) and the renin/angiotensin/aldosterone axis were assessed in order to establish a potential mechanism for the changes observed in previous studies.

QTc Interval

12-Lead recordings were performed at approximately 0800, 1200, 1700, and 2200 on Days -3 to -1, 0800 and 1200 on Days 1 to 5 and at 0900 on Day 6. A QTc value on a single ECG (based on automatic ECG interpretation) exceeding 500 msec triggered a premature withdrawal from the study.

STATISTICAL METHODS

Sample Size

Previous studies have shown that the inter-subject variation for the change in BUN in serum is larger than for serum creatinine. Thus, power calculations were based on BUN. A sample size of 14 subjects provides 80% power to detect a difference of 2.3 mg/dL in serum BUN, assuming a standard deviation of the intra-subject variation of 2.8 mg/dL, using a two sided Analysis of Variance (ANOVA) contrast t-test at the 0.05 significance level. Therefore, 18 subjects were recruited so that at least 14 subjects would complete the study.

Statistical Analysis

Prior to the main statistical analysis a check for carry-over was performed on the baseline values for all PD variables for which baseline values were measured.
In the main analysis a mixed effects ANOVA model with treatment, period and sequence as fixed effects was used. Subject within sequence was included as random effect. The Kenward-Roger correction was applied to the degrees of freedom and 95% confidence limits calculated for differences between treatments, periods and sequences.
PD variables were then compared between treatments using repeat measures mixed effects Analysis of Covariance (ANCOVA) model based on Residual Maximum Likelihood Estimation (REML). Treatment, period, measurement time, treatment by measurement time and sequence were included as fixed effects. Subject by period within sequence was included as random effect. The repeated measures were taken over time with subject taken as subject by period. Pre-dose measurements were included as covariate. The Kenward-Rogers correction was applied to the degrees of freedom and 95% confidence limits calculated for treatment differences at each time point. The point estimate was obtained from the ratio of the ranolazine (Test) LS mean/placebo (Reference) LS mean expressed as percentage. The 95% confidence limits were also expressed as percentage of the reference mean.
The SAS default covariance structure was applied to the repeated measurements. For PD markers with more than one pre-dose measurement, the value measured on the last occasion prior to drug treatment was included.

For the amino acids excreted in urine no baseline concentration determinations were carried out. The statistical model used was as described above but ANOVA was used.

For supine blood pressure a carry-over effect was noted. Hence the statistical analysis was repeated using data from Period 1 only. A repeated measures mixed effects ANCOVA model based on REML was used with treatment, period, measurement time and treatment by measurement time included as fixed effects and subject as random effect. Pre-dose measurements were included as covariate in the analysis.
In order to check the model assumptions, residuals were plotted against predicted values. Residuals were also checked for normality of distribution by means of normal probability plots. The level of statistical significance was set at 0.05.

RESULTS

Eighteen subjects of mean age 28.6 (7.5) years and mean body weight 73.4 (9.0) kg were randomized for inclusion into the study. Subject 2765 was withdrawn on Day-1 of Session 1 due to adverse events (AE) possibly attributable to Inutest®. Subject 2767 was withdrawn on Day 3 of Session 2 due to adverse events possibly attributable to ranolazine. Neither of these subjects was replaced. Subject 2758 attended Session 2 but experienced nausea, vomiting and diarrhea during the baseline period of assessments (Day-3 to Day-2). The symptoms resolved fully, but the subject was deferred, because of possible confounding of the PD variables. The subject returned three days later and repeated the baseline period of assessments before commencing the dosing period.

SAFETY

Tolerability of the study drugs was generally good. There were no deaths or serious AEs. Following the ranolazine administration there were 61 AEs of mild or moderate intensity in 13 subjects. Forty six of the events were considered possibly related to treatment. The most commonly reported AEs included headache (15 reports in 7 subjects), abdominal pain (7 reports in 4 subjects) and nausea (6 reports in 5 subjects). Following administration of placebo there were 40 AEs of mild or moderate intensity reported in 14 subjects. Twenty six of these AEs were considered as possibly related to treatment.

Subject 2767 was withdrawn due to a syndrome consisting of nausea, dizziness and visual disturbancies. On the morning of Day 3 of Session 2, approximately 2 hours after the morning dose the subject was feeling faint (dizziness/light-headed) and nauseating. His blooded pressure was 113/69 mm Hg and heart rate was 76 bpm. Physical examination was normal, aside from some mild epigastric tenderness and some diplopia on lateral gaze on examination of eye movement. He also reported to have a headache this morning and altered sensation in the tips of his fingers and toes that had been persistent this morning. The ECG showed repolarization anomalies. The plasma concentration of ranolazine in the subject was not larger than in the other subjects.

Subject 2565 was withdrawn from the study before receiving ranolazine in Session 1 on Day -1 because of AEs suggesting a possible, but not definite, anaphylactoid reaction deemed potentially attributable to Inutest® administration.

PHARMACOKINETICS

The individual and mean plasma concentrations of ranolazine measured are listed in the below table:

16.2.8.2 Individual and Summary Plasma Ranolazine Concentration (ng/mL) Data

Day	Nominal Time (hr)	Subject											
		2751	2752	2753	2754	2755	2756	2757	2758	2759	2760	2761	2762
1	0	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
1	4	[											
3	48												
3	52												
5	96												
5	100												]

Day	Nominal Time (hr)	Subject					Descriptive Statistics						
		2763	2764	2766	2767[1]	2768	N	Mean	SD	Min	Median	Max	CV%
1	0	[					16						
1	4						16	2062.0	838.2		1730		40.7
	48						16	1807.8	1122.6	\	1380	\	62.1
3	52						16	3147.5	1438.8		2985		45.7
5	96						16	2050.4	1041.5		2155		50.8
5	100					]	16	2700.6	1086.6		2370		40.2

[1] Subject No. 2767 was withdrawn and is excluded from the summary statistics.
[2] It appears that this sample was substituted with that taken at the same time-point from Subject No. 2752 where a concentration of 1880 mg/mL was reported though this subject was receiving placebo at the time.

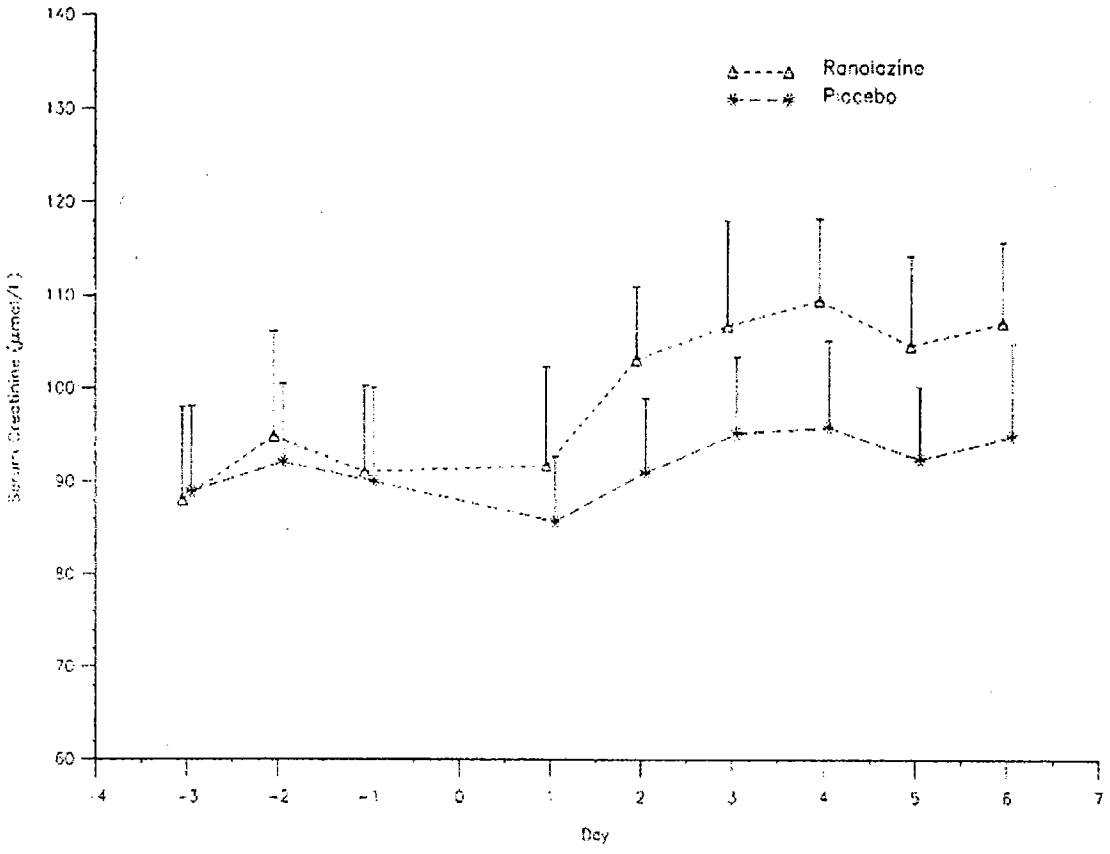
The mean (SD) trough concentrations measured in the mornings of Days 3 and 5 were 1807.8 (1122.6) ng/mL and 2050.4 (1041.5) ng/mL, respectively, indicating a high inter-subject variation of 68% and 51%, respectively, in agreement with the findings in other studies. The corresponding nominal peak concentrations measured 4 hours after administration were 3147.5 (1438.8) ng/mL and 2700.6 (1086.6) ng/mL.

PHARMACODYNAMICS

Serum Creatinine Concentrations, Creatinine Daily Excretions and Clearances

The serum creatinine values during the ranolazine and placebo treatments are shown in the below graph and tables:

14.3.1.3 Mean + SD Profiles of Serum Creatinine Concentrations



Error bars are +/- 1 standard deviation

Program: graphs.sas Graph: avser_CREA.cgm printed on 17 November 2003 at 14:27 h

Best Possible Copy

14.5.2 Summary of the Statistical Analysis of Serum Creatinine Concentrations

Treatment Comparison		LS Means (µmol/L)			95 % Confidence Limits for Difference (Ran - Plac)		Point	95 % Confidence Limits for Point Estimate[2]		
Study Day	Sampling Time	Ranolazine	Placebo	Difference (Ran - Plac)	Lower limit (µmol/L)	Upper limit (µmol/L)	Estimate (%)[1]	Lower Limit (%)	Upper Limit (%)	p-value
Day 1	2 h	91.388	86.212	5.276	0.891	9.661	106.13	101.03	111.22	0.0189
Day 2	26 h	102.760	91.362	11.401	7.016	15.786	112.48	107.68	117.28	<0.0001
Day 3	50 h	106.390	95.550	10.838	6.453	15.224	111.34	106.75	115.93	<0.0001
Day 4	74 h	109.140	96.175	12.963	8.578	17.349	113.48	108.92	118.04	<0.0001
Day 5	98 h	104.260	92.800	11.463	7.078	15.849	112.35	107.63	117.08	<0.0001
Day 6	122 h	106.700	95.237	11.463	7.078	15.849	112.04	107.43	116.64	<0.0001

Data source: Appendix 16.2.10.

Model tested: response = Treatment + Period + Day + Sequence + Treatment by Day + Subject by Period nested within Sequence + Covariate + Error, where Subject by Period nested within Sequence was included as a random effect, the covariate (pre-dose) and all other terms as fixed effects. Day was repeated over Subject by Period.

Statistical analysis performed using SAS version 8.2 on 17 November 2003 at 10.22 h.

[1] The point estimate was obtained as [100x(Ranolazine LS Mean/Placebo LS Mean)].

[2] Confidence Limits for the point estimate was expressed as a percentage of the reference treatment.

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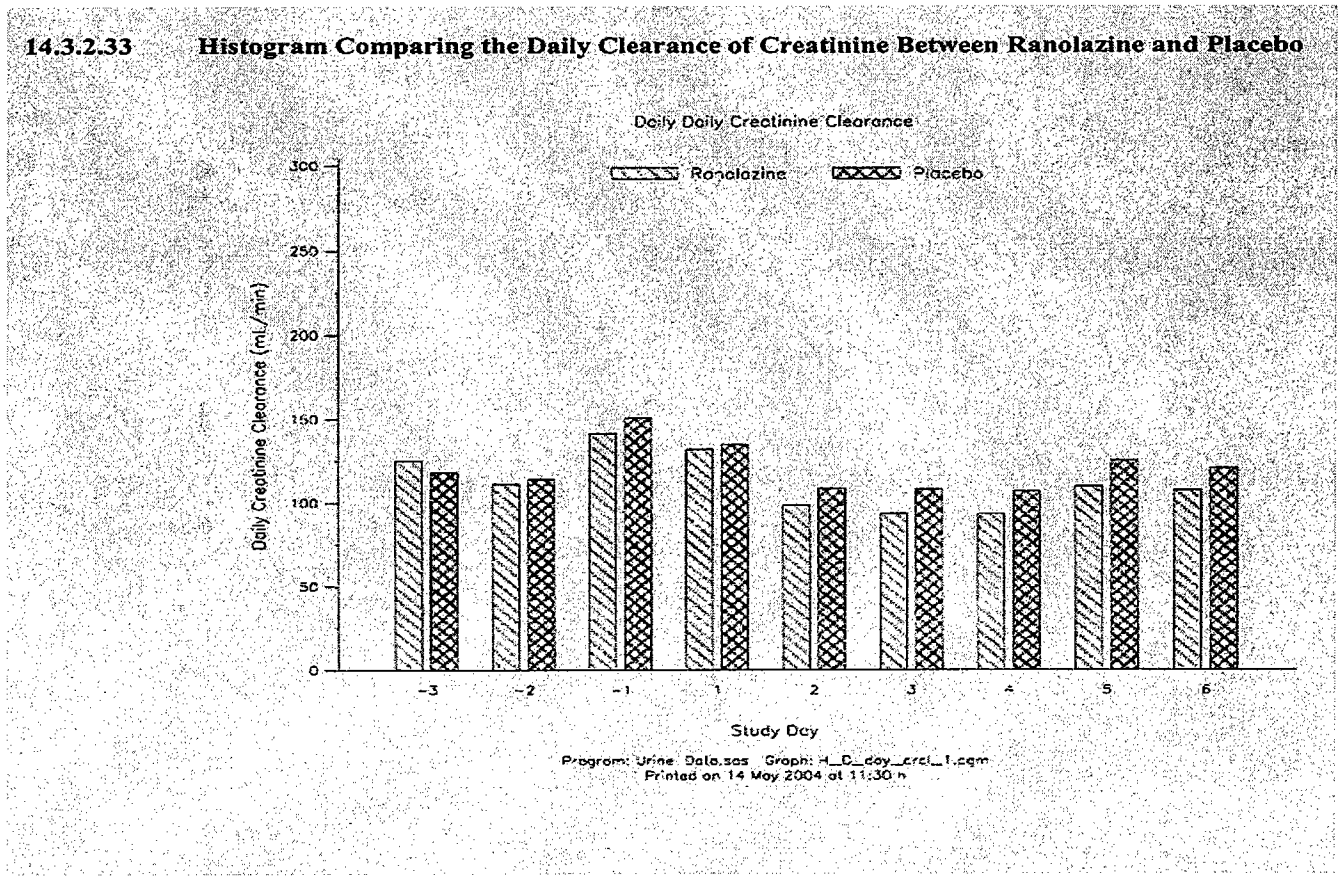
14.3.2.33 Histogram Comparing the Daily Clearance of Creatinine Between Ranolazine and Placebo



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14.5.18 Summary of the Statistical Analysis of Daily Creatinine Clearance

Study Day	Sampling Time	LS Means (mL/min) Ranolazine	Placebo	Difference (Ran - Plac)	95 % Confidence Limits for Difference (Ran - Plac) Lower limit (mL/min)	Upper limit (mL/min)	Point Estimate (%)[1]	95 % Confidence Limits for Point Estimate[2] Lower Limit (%)	Upper Limit (%)	p-value
Day 1	Total 24 h	131.500	134.360	-2.858	-17.945	12.230	97.87	86.64	109.10	0.7086
Day 2	Total 24 h	98.521	107.830	-9.308	-24.128	5.511	91.37	77.62	105.11	0.2163
Day 3	Total 24 h	94.285	106.300	-12.019	-26.672	2.633	88.69	74.91	102.48	0.1071
Day 4	Total 24 h	93.766	104.890	-11.126	-26.042	3.790	89.39	75.17	103.61	0.1425
Day 5	Total 24 h	110.560	124.190	-13.629	-27.995	0.738	89.03	77.46	100.59	0.0628
Day 6	6 h (morning)	108.040	119.430	-11.388	-27.421	4.644	90.46	77.04	103.89	0.1624

Data source: Appendix 16.2.10.

Model tested: response = Treatment + Period + Day + Sequence + Treatment by Day + Subject by Period nested within Sequence + Covariate + Error, where Subject by Period nested within Sequence was included as a random effect, the covariate (pre-dose) and all other terms as fixed effects. Day was repeated over Subject by Period.

Statistical analysis performed using SAS version 8.2 on 05 November at 8:23 h.

[1] The point estimate was obtained as [100x(Ranolazine LS Mean/Placebo LS Mean)].

[2] Confidence Limits for the point estimate was expressed as a percentage of the reference treatment.

Apart from Subject Nos. 2765 and 2767 who withdrew from the study, the following data were excluded from the above statistical analysis:

Subject	Period	Day	Subject	Period	Day
2753	2	2, 6	2761	1	-3, 3, 4, 6
2754	1	6	2761	2	1
2754	2	6	2762	2	6
2755	1	2	2763	1	-1
2759	1	6	2764	all	
2759	2	1	2766	1	-2
2760	1	-1	2766	2	1, 4

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14.5.17 Summary of the Statistical Analysis of Daily Creatinine Excretion

Study Day	Sampling Time	LS Means (mmol) Ranolazine	Placebo	Difference (Ran - Plac)	95 % Confidence Limits for Difference (Ran - Plac) Lower limit (mmol)	Upper limit (mmol)	Point Estimate (%)[1]	95 % Confidence Limits for Point Estimate[2] Lower Limit (%)	Upper Limit (%)	p-value
Day 1	Total 24 h	17.486	16.464	1.022	-0.751	2.794	106.20	95.44	116.97	0.2559
Day 2	Total 24 h	14.750	14.038	0.712	-1.032	2.455	105.07	92.65	117.49	0.4204
Day 3	Total 24 h	14.485	14.423	0.062	-1.664	1.787	100.43	88.47	112.39	0.9437
Day 4	Total 24 h	14.856	14.332	0.524	-1.229	2.276	103.66	91.43	115.88	0.5549
Day 5	Total 24 h	16.714	16.535	0.180	-1.516	1.876	101.09	90.83	111.34	0.8339
Day 6	6 h (Morning)	2.761	2.378	0.383	-1.487	2.252	116.09	37.49	194.68	0.6861

Data source: Appendix 16.2.10.

Model tested: response = Treatment + Period + Day + Sequence + Treatment by Day + Subject by Period nested within Sequence + Covariate + Error, where Subject by Period nested within Sequence was included as a random effect, the covariate (pre-dose) and all other terms as fixed effects. Day was repeated over Subject by Period.

Statistical analysis performed using SAS version 8.2 on 05 November 2003 at 08:20 .

[1] The point estimate was obtained as [100x(Ranolazine LS Mean/Placebo LS Mean)].

[2] Confidence Limits for the point estimate was expressed as a percentage of the reference treatment.

Apart from Subject Nos. 2765 and 2767 who withdrew from the study, the following data were excluded from the above statistical analysis:

Subject	Period	Day	Subject	Period	Day
2753	2	2, 6	2761	1	-3, 3, 4, 6
2754	1	6	2761	2	1
2754	2	6	2762	2	6
2755	1	2	2763	1	-1
2759	1	6	2764	all	
2759	2	1	2766	1	-2
2760	1	-1	2766	2	1, 4

The data show a statistically significant immediate, sustained increase of about 15% (Days 1 trough 6). The creatinine clearance during ranolazine treatment tended to be smaller than during placebo treatment, but the difference was not statistically significant. The daily amounts of creatinine excreted in urine were also not statistically significantly different between the treatments.

The statistical evaluation of the sinistrin clearance values and the ratio of the creatinine to sinistrin clearances on Days 1 and 5 are shown in the following tables:

14.5.24 Summary of the Statistical Analysis of Glomerular Filtration Rate Based on Inulin Clearance derived from Infusion Rate and Inulin Serum Concentration

Study Day	LS Means (mL/min) Ranolazine	Placebo	Difference (Ran - Plac)	95 % Confidence Limits for Difference (Ran - Plac) Lower limit (mL/min)	Upper limit (mL/min)	Point Estimate (%)[1]	95 % Confidence Limits for Point Estimate[2] Lower Limit (%)	Upper Limit (%)	p-value
Day 1	126.33	130.33	-4.0046	-12.9975	4.9883	96.93	90.03	103.83	0.3742
Day 5	121.68	122.56	-0.881	-9.8738	8.1119	99.28	91.94	106.62	0.8444

Data source: Appendix 16.2.10.

Model tested: response = Treatment + Period + Day + Sequence + Treatment by Day + Subject by Period nested within Sequence + Covariate + Error, where Subject by Period nested within Sequence was included as a random effect, the covariate (pre-dose) and all other terms as fixed effects. Day was repeated over Subject by Period.

Statistical analysis performed using SAS version 8.2 on 13 November 2003 at 09:18 h.

[1] The point estimate was obtained as [100x(Ranolazine LS Mean/Placebo LS Mean)].

[2] Confidence Limits for the point estimate was expressed as a percentage of the reference treatment.

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14.5.25 Summary of the Statistical Analysis of Glomerular Filtration Rate Based on Renal Inulin Clearance

Study Day	Sampling Time	LS Means (mL/min) Ranolazine	Placebo	Difference (Ran - Plac)	95 % Confidence Limits for Difference (Ran - Plac) Lower limit (mL/min)	Upper limit (mL/min)	Point Estimate (%)[1]	95 % Confidence Limits for Point Estimate[2] Lower Limit (%)	Upper Limit (%)	p-value
Day 1	2h to 6h	111.56	112.15	-0.5886	-20.3015	19.1244	99.48	81.90	117.05	0.9524
Day 5	2h to 6h	112.57	107.47	5.0977	-14.6152	24.8106	104.74	86.40	123.09	0.6056

Data source: Appendix 16.2.10.

Model tested: response = Treatment + Period + Day + Sequence + Treatment by Day + Subject by Period nested within Sequence + Covariate + Error, where Subject by Period nested within Sequence was included as a random effect, the covariate (pre-dose) and all other terms as fixed effects. Day was repeated over Subject by Period.

Statistical analysis performed using SAS version 8.2 on 13 November 2003 at 10:00 h.

[1] The point estimate was obtained as [100x(Ranolazine LS Mean/Placebo LS Mean)].

[2] Confidence Limits for the point estimate was expressed as a percentage of the reference treatment.

Subject No. 2758 (Period 2) had a missing baseline value and was therefore excluded from the statistical analysis.

14.5.26 Summary of the Statistical Analysis of Creatinine Clearance / Inulin Clearance Ratio

Study Day	Collection	LS Means Ranolazine	Placebo	Difference (Ran - Plac)	95 % Confidence Limits for Difference (Ran - Plac) Lower limit	Upper limit	Point Estimate (%)[1]	95 % Confidence Limits for Point Estimate[2] Lower Limit (%)	Upper Limit (%)	p-value
Day 1	Afternoon	1.7723	1.8065	-0.0341	-0.6614	0.5931	98.11	63.39	132.83	0.9133
Day 5	Afternoon	1.7787	1.6039	0.1748	-0.4626	0.8122	110.90	71.16	150.64	0.5839

Data source: Appendix 16.2.10.

Model tested: response = Treatment + Period + Time + Sequence + Treatment by Time + Subject by Period nested within Sequence + Covariate + Error, where Subject by Period nested within Sequence was included as a random effect, the covariate (pre-dose) and all other terms as fixed effects. Time was repeated over Subject by Period.

Statistical analysis performed using SAS version 8.2 on 13 November 2003 at 09:18 h.

[1] The point estimate was obtained as [100x(Ranolazine LS Mean/Placebo LS Mean)].

[2] Confidence Limits for the point estimate was expressed as a percentage of the reference treatment.

Subject No. 2758 (Period 2) and Subject No. 2763 (Period 1) had a missing baseline value and were therefore excluded from the statistical analysis.

GFR as measured by sinistrin clearance and the ratio of the clearances of sinistrin to creatinine did not show a statistically significant difference between treatments.

Markers in Plasma or Serum

No statistically significant and consistent difference between ranolazine and placebo treatments was found for BUN, serum albumin, hemoglobin, PVC, osmolality, AVP, ANP or the serum AVP to serum osmolality ratio. Similarly, there was no statistically significant and consistent difference between treatments for renin, angiotensin and aldosterone in the supine or standing position or for the difference between supine and standing blood pressure.

Markers of Volume Status and Renal Proximal and Distal Tubular Function

No statistically significant and consistent treatment differences were found for sodium, glucose and urea excretion, sodium clearance, amino acid excretion, daily urine volumes, NAG and β2-microglobulin.

Blood Pressure

Supine systolic blood pressure showed a carry-over effect. The analysis of the data obtained during Period 1 only showed a statistically significant elevation of the supine systolic blood pressure at some time points (23, 56, 85, 104 and 109 h post dose). No carry-over effect was seen either supine diastolic blood pressure or heart rate. No consistent statistically significant effects of ranolazine on diastolic supine or systolic and diastolic standing blood pressure or heart rate were seen.

CONCLUSIONS

1. Ranolazine elevates statistically significantly and immediately serum creatinine concentrations by approximately 15% in agreement with previous studies. In contrast, BUN and albumin were not found to be elevated by ranolazine in the present study. While serum creatinine is increased, no statistically significant treatment differences for creatinine clearance, daily amounts of creatinine excreted in urine, GFR assessed by sinistrin clearance and the ratio of creatinine clearance to sinistrin clearance were found. The mechanism for the elevated serum concentrations of creatinine remains unclear.

2. Ranolazine has no consistent effect on markers of volume and glomerular and tubular function.

3. The serum creatinine concentrations were still elevated on Day 6 of the study. The last dose of ranolazine was administered to the subjects on the evening of Day 5.

4. The treatments were tolerated by the large majority of the participants. Two subjects were terminated prematurely. Subject 2765 was withdrawn on Day-1 of Session 1 due to adverse

events (AE) possibly attributable to Inutest®. Subject 2767 was withdrawn on Day 3 of Session 2 due to adverse events possibly attributable to ranolazine.

COMMENTS

1. The sponsor's conclusion is that the consistent and statistically significant elevations of the creatinine serum concentrations are due to an interference of ranolazine with the tubular secretion of creatinine. The creatinine clearance during ranolazine treatment tended to be smaller than during placebo treatment. However, the difference was not statistically significant. The daily excreted amounts of creatinine excreted in urine were similar during the treatments. Also, the ratio of the creatinine clearance to the sinistrin clearance was not statistically significantly different between treatments. Thus, the data do not support the mechanism postulated by the sponsor.

2. The study was not designed to demonstrate the reversibility of the creatinine serum concentrations by ranolazine. Hence, the sponsor's claim that the effect of ranolazine on serum creatinine concentration is reversible is not supported by the data from this study. Creatinine serum concentrations and clearance should have been measured until normalization of the creatinine levels.

3. A study of longer duration and more participants including females would have been more appropriate.

4. Elevation of other biomarkers including BUN and albumin seen in previous studies after administration of ranolazine could not be confirmed by the present study.

5. GFR was assessed by sinistrin not inulin, although in the report tables and equations refer to inulin (see e.g. pp. 47 and 50). This is confusing. In support of the reliability of the novel methodology the report should include reference articles on sinistrin. A listing of the sinistrin plasma/serum concentrations could not be found in the report. Also, the method validation report for Inutest® could not be located.

6. The single blind design of the study could have been possibly affected by the fact that the verum tablet carried the logo of the sponsor in contrasts to the placebo tablet.

7. Only male subjects were included in the study although the sponsor seeks an indication in females.

8. To facilitate the review tables and graphs showing the most relevant findings of the study should be integrated in the text of the report and not be buried in the Appendices.

STUDY CVT 3112- A SINGLE SITE, OPEN-LABEL, CROSS-OVER STUDY OF THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF AN INTRAVENOUS LOADING DOSE REGIMEN OF RANOLAZINE IN THE PRESENCE AND ABSENCE OF VERAPAMIL AND DILTIAZEM IN HEALTHY MALE AND FEMALE VOLUNTEERS

STUDY INVESTIGATOR AND SITE: [redacted]

Report No.: CVT 3112
Volume No.: 1, Item 6

OBJECTIVES:

Primary: To evaluate the pharmacokinetic profile of ranolazine administered as an iv loading and maintenance infusion with the goal to rapidly achieve and maintain plasma concentrations in the range of 1500 to 3000 ng/mL.

Secondary: To evaluate the safety and tolerability of ranolazine administered as an iv loading and maintenance infusion and to examine the effects of verapamil and diltiazem on the pharmacokinetics, safety and tolerability of ranolazine administered as an iv loading and maintenance infusion.

FORMULATIONS

Ranolazine injection, 25 mg/mL (Batch No. N01005F, expiry date July 2004) was provided by the sponsor.
Diltiazem [redacted] 90 mg tablets (Batch No. XP245, expiration date November, 2004), verapamil [redacted] 120 mg tablets (Batch No. 060998D, expiration date: March 2008) and verapamil [redacted] 240 tablets (Batch Nos. 014018D and 014048D, expiration date July 2007) and moxifloxacin [redacted] 400 mg tablets (Batch No. 13X13K4KB1, expiration date June 2004) were commercially available and were obtained by [redacted]

STUDY DESIGN

This was an open-label, partial crossover study. In the first part of the study, on Days 1 and 6, subjects received single 24-hour iv ranolazine infusions as follows: Day 1: 100mL/h (250 mg/h) for 1 hour, then 26 mL/h (65 mg/h) for 23 hours and on Day 6: 100 mL/h (250 mg/h) for 1 hour, then 26 mL/h (65 mg/h) for 6 hours and then 16 mL/h (40 mg/h) for 17 hours. The individuals

were randomized to receive either co-administered diltiazem (n=12) or verapamil (n=12) prior to Day 1. On Days 3 and 6, the subjects of Treatment Group A received oral doses of either diltiazem SR (90 mg bid on Day 3 and 180 mg bid on Days 4 to 6) and those of Treatment Group B received verapamil SR (120 m bid on Day 3 and 240 mg bid on Days 4 to 6). During the dose escalation phase of verapamil dosing, careful attention was paid to the PR interval of the ECG. Subjects were residents of the Clinical Unit from Day -1 until the afternoon of Day 7. In Phase 2 of the study eligible subjects returned to the Clinical Unit to participate in an additional treatment period (a positive control treatment period), during which each subject received a single, 400 mg dose of moxifloxacin, which is known to prolong the QT interval. Part 2 of the study represented an amendment to the original protocol.

The study assessments are shown in the following scheme:

Table 2: Study Assessments

	Part 1 Day										Part 2			
Procedures	-21 to -1	-1	1	2	3	4	5	6	7	Follow-up	Re-screen	Day -1	Day 1	Follow-up
Written Informed Consent	X										X			
Residential Period		X	X	X	X	X	X	X	X			X	X	
Demographic Data	X													
Medical History	X													
Physical Examination	X	X							X				X	
Vital Signs[a]	X	X	X	X	X	X	X	X	X					
Height and Weight	X													
12-lead ECG[b]	X	X	X	X	X	X	X	X	X		X		X	
Clinical Labs	X	X							X		X		X	
Virology	X													
Drugs of Abuse Screen	X	X									X	X		
Alcohol Breath Test	X	X									X	X		
Urine Pregnancy Test	X	X									X	X		
Inclusion/Exclusion	X	X									X			
Glucose-6-phosphate dehydrogenase activity											X			
Ranolazine Administration[e]			X	X				X	X					
Verapamil/Diltiazem Administration[d]					X	X	X	X						
Moxifloxacin Administration													X	
PK Blood Sampling[c]			X	X				X	X					
Holter Monitoring			X	X			X	X	X				X	
Adverse Events/Concomitant Medications		X	X	X	X	X	X	X	X	X				X

[a] Vital signs (BP and HR) on Days 1, 3, 4, 5 and 6, at approximately 0800, 0900, 1000, 1200, 1400, 1600 and 2000 hours, on Days 2 and 7 at approximately 0800 hours.
[b] ECGs on Days 1, 3, 4, 5 and 6, at approximately 0800, 0900, 1000, 1200, 1400, 1600 and 2000 hours, on Days 2 and 7 at approximately 0800 hours and on Day 1 of the additional treatment period at pre-moxifloxacin dose and at 0.5,1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8 and 12 hours post-moxifloxacin dose.
[c] PK samples for ranolazine analysis taken on: Days 1 and 6: pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8, 12 and 24 hours after the start of infusion.
[d] Subjects allocated to receive either verapamil or diltiazem b.i.d.
[e] A 24 hour ranolazine infusion administered on Days 1 and 6.

ASSAY

All samples were assayed at CV Therapeutics at Palo Alto, CA. Ranolazine and its metabolites RS-88930 (CVT-2514), RS-88640 (CVT-2512) and RS-94287 (CVT-2738) were determined by a validated [ ] method [ ].The internal standard was d3-ranolazine and the quantification range was 50-10 000 ng/mL using 0.1 mL plasma.

Blood Sample Collection

Blood samples in the first part of the study were collected on Days 1 and 6 at the following times: pre-dose and 0.5, 1, 1.5, 2, 4, 6, 8, 12 and 24 hours after start of the infusion.

PK AND STATISTICAL ANALYSIS

The pharmacokinetic analysis was performed by [ ]using non-compartment model dependent methods and the software WinNonlin®. The following pharmacokinetic variables were determined for ranolazine:

Cmax, tmax, the plasma concentration at the end of the 60 mniute loading dose infusion, C60min, AUC0-t, Css, and CLss. Cmax, tmax and C60min were obtained directly from the experimental observations. AUC0-t was calculated using the linear trapezoidal rule, using actually elapsed time values. For the purpose of calculating AUC0-t, when two consecutive plasma concentrations that were below the limit of quantitation (BLQ) of the assay were encountered, all subsequent values were excluded from the analysis. When embedded single BLQ or missing values occurred, they were excluded from the analysis. If any, pre-dose values were set to zero.

Css was calculated as the average of the plasma concentrations at steady-state, which was evaluated during the maintenance infusion only on Day 1 and during each of the maintenance infusion steps on Day 6. The concentrations to be included were decided subjectively by the pharmacokineticist performing the analysis and included at least three concentrations that formed the plateau. CLss for ranolazine was calculated as the product of the infusion rate (in mg/h) at the time of the observed plateau divided by Css.

The variables Css and CLss of ranolazine in the presence of diltiazem or verapamil (Test) were compared to those of ranolazine alone (Reference) using ANOVA of log transformed data (for each PK variable). The statistical model included factors accounting for variation due to treatment. The difference between the mean log-transformed endpoints were estimated, together with the 90% confidence interval (CI) for these differences. The procedure was carried out using the LSMEANS statement of the SAS GLM procedure. The results were anti-logged to give point estimates of the geometric mean ratios (Test/Reference) and associated 90% CI for each PK

variable. These were then presented as percentages. For there to be a statistically significant effect of diltiazem or verapamil on ranolazine Css or CLss, the 90% CI should not have included 100%.

The methodology used for the statistical analysis of Css and CLss is different from that described in the protocol, which states CI were to be computed from the ratio of PK variables of ranolazine only and for the combination of ranolazine with diltiazem or verapamil. The analysis performed as presented in this report is considered to be more robust.

Sample Size

This was an exploratory study and the sample size was not calculated based on formal power calculations.

PHARMACODYNAMICS

The change from baseline for the intervals PR, QRS and QTc (both Bazett's and Fridericia's formulae) were calculated and the means presented graphically. No formal statistical analysis was performed on the pharmacodynamic parameters.
The effects of ranolazine on the PR, QRS and QTc intervals were evaluated separately for ranolazine only on Day 1, and ranolazine and diltiazem or ranolazine and verapamil on Day 6 of the first part of the study.
The average value of the respective interval measurements at screening, admission (Day-1) and prior to start of the ranolazine infusion on Day 1 constituted baseline for the Day 1 measurements for each subject. Change from baseline was calculated for each ECG recording after start of the ranolazine infusion up to the morning of Day 2.
The ECG recordings form Day 5 constituted baseline for the Day 6 measurements.
Change from baseline was calculated for each subject as the difference between the corresponding time points on Day 6 and Day 5, starting at the first recording after initiation of the ranolazine infusion up to the morning of Day 7 (i.e. difference between the following nominal time points: 121 h- 97 h, 122 h-98 h, 124 h-100 h, 126 h-102 h, 128 h-104 h and 132 h - 108 h).

PHARMACOKINETIC-PHARMACODYNAMIC RELATIONSHIP

The relationship between the observed ranolazine plasma concentrations and the change in the ECG interval measurements from baseline were evaluated graphically only using the individual data. Only time points where the PK and PD measurements coincided were considered.

RESULTS

Twenty-four subjects were enrolled in the study and received at least the first 24-hour infusion of ranolazine. 13 subjects completed Part 1 of the study according to the protocol, and one subject (subject 2814)) withdrew consent on Day 6. Of the 23 subjects recalled for Part 2 of the study 19

enrolled in, and completed the additional treatment period. Subject 2805 did not respond to the invitation, subject 2815 had a timing conflict and subjects 2806 and 2817 were for medical history reasons not eligible to receive moxifloxacin (abnormal liver function test and history of brain ischemia).

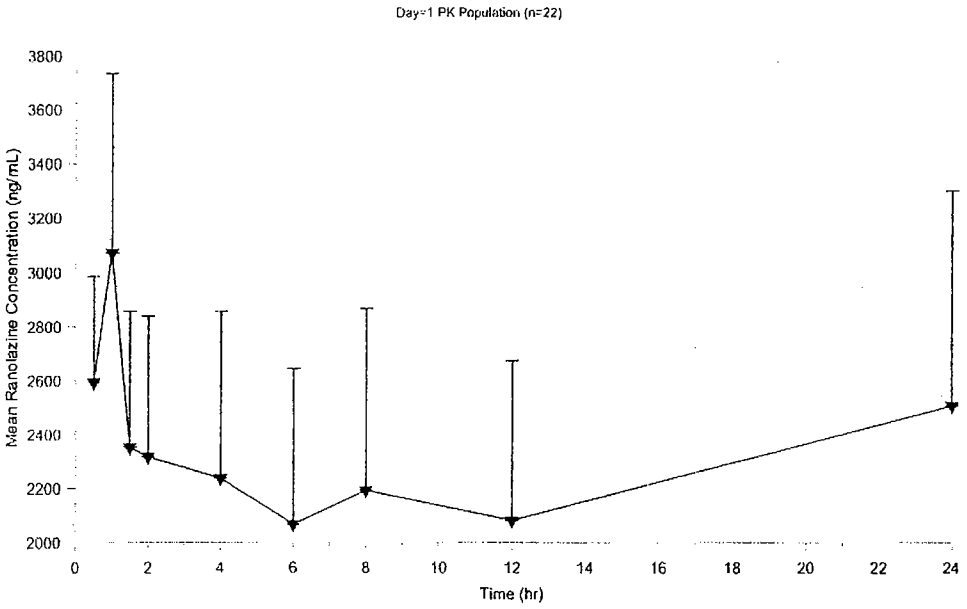
Of the 24 subjects enrolled in the study 12 were males and 12 females of mean age 54.3 (±10.5 years) and body weight of 71.2 (±10.6) kg. 23 of the subjects were of Caucasian and one subjects of black origin.

PK

Ranolazine

The time course of the plasma concentrations of ranolazine on Day 1 of the ranolazine alone treatment in both Treatment Groups is depicted below:

Figure 2: Mean (+SD) Plasma Ranolazine Profile for Day 1 (Ranolazine Alone) from the PK Population



Following administration of ranolazine on Day 1, at a loading dose of 250 mg/h for 1 hour followed by a maintenance infusion of 65 mg/h over 23 hours, steady-state plasma concentration s of ranolazine were reached after 1.5 and 6 hours. The mean Css for both groups was 2198.3 ng/mL with a range of 1120 to 4020 ng/mL. Mean Css for Treatment Group A was 2018 ng/mL and Treatment Group B 2379 ng/mL. Mean CL_{SS} for both treatment groups was 529 mL/min with a range of 270 mL/min and 967 mLmin.

The mean plasma concentrations in the presence of diltiazem or verapamil observed on Day 6 in Treatment Groups A and B are shown below:

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Figure 3: Mean (+SD) Plasma Ranolazine Profile on Day 6 for Treatment Group A (Ranolazine/Ranolazine+Diltiazem)

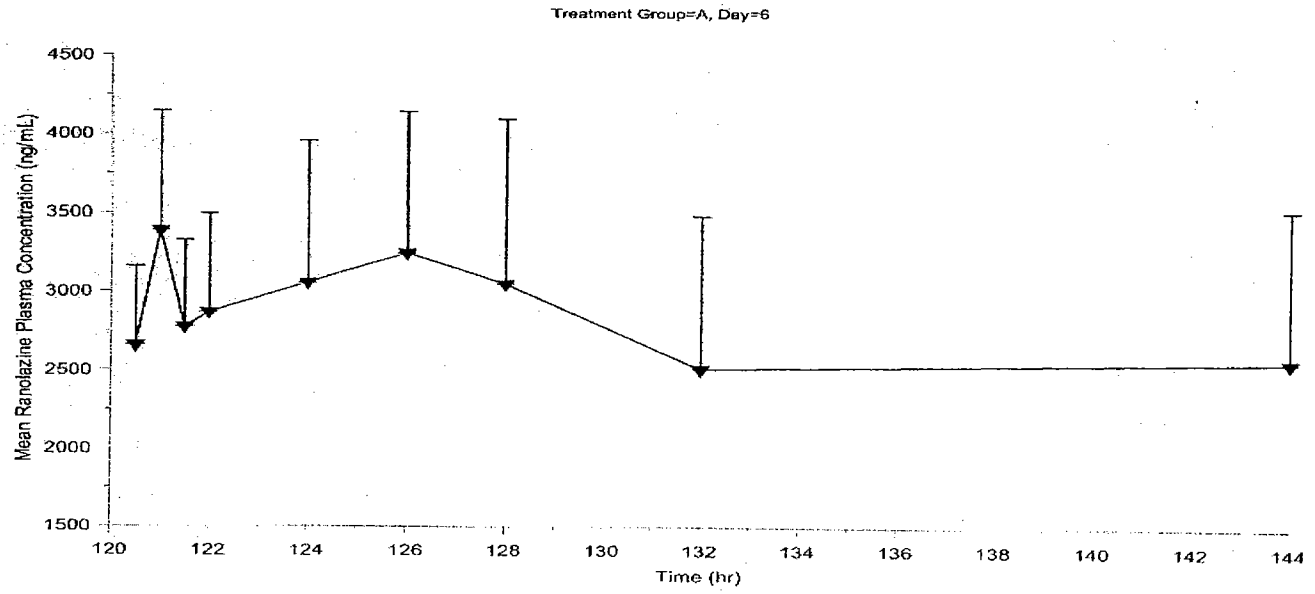
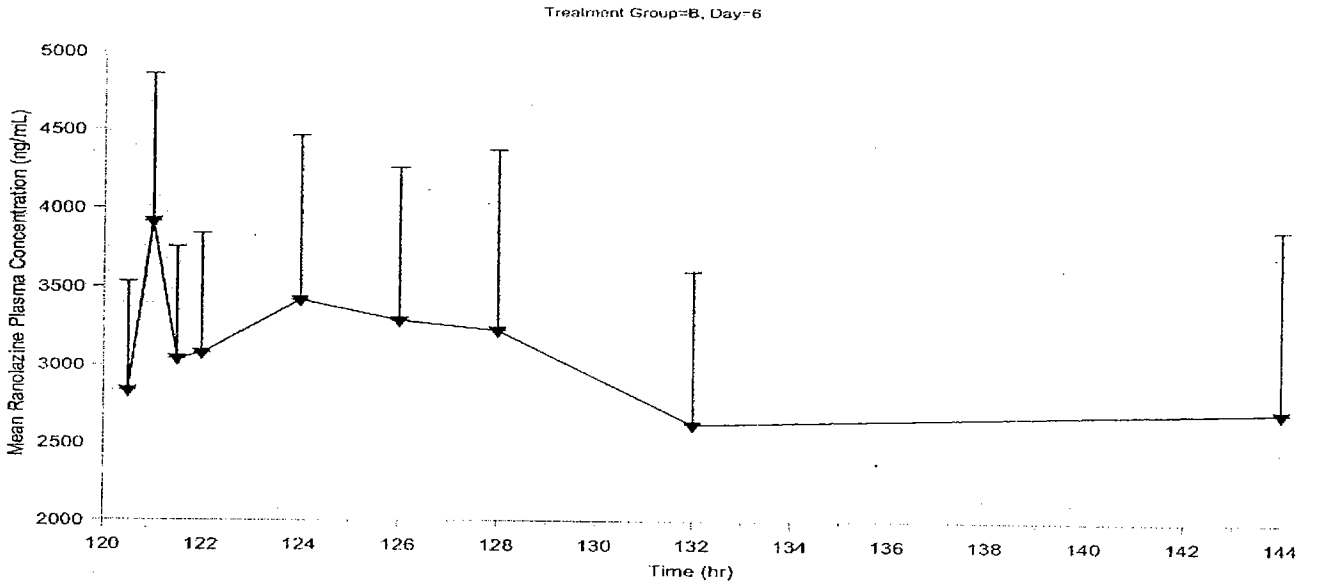


Figure 4: Mean (+SD) Plasma Ranolazine Profile on Day 6 for Treatment Group B (Ranolazine/Ranolazine+Verapamil)



Point estimates (LS Means) and 90% confidence intervals for Css and CLss for the treatment comparisons ranolazine versus ranolazine + diltiazem or ranolazine versus ranolazine + verapamil are shown in the below tables:

Point Estimates and 90% CI for the Treatment Comparisons of Pharmacokinetic Parameters Following Administration of Ranolazine+Diltiazem vs Ranolazine: Treatment Group A

		LS Means			90% CI		
Parameter	n	Test (Ranolazine+Diltiazem) Step 1	Reference (Ranolazine)	Point Estimate(%)	Lower	Upper	p-value
C_{ss} (ng/mL)	11[1]	2953.48	1955.01	151.072	123.46	184.86	0.0024
CL_{ss} (mL/h	11[1]	22.01	33.24	66.22	54.13	81.03	0.0024

		LS Means			90% CI		
Parameter	n	Test (Ranolazine+Diltiazem) Step 2	Reference (Ranolazine)	Point Estimate(%)	Lower	Upper	p-value
C_{ss} (ng/mL)	11	2559.44	1955.01	130.91	104.02	164.77	0.0570
CL_{ss} (mL/h	11	15.63	33.24	47.01	37.36	59.16	<0.0001

[1] n=8 for Day 6.

Point Estimates and 90% CI for the Treatment Comparisons of Pharmacokinetic Parameters Following Administration of Ranolazine+Verapamil vs Ranolazine: Treatment Group B

		LS Means			90% CI		
Parameter	N	Test (Ranolazine+Verapamil) Step 1	Reference (Ranolazine)	Point Estimate(%)	Lower	Upper	p-value
C_{ss} (ng/mL)	11	3131.36	2305.26	135.84	111.64	165.28	0.0140
CL_{ss} (mL/h	11	20.75	28.22	73.55	60.44	89.51	0.0138

		LS Means			90% CI		
Parameter	N	Test (Ranolazine+Verapamil) Step 2	Reference (Ranolazine)	Point Estimate(%)	Lower	Upper	p-value
C_{ss} (ng/mL)	11	2665.46	2305.26	115.63	90.84	147.18	0.3118
CL_{ss} (mL/h	11	15.01	28.22	53.18	41.78	67.71	0.0002

Arithmetic mean (SD) steady-state plasma concentration- and clearance values for ranolazine in the presence of diltiazem (Treatment A) and verapamil (Treatment B) and in the absence of the calcium antagonists are shown in the below table:

Statistic	Day 1		Day 6 Step 1		Day 6 Step 2	
	C_{ss} (ng/mL)	CL_{ss} (L/h)	C_{ss} (ng/mL)	CL_{ss} (L/h)	C_{ss} (ng/mL)	CL_{ss} (L/h)
N	22	22	-	-	-	-
Arithmetic mean	2198.3	31.73	-	-	-	-
SD	606.3	8.97	-	-	-	-
Min	[illegible]					[illegible]
Median	2175.0	29.89	-	-	-	-
Max	[illegible]					[illegible]
CV%	27.6	28.3	-	-	-	-
N	11	11	8	8	11	11
Arithmetic mean	2018.1	34.47	3012.7	22.43	2705.2	16.50
SD	502.9	10.31	661.6	4.63	975.2	5.81
Min	[illegible]					[illegible]
Median	2018.0	32.21	2918.3	22.28	2590.0	15.44
Max	[illegible]					[illegible]
CV%	24.9	29.9	22.0	20.6	36.0	35.2
N	11	11	11	11	11	11
Arithmetic mean	2378.6	28.99	3241.4	21.51	2849.4	16.08
SD	669.0	6.80	887.6	6.17	1080.7	6.37
Min	[illegible]					[illegible]
Median	2213.3	29.37	3086.7	21.06	2686.7	14.89
Max	[illegible]					[illegible]
CV%	28.1	23.4	27.4	28.7	37.9	39.7

After administration of ranolazine on Day 6, at a loading dose of 250 mg/h for 1 hour, followed by a maintenance infusion of 65 mg/h from 1 to 7 hours and thereafter 40 mg/h from 7 to 24 hours in Group A (ranolazine and diltiazem) several subjects showed increasing ranolazine plasma concentration during the first of the two maintenance infusions administered between 1 and 7 hours after start of the loading dose infusion. During the second part of the maintenance infusion, steady-state was generally reached in both treatment groups.

In the presence of diltiazem mean CLss of ranolazine was reduced by 34.7% relative to the monotherapy value during the first and faster maintenance infusion and by 52.1% during the second and slower maintenance infusion despite a reduction in the infusion rate. The plasma concentrations of ranolazine in the presence of diltiazem were increased by 49.3% and 34.0 % during the faster and slower maintenance infusions, respectively.

Following co-administration of ranolazine and verapamil, CLss of ranolazine was reduced by 25.8% relative to the monotherapy value during the first and faster maintenance infusion and by 44.5% relative to the monotherapy value during the second and slower maintenance infusion of ranolazine. The steady-state plasma concentrations of ranolazine were increased by 36.3% and 19.8% during the faster and slower maintenance infusions of ranolazine in the presence of verapamil.

The impact of daily doses of 360 mg diltiazem or 480 mg verapamil on the PK of intravenously administered ranolazine is comparable. The plasma concentrations of ranolazine increase and the clearance decreases in the presence of the calcium antagonists. A comparison of the maintenance infusions rates and resulting plasma concentrations during the faster and slower maintenance infusions shows that the reduction of the plasma concentrations during the slower maintenance infusion is smaller than expected based on the difference in the infusion rates. This finding appears to suggest a time dependent dissociation between inhibition of CYP3A by the calcium antagonists and the ranolazine plasma concentrations. Diltiazem and verapamil are known CYP 3A and P-glycoprotein inhibitors and are likely to be co-administered with ranolazine, a CYP 3A and P-glycoprotein substrate, in subjects with chronic stable angina. The results of the study indicate that the two calcium antagonists in the administered doses inhibited the main eliminatory route of ranolazine via CYP 3A catalyzed metabolism significantly. The observed apparent dissociation between degree of CYP 3A inhibition by the calcium antagonists and systemic plasma concentrations of ranolazine is difficult to interpret. The concentration ratio of substrate to either inhibitor was greater during the faster compared to the slower maintenance infusion and the extent of exposure of CYP 3A to either calcium antagonist during the shorter and faster maintenance infusion may have also differed.

Metabolites

The mean (SD) concentrations of the metabolites and ranolazine in the presence and absence of co-administered diltiazem or verapamil are depicted in the below linear plots:

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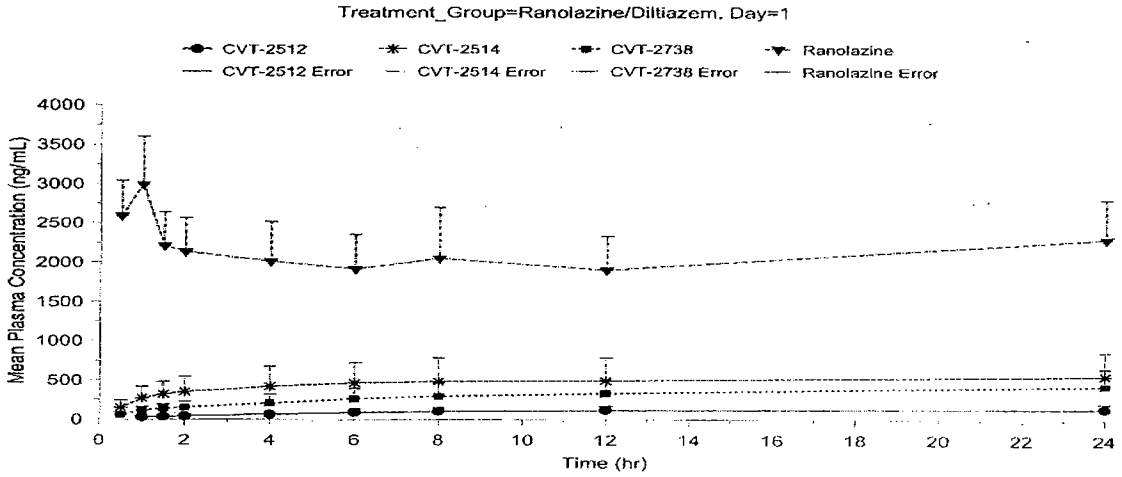
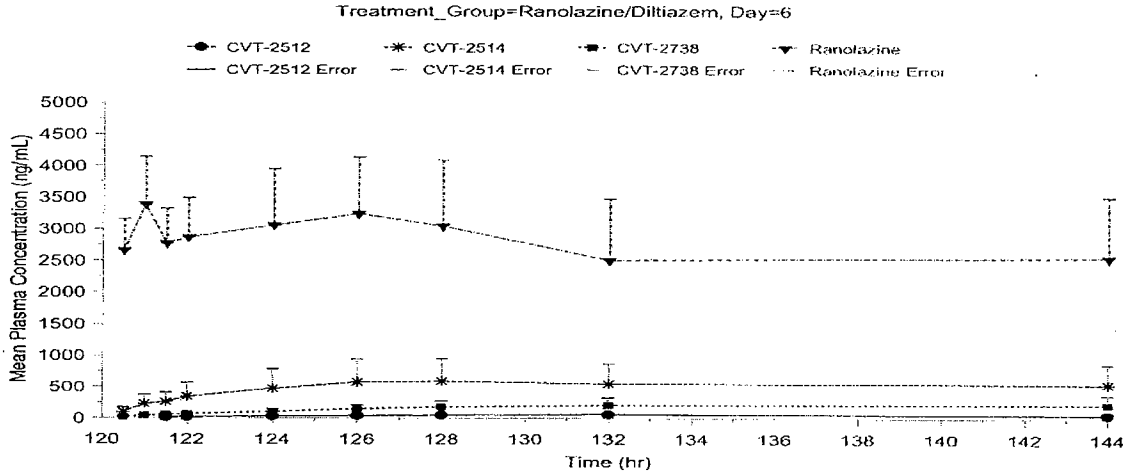
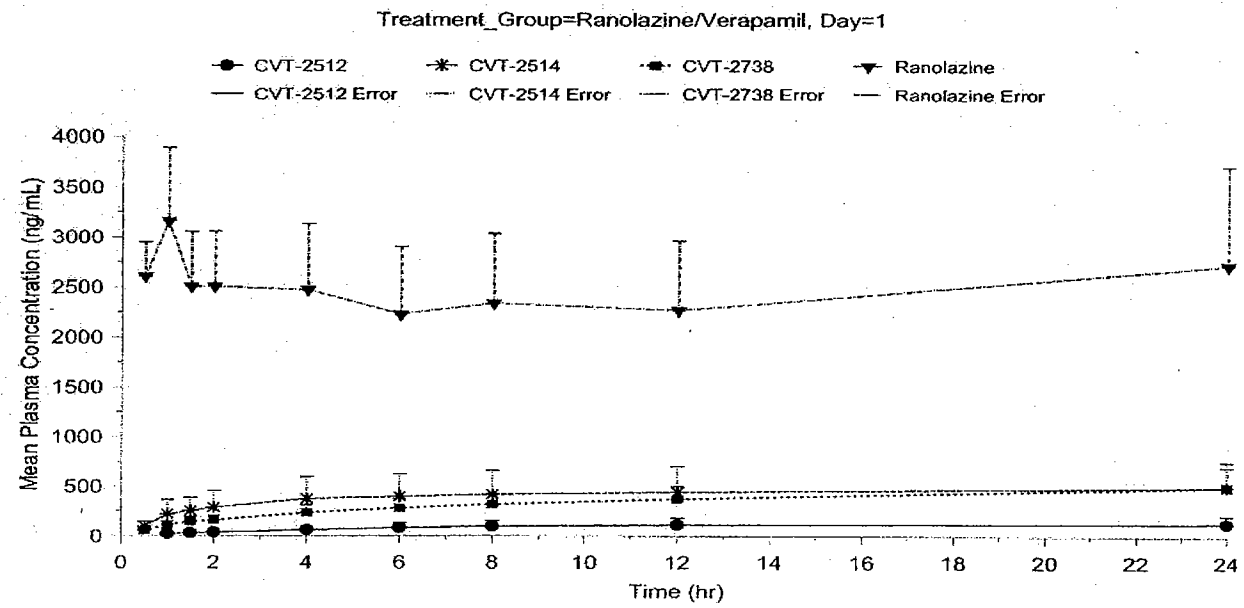
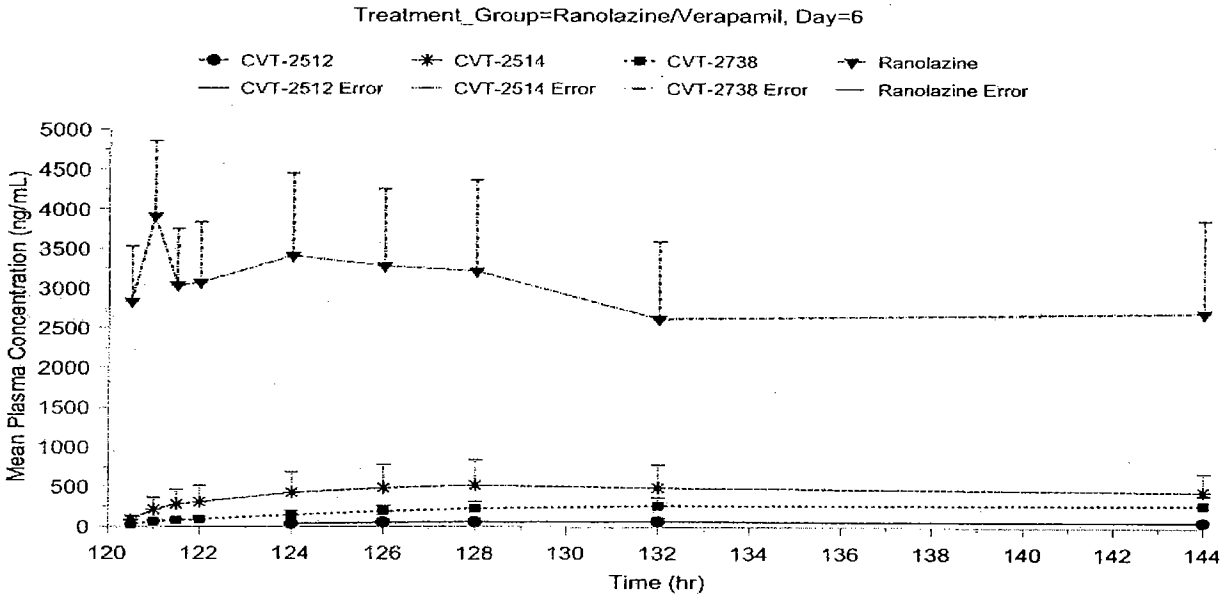
14.3.2 Mean (+SD) Linear Plasma Ranolazine and Metabolite Concentration-time Profiles Following Administration of Ranolazine as an i.v. Infusion Alone and in the Presence of Diltiazem: PK Population Treatment Group A





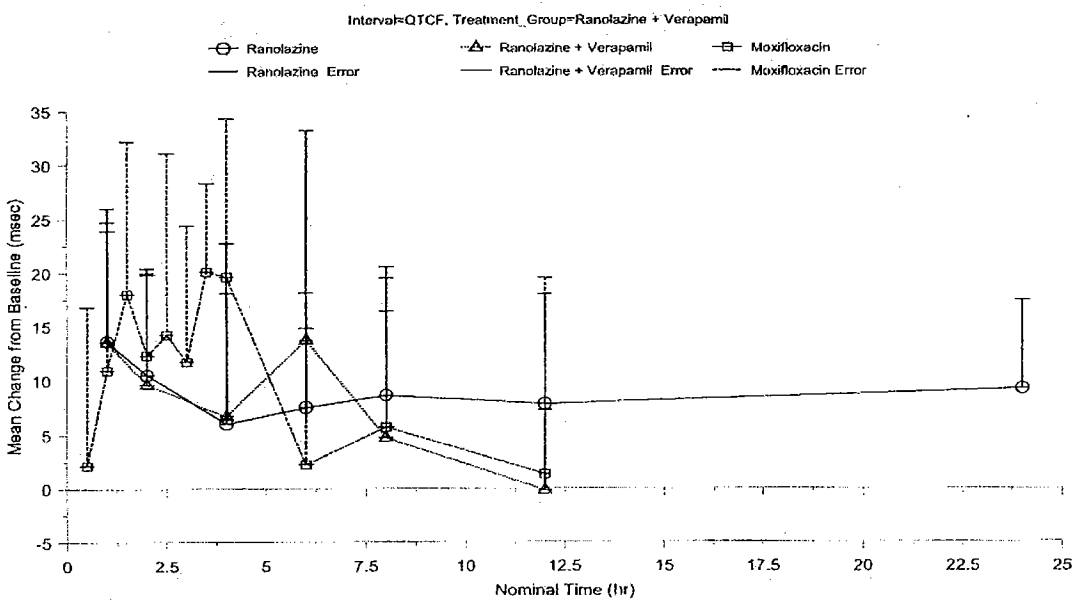
14.3.3 Mean (+SD) Linear Plasma Ranolazine and Metabolite Concentration-time Profiles Following Administration of Ranolazine as an i.v. Infusion Alone and in the Presence of Verapamil: PK Population Treatment Group B





The plots appear to suggest that the plasma concentrations of the metabolite RS-94287 (CVT 2738) generated by the CYP 3A pathway tend to be smaller in the presence of the CYP 3A inhibitors.
The mean QTcF time profiles following treatment with ranolazine alone, co-administration of ranolazine and diltiazem or verapamil and moxifloxacin alone are shown in Figures 5 and 6:

Figure 6: Mean QTcF Values after Administration of Ranolazine, Ranolazine+Verapamil or Moxifloxacin (N = 12)



An increase in mean QTcF of generally < 10 msec was found after ranolazine alone and in the presence of diltiazem or verapamil. After a single dose of 400 mg moxifloxacin the mean QTcF values showed an increase of approximately 10-20 msec for approximately 4-6 hours after administration

In Treatment Group A, an increase from baseline in the mean PR interval by approximately 5 msec was observed at ranolazine plasma concentrations above 2200 ng/mL. The presence of diltiazem appeared not to have an additional effect on the PR interval. In Treatment Group B ranolazine had no consistent effect on the mean PR interval and in the presence of verapamil an increase of 3 to 5 msec was observed.

For both treatment groups the QRS interval remained unchanged.

Within the concentration range studied there was no clear plasma concentration -QTcF effect relationship noticeable.

SAFETY

Ranolazine in Presence and Absence of Diltiazem or Verapamil

The most frequently reported adverse events included dizziness (12/24, 50%), postural hypotension (8/24, 33.3%) nausea (8/24, 33.3%), asthenia (7/24, 29.2%), and headache (7/24, 29.2%). A total of 8 subjects reported 13 postural hypotension events: 5 events occurred after the subject had received ranolazine alone, 4 after administration of both ranolazine and diltiazem, 3 after administration of both ranolazine and verapamil, and 1 after diltiazem alone. For all events, the subjects reported lightheadedness on standing which coded to postural hypotension. In general, postural hypotension lasted for only a few minutes, and in all cases resolved spontaneously, without treatment. For approximately half of the reported postural hypotension events, a blood pressure measurement was not obtained at the time of the event. Of the remaining events, 2 (for subjects 2811 and 2818) were associated with a blood pressure drop of $\geq$ 20 mm Hg and the others had little or no change in blood pressure as the subjects went from the supine to the standing position.

Subject 2809 had a mild vasovagal attack on standing. The event occurred approximately 11 minutes after dosing with the combination of ranolazine and verapamil. During this episode the subject did not loose consciousness. The vaso-vagal symptoms continued for approximately 28 minutes and resolved without intervention. The investigator considered the event related to study medication. Holter monitoring was unremarkable with no recorded arrhythmias.

Subject 2814 withdrew consent on Day 6. The subject had experienced several mild to moderate adverse events including headache, asthenia, dizziness, nausea) throughout the study. None of these events were considered intolerable enough by the investigator to warrant termination from the study.
Twenty-four continuous 12-Lead Holter monitoring performed on Days 1.5 and 6 showed no abnormalities. There were no deaths or other serious adverse events reported.

Two subjects showed mild increases in ALT after concomitant administration of ranolazine and verapamil. Both events were considered possibly related to study medication.

Moxifloxacin

After administration of a single oral 400 mg moxifloxacin dose a total of 8 adverse events were reported by 5 subjects. All were mild and included headache (3/19, 15.8%), nausea (2/19, 10.5%), vomiting (1/19, 5.3%) glycosuria (1/19, 5.3%) and abnormal vision (1/19, 5.3%).

CONCLUSIONS

1. Co-administration of oral formulations of diltiazem 180 mg bid or verapamil 240 mg bid to ranolazine decrease the clearance of ranolazine statistically significantly and clinically relevantly by 52.1% and 44.5% , respectively, during the second slower maintenance infusion.

2. Ranolazine and moxifloxacin appeared to have an effect on QTc. Considering the deficiencies in design of the study (non-randomized cross-over, no placebo, no time matched baseline values) and evaluation of the data (no information how the QT interval was measured) a meaningful quantification of the prolongation of QTc is not possible.

3. The postural hypotension, vasovagal attack and dizziness seen after intravenous administration of ranolazine had been reported after oral administration of ranolazine.

COMMENTS

1. The maintenance infusion rate of ranolazine in the presence of diltiazem or verapamil should have been the same as the maintenance infusion rate of ranolazine in the ranolazine alone treatment. True steady-state concentrations would have been reached faster and more consistently and the levels would have been higher. Interpretation of the kinetics of the inhibition of ranolazine's metabolic clearance by the calcium antagonists would have been easier.

2. Plateau concentrations of ranolazine and the metabolites were identified using subjective judgment by the Pharmacokineticist, instead of testing statistically whether or not a steady-state of the ranolazine concentrations was reached. Therefore, one cannot be sure that the measured values reflect true steady-state concentrations and clearances.

3. The relationship between AEs, particularly hypotension and dizziness, and plasma concentrations of ranolazine and metabolites has not been evaluated.

4. Blood pressure should have been measured by the medical staff of the clinic in all individuals at the time they experienced lightheadedness.

5. The relationship between AEs, particularly hypotension and dizziness, and plasma concentrations of ranolazine and metabolites has not been evaluated.

6. A non-compartment model analysis of the metabolites was performed, but the report did not summarize or discuss the data obtained. Only plots of the mean (SD) plasma concentrations of the metabolites are reported.

7. The protocol does not describe how the QT intervals were determined.

8. The baseline QT values taken prior to the ranolazine treatment on Day 1 were not time matched to those on Day 1 when the subjects received ranolazine.

9. It is unclear what baseline values were used for determining the change in QTc following moxifloxacin treatment.

10. The report does not indicate whether the suitability of the Bazett or Fridericia corrections was tested using the baseline QT values.

STUDY CVT303.010-C ASSESSMENT OF CHANGES IN HEART RATE CORRECTED QT INTERVALS MEASURED IN ELECTROCARDIOGRAMS RECORDED DURING CLINICAL STUDY CVT 3018 SPONSORED BY CV THERAPEUTICS INC.

TECHNICAL REPORT: [ ]

Report No.: CVT 303.010-C

Volume No.: 10, Item 6

OBJECTIVES

The technical report summarizes the methods used and results obtained when analyzing the heart rate and QT interval data measured in ECGs recorded in Study 3018 sponsored by CVT 3018.

CVT 3018 was a study with the goal to investigate the impact of hepatic impairment on the pharmacokinetics of ranolazine and the metabolites RS-88390 and RS-94287. Following an initial dose of 875 mg ranolazine in the morning of Day 1 the participants of the study received a maintenance dose of 500 mg bid starting in the evening of Day 1and ending with the morning dose of Day 3. The subjects were enrolled in 3 study groups: Group 1: 8 subjects (3 females) with mild hepatic impairment, Group 2: 8 subjects (2 females) with moderate hepatic impairment, and Group 3 16 healthy subjects (5 females). Mild and moderate hepatic impairment were defined by the Child-Pugh classification system. The healthy subjects were matched for age, gender and body weight.

AVAILABLE DATA

Twelve Lead 10-second ECGs were obtained in all study participants at screening, at 9 time points on Day -1 (24, 23, 22, 21, 20, 19, 17, 15, and 12 hours before the first dosing), immediately before first dosing, and at 23 time points after dosing (1, 2, 3, 4, 5, 7, 9, 12, 48, 49, 50, 51, 52, 53, 55, 57, 60, 88, 96, 100, 108, and 144 hours after the first dose). In some subjects some recordings were repeated while in some were not available. Altogether, the study involved 1089 ECG recordings.

The ECGs were measured by a central ECG processing laboratory independent of the sponsor. The QT intervals were measured manually using standard paper printouts of the recordings and a computer assisted digitizing board. In each recording, the measurements were obtained in all measurable ECG leads. The author received a spreadsheet listing the heart rates in beats per minute and the duration of the QT interval in every measurable lead for each ECG of the study.

METHODS

For the purpose of the analysis the heart rate values were converted into RR intervals in msec. In 7 ECGs fewer than 9 leads were measured (minimum number of measured leads being 3), 9, 10, 11 and 12 leads were measured in 13 (1.18%), 156 (14.2 %), 412 37.5%) and 500 (45.5 %) ECGs, respectively.

QT Interval Expression

From the individual measurements of QT interval in separate ECG leads, the median QT interval over all measurable leads was selected as the principal QT interval expression characterizing the given ECG. The preference of this QT interval expression was based on independent studies of QT interval distribution across leads of standard 12-lead recordings.

The relationship between the median QT interval recorded at baseline and during treatment and heart rate is shown in Figure 2:

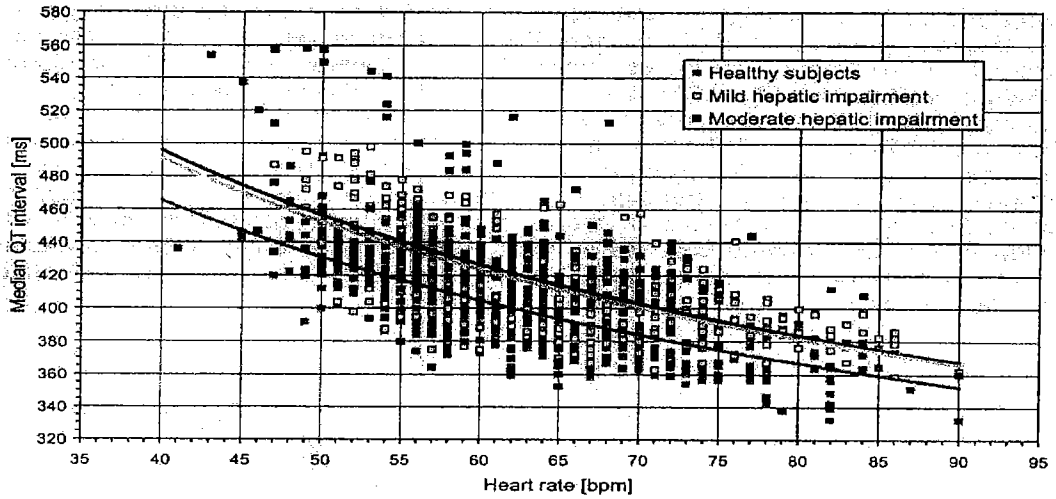


Figure 2: Relationship between median QT interval (principal QT interval expression) and heart rate in all electrocardiograms of the study. The graph also shows exponential regressions between heart rate and QT interval (green – healthy subjects, dark yellow – mild hepatic impairment, brown – moderate hepatic impairment). Although this graph pools baseline (drug-free) and on-treatment recordings together, there are obvious differences between healthy subjects and hepatic patients who have, almost independent of heart rate, the QT interval prolonged by approximately 20-25 ms. Note also that there are minimum differences between the averages of QT intervals in the groups of hepatic patients although the group of moderate hepatic impairment shows a larger variability of the QTc values with some readings of up to 560 ms (at correspondingly low heart rates).

Figure 2 indicates that subjects with hepatic impairment have longer median QT intervals than healthy subjects over the observed heart rate range.

Heart Rate Correction of QT Interval

Previously published and ad hoc developed population formula correcting the QT interval for heart rate were shown to be subject to over- or under correction, particularly if a drug is positive or negative chronotropic. To avoid this well known problem, in a fist step, all drug free QT and RR interval measurements were pooled from all the individual subjects of the study. Then the relationship between the QT and RR intervals was modeled using linear or (more appropriately) non-linear regression analysis, and a heart rate correction was derived from the optimized regression model. Such a heart rate correction formula ensures that drug-free QTc intervals are independent of RR intervals when considering all the subjects of the study together. However, it is well established that the QT/RR interval relationship differs in different individuals. Therefore, it is mandatory to derive the QT/RR relationship in each individual subject. For the determination of the individual QT/RR interval relationship it is important that enough baseline data are available and that the range of RR intervals is sufficiently large.

Regression QT/RR Analysis

The baseline QT/RR data points (screening + Day-1+ zero hour of Day 1) of all subjects individually or in each study group were processed involving 12 different regression models. These models were selected to create a comprehensive spectrum of physiologic plausible patterns of QT/RR relationships reflecting the fact that QT interval adaptation is steeper at faster heart rates and flatter at slower heart rates. The following regression equations were used:

- Linear model $QT = \beta + \chi \times RR$
- Hyperbolic model $QT = \beta + \chi / RR$
- Parabolic log/log model $QT = \beta \times RR^{\chi}$
- Logarithmic model $QT = \beta + \chi \times \ln(RR)$
- Shifted logarithmic model $QT = \ln(\beta + \chi \times RR)$
- Exponential model $QT = \beta + \chi \times e^{-RR}$
- Arcus tangent model $QT = \beta + \chi \times \arctan(RR)$
- Hyperbolic tangent model $QT = \beta + \chi \times \mathrm{tgh}(RR)$
- Arcus hyperbolic sine model $QT = \beta + \chi \times \mathrm{arcsinh}(RR)$
- Arcus hyperbolic cosine model $QT = \beta + \chi \times \mathrm{arccosh}(RR+1)$
- Square root model $QT = \beta + \chi \times RR^{0.5}$
- Cube root model $QT = \beta + \chi \times RR^{0.33}$

For each regression equation the regression residuals were also investigated in order to characterize the closeness of the fit to the QT/RR pattern modelled by the regresion formula. The regression formula that led to the lowest residuals in each subject was considered the optimum regression shape for the purposes of the principal heart rate correction formula.

Each regression type was converted into a specific heart rate correction formula using the following equations derived by appropriate mathematical manipulation:

(A)	Linear	$QTc = QT + \alpha \times (1 - RR)$
(B)	Hyperbolic	$QTc = QT + \alpha \times (1/RR - 1)$
(C)	Parabolic log/log	$QTc = QT/RR^{\alpha}$
(D)	Logarithmic	$QTc = QT - \alpha \times \ln(RR)$
(E)	Shifted logarithmic	$QTc = \ln(e^{QT} + \alpha \times (1 - RR))$
(F)	Exponential	$QTc = QT + \alpha \times (e^{-RR} - 1/e)$
(G)	Arcus tangent	$QTc = QT + \alpha \times (\text{arctg}(1.0) - \text{arctg}(RR))$
(H)	Hyperbolic tangent	$QTc = QT + \alpha \times ((e^2-1)/(e^2+1) - \text{tgh}(RR))$
(I)	Arcus hyperbolic sine	$QTc = QT + \alpha \times (\ln(1+\sqrt{2}) - \text{arcsinh}(RR))$
(J)	Arcus hyperbolic cosine	$QTc = QT + \alpha \times (\ln(2+\sqrt{3}) - \text{arccosh}(RR+1))$
(K)	Square root	$QTc = QT + \alpha \times (1 - RR^{0.5})$
(L)	Cube root	$QTc = QT + \alpha \times (1 - RR^{0.33})$

In each of these formulae the correction parameter α was optimized for the drug free data by solving the equation requiring the Pearson correlation coefficient between the drug free QTc intervals and corresponding RR intervals is 0. In other words the correction parameter α was identified by solving the equation

$$r(RR, QTc(\alpha))=0$$

where $r(\Phi, \Xi)$ is the Pearson correlation coefficient between vectors Φ and Ξ, RR is the vector of all drug free RR intervals, and $QTc(\alpha)$ is the vector of pair-wise corresponding QTc values calculated by the given regression related formula with the parameter α. The equation was solved in double precision by the iterative golden cut algorithm with a target precision of 10^{-15}. In this way each type of regression type satisfies the independence of heart rate corrected QTc intervals of the drug related heart rate changes. Each of these regression based heart rate correction formulae was used to calculate the outcome variables and the results were compared investigating the stability of the QT/RR regression modeling.

Principal and Secondary Analyses

All participants of the study had at least 8 ECG recordings obtained at baseline which is considered a minimum for delineating an individual QT/RR relationship. All study subjects had 11 baseline ECG recordings with the exception of mild hepatic impairment subjects 3353 and 3354 who had both 12 baseline ECG recordings and moderate hepatic impairment patient 3363 who had 13 based ECG recordings. However, with 11 baseline ECG recordings per person for some of the subjects relatively wide confidence intervals were obtained.

Specifically further guidance was obtained from the results of an academic study based on the graphs of the solution of the equation

R (RR,QTc (α))=0 discussed above. The below Figure 4 shows that the correlation r (RR,QTc(1) is in all subjects close to 1 and similarly r(RR,QTC(0)is in all subjects close to-1:

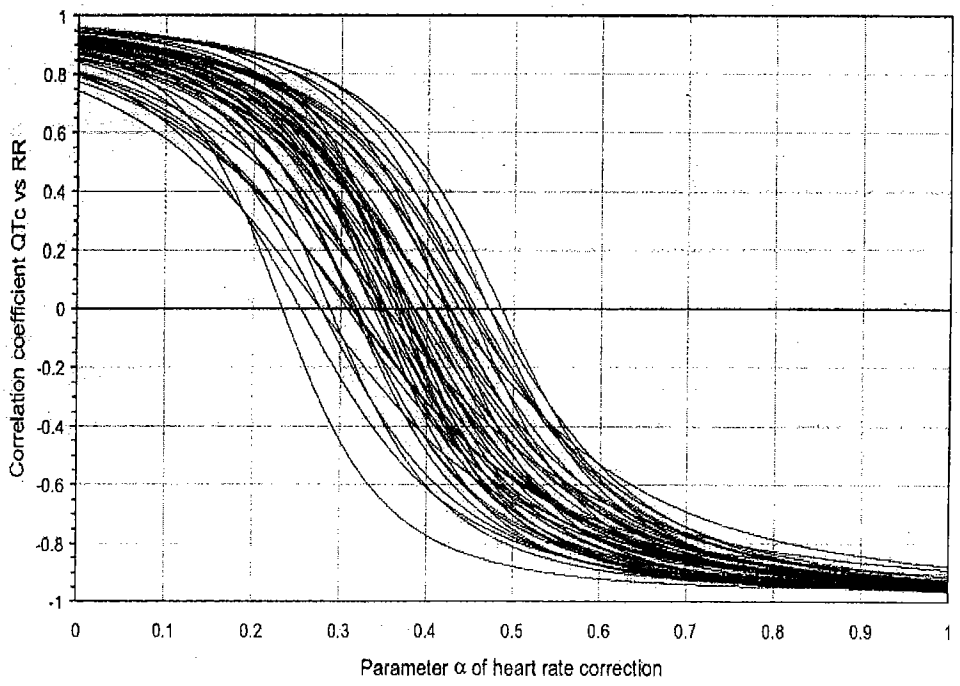


Figure 4: Solution of the individual equations r(RR,QTc(a))=0 of the parabolic log/log model in independent data [3].

From these independent data, additional criteria for the stability of the regressions were developed. For each regression model, the distribution of the r (RR, QTC(0)) and r (RR,QTc(1)) values were obtained. Their respective means were denoted, μ_0 and μ_1, and their respective standard deviations, σ_0 and σ_1 for r (RR, QTc(0)) and r (RR, QTc(1)).

If for a given subject of study CVT 3018, either

$R(RR, QTc(0)) < \mu_0 - 3 \times \sigma_0$

or

$r(RR, QTc(1)) < \mu_1 - 3 \times \sigma_1$

the regression stability of the subject specific data was considered invalid and the correction parameter α for the given subject was replaced by the mean of the valid correction parameters α of the other study participants of the same study group.. The window of 3 SDs of the independent data was designed experimentally using both the data of this study as well as independent data that were available for this purpose.

In addition to this procedure to improve stability, the data specific heart rate correction was also repeated for al baseline data of all study participants pooled together, healthy subjects and patients with hepatic impairment pooled together and patients and healthy subjects pooled together, so that there were the following 4 different modes of defining the specific heart rate corrections of QT:

- Pooled correction for all participants (1 common formula for all participants)
- Healthy subjects and hepatic patients of the study protocol together (1 formula for healthy subjects, 1 formula for hepatically impaired subjects)
- Pooling the data of each individual study group (1 formula each for healthy subjects and patients with mild and moderate hepatic impairment)
- Individual hart rate correction (specific formula for each subject) with the adjustment of the regression validity as described above

As a principal analysis, the individual heart rate correction was used while the other 3 possibilities were considered to document the stability of the regression analysis.

Stability of Heart Rate Correction

In addition to documenting the regression stability, confidence intervals of the equation requiring that the correlation coefficient between RR and QTc data is zero were considered.
In addition to the point estimate α and the lower and upper band of the 95% confidence intervals were determined for the baseline QT and RR intervals for each solution of this equation with all the regression possibilities described above. The correction coefficients α_L and α_U were also used to derive the QTc intervals.

The individual correction coefficients α together with the 95% confidence intervals using the parabolic log/log regression model ($QTc = QT/RR^{\alpha}$) for all individuals and the logarithmic QT/RR regression in one subject are shown in Figures 5 and 6:

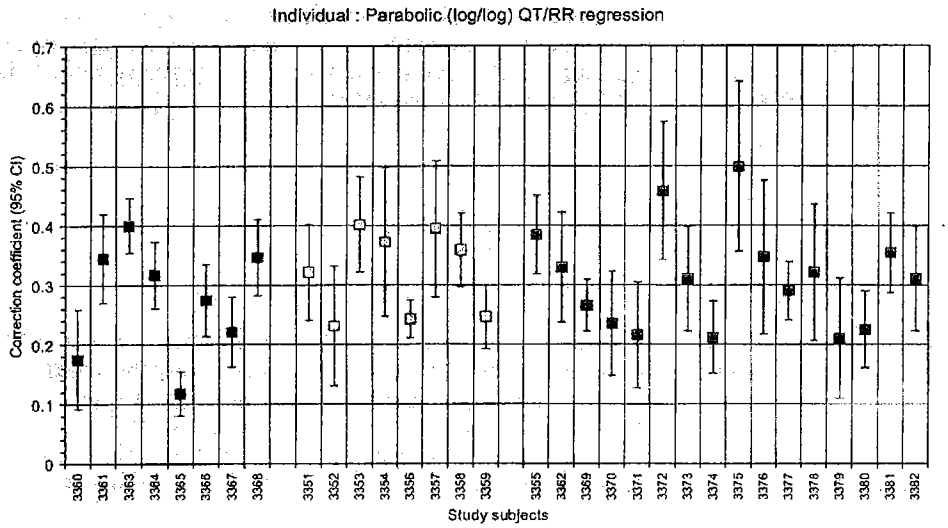


Figure 5. Individual correction coefficients obtained for separate study participants with the parabolic log/log regression model, that is coefficients corresponding to the individually optimised heart rate corrections in the form of $QTc = QT/RR^{\alpha}$. The three groups of the study are distinguished using the colour coding of Figures 1 and 2.

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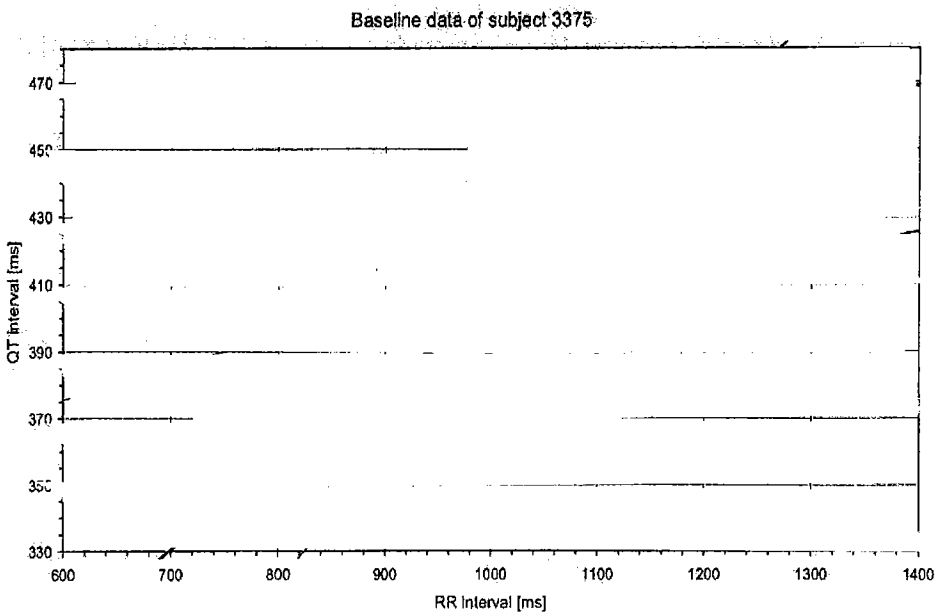


Figure 6: Logarithmic QT/RR regression of drug-free data in healthy female subject 3375. The drug-free QT/RR relationship is reasonably defined.

Optimum Heart Rate Correction

All different QT/RR regression models were considered. The regression residual was evaluated for all 12 linear and nonlinear QT/RR regression models as described. The regression model leading to the lowest regression residual, fitting the QT/RR interval best, was considered the principal data driven heart rate correction. This approach was prospectively defined in the re-analysis plan of the study and the results obtained with this approach applied to the individual heart rate correction in separate study subjects. To study the stability of the optimum QT/RR model, averages of different number of optimum regression models (with the lowest residuals) were also considered. Calculation of the outcome variables of the study was repeated ranging the averaged regression models from 2 to 6.

Outcome Variables and Structure of Results

For each outcome variable (namely RR intervals and different calculations of QTc interval) the following results were obtained:

Scatter diagram of changes from baseline versus ranolazine plasma concentrations

Averages per subject of the changes in the outcome variable per 1000 ng/mL ranolazine plasma concentrations, calculated separately for Day 1 and Days 2 + 3

Pearson correlation coefficients of the changes in the outcome variable versus ranolazine plasma concentrations calculated individually for each study participant and separately for Day 1 and Day 2+3.

Absolute values of the variable summarized per study group calculated per study time-point and per study day

Changes in the outcome variables versus baseline summarized per study group and calculated per study-time-point and per study day

Individual outlier analysis summarizing the changes in the outcome variable per study day in individual participants separately

For each study participant a sequential scatter graph was produced showing the development of ranolazine plasma concentrations together with the development of changes in the outcome variable

For each study participant, a sequential scatter diagram was produced showing the development of changes in the outcome variable versus the ranolazine plasma concentrations

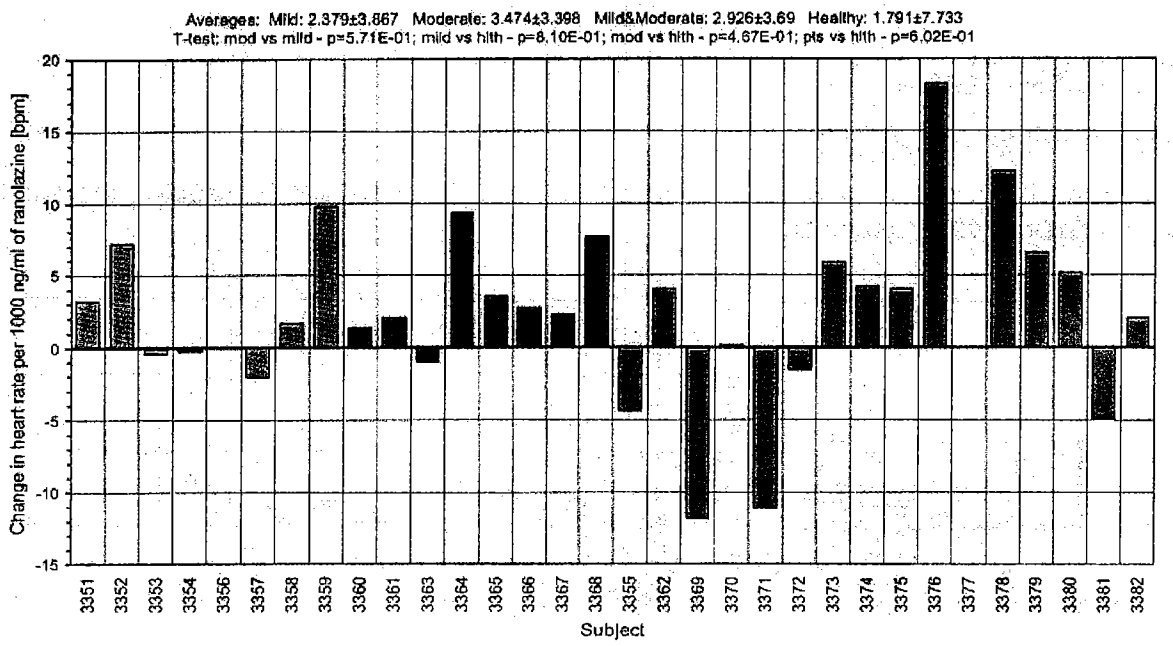
The dependency on ranolazine plasma levels both in terms of individual linear slopes and in terms of Pearson correlation coefficients was statistically tested in the different study groups using the two-sample two-tail t-test. In these comparisons the patients with mild and moderate hepatic impairment were tested together as one group or as separate groups.

RESULTS

Heart rate and RR Interval

Changes in heart rate and RR interval were obtained by subtracting from the baseline values the on-treatment values obtained at corresponding times.

The changes in heart rate and the RR-interval per 1000 ng/mL ranolazine plasma concentration are shown for each individual in the Figures below:


Averages: Mild: 2.379±3.867 Moderate: 3.474±3.398 Mild&Moderate: 2.926±3.69 Healthy: 1.791±7.733
T-test: mod vs mild - p=5.71E-01; mild vs hlth - p=8.10E-01; mod vs hlth - p=4.67E-01; pts vs hlth - p=6.02E-01
Change in heart rate per 1000 ng/ml of ranolazine [bpm]
20
15
10
5
0
-5
-10
-15
3351
3352
3353
3354
3356
3357
3358
3359
3360
3361
3363
3364
3365
3366
3367
3368
3355
3362
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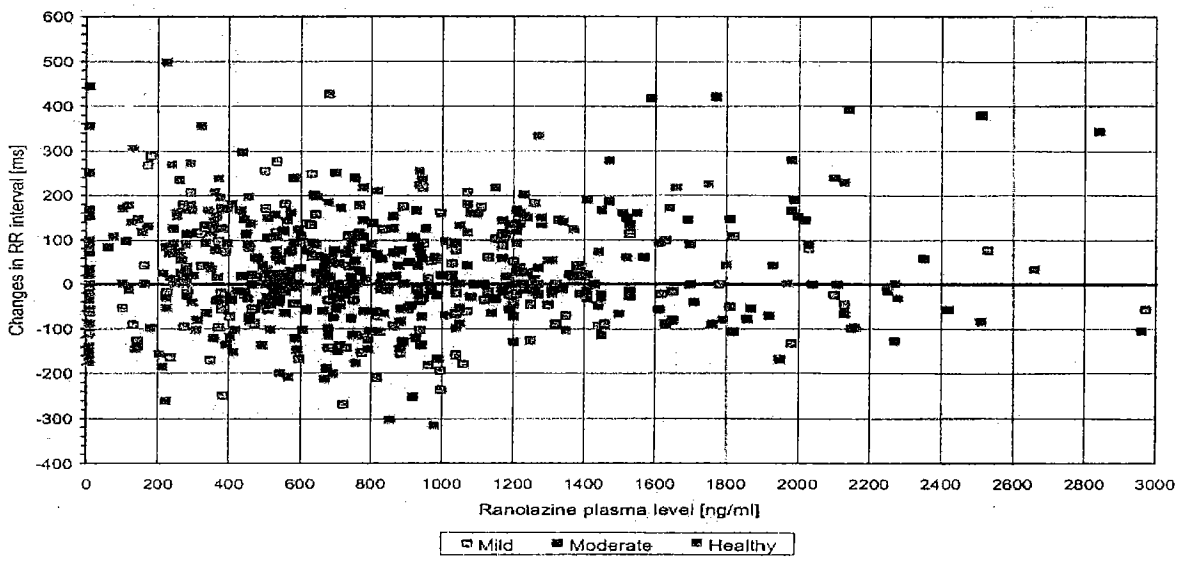
Subject


Changes in RR interval [ms]
600
500
400
300
200
100
0
-100
-200
-300
-400
0
200
400
600
800
1000
1200
1400
1600
1800
2000
2200
2400
2600
2800
3000
Ranolazine plasma level [ng/ml]
Mild
Moderate
Healthy

In most subjects of the three study groups the heart rate increased and the RR-intervals decreased with increasing ranolazine plasma concentrations.

Plots of the mean (SEM) change in heart rate and RR interval versus time for the 3 study groups are shown in Figure 17 below:

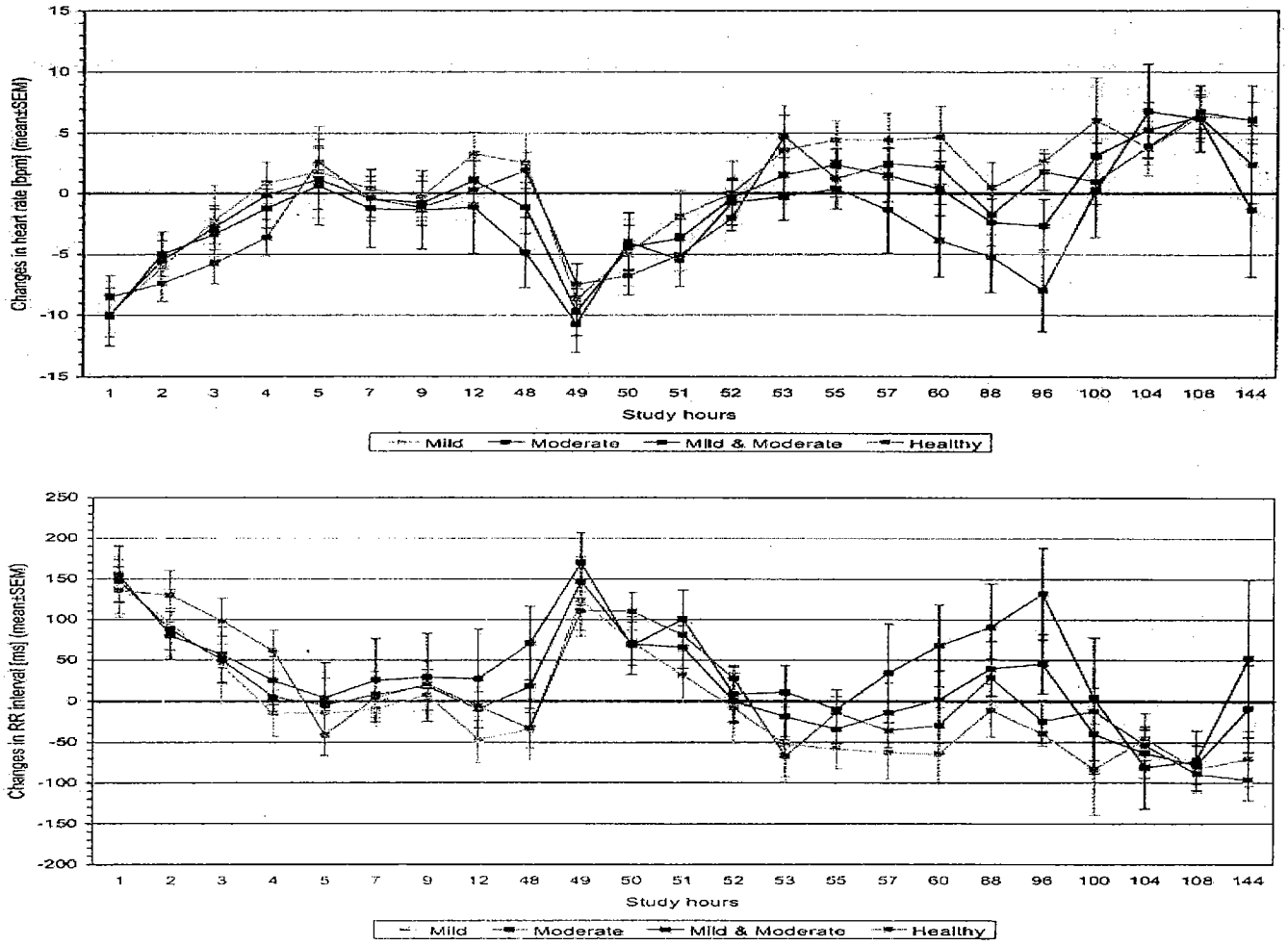


Figure 17: Changes in heart rate (top) and RR interval (bottom) during the on-treatment time-points of the study. The changes were calculated versus the readings on pre-dose Day -1, each on-treatment value was compared with the pre-dose value obtained at the same time of the day.

The plots indicate that the changes in heart rate and RR-interval peak after each drug administration and then decrease to a trough prior to the next dose. The heart rate and RR-intervals during treatment days are lower than during the corresponding times at baseline.

Optimum QTc Analysis

The means (SEM) at each time point and the averages for each treatment day of the absolute individually optimized QTc values for the different study groups are depicted in Figure 18:

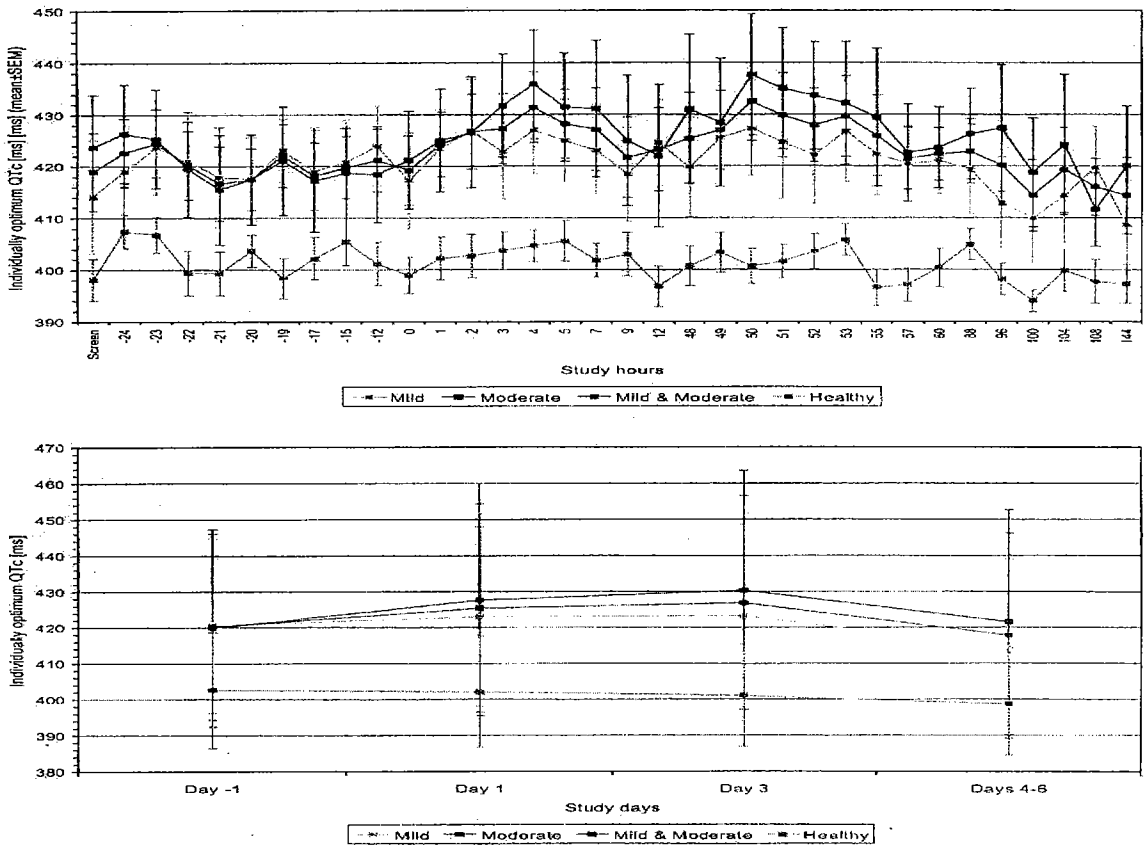


Figure 18. Absolute values of optimally corrected QTc intervals in individual time points of the study (top) and their averages over the individual days of the study (bottom).

The graphs indicate a time dependent increase of the mean absolute individually optimized QTc intervals with peaks after drug administration and trough at the end of the dose interval in all study groups. The mean absolute QTc intervals during the treatment days are larger than at baseline for all study groups. The patients with moderate hepatic impairment display the largest absolute QTc values during treatment. After treatment stop the absolute QTc intervals are approaching the baseline values. The baseline values in the hepatically impaired subjects are larger than in the healthy subjects.

Changes in the QTc interval at each time point during treatment were obtained by subtracting the corresponding values obtained during the baseline phase.
The means (SEM) at each time point and the averages for each treatment day of the change of the individually optimized QTc values for the different study groups are shown in Figure 19:

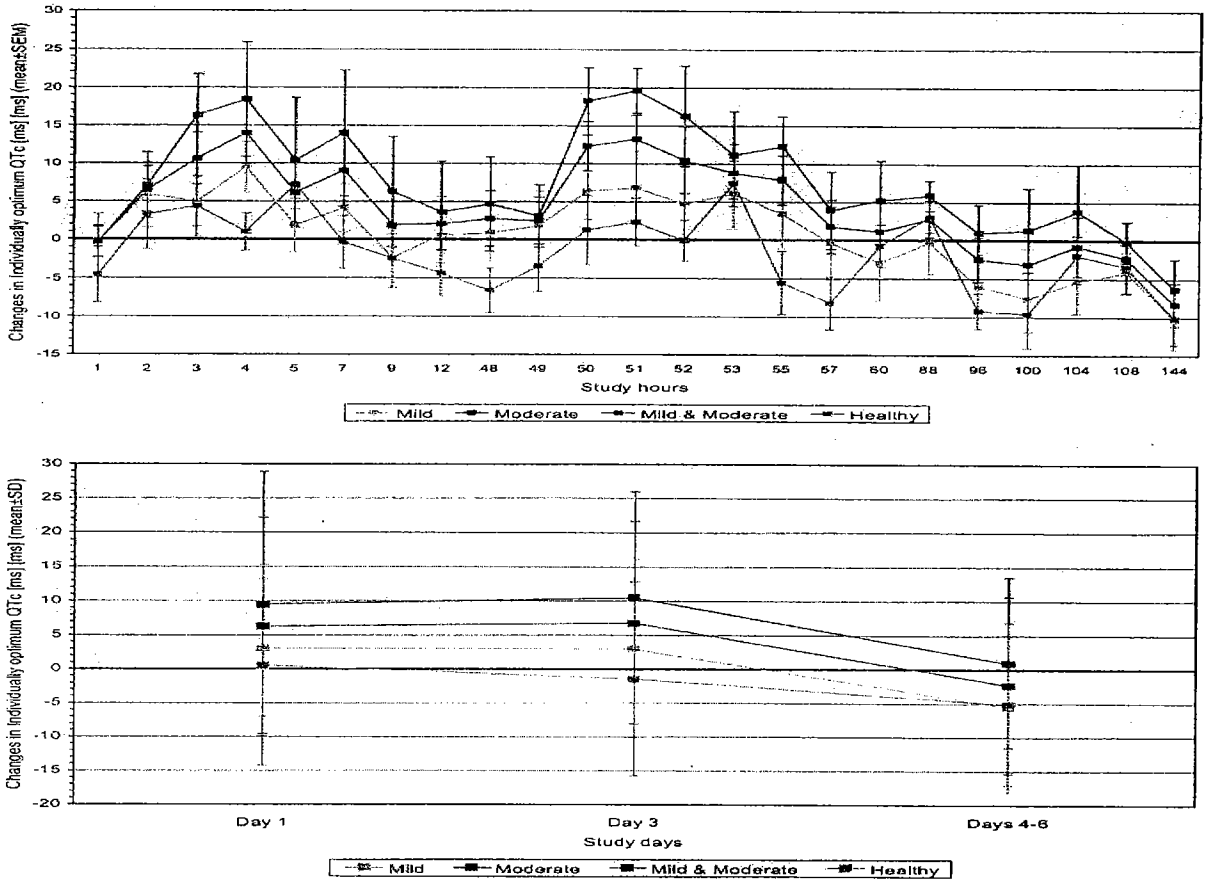


Figure 19. Differences between on-treatment and baseline values of optimally corrected QTc intervals in individual on-treatment study points (top) and their averages over study days (bottom). The changes were calculated versus the readings on pre-dose Day -1, each on-treatment value was compared with the pre-dose value obtained at the same time of the day.

The mean (SEM) changes of the individually optimized QTc intervals for each of the study participants are shown in Figure 20:

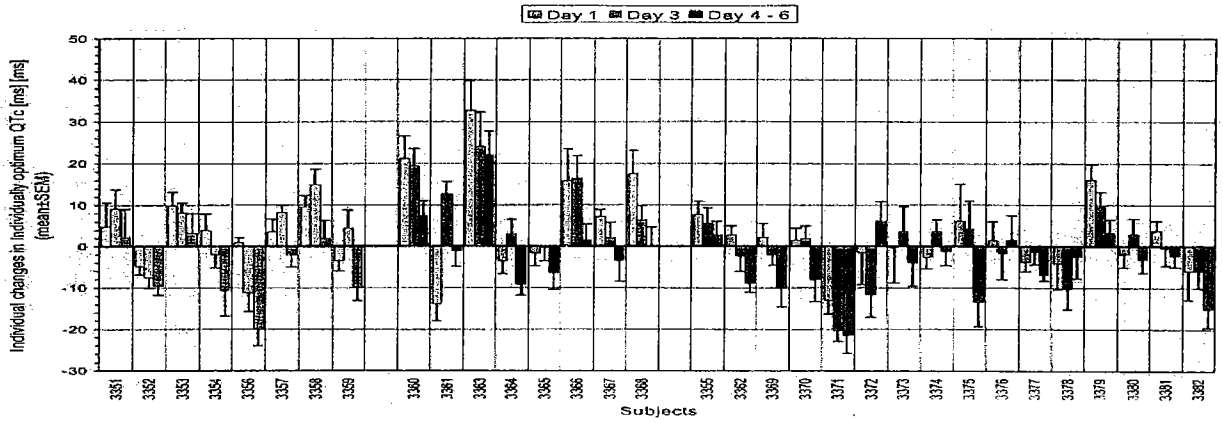


Figure 20. Individual changes in optimally corrected QTc value in separate study participants. The group of healthy volunteers is shown in green, the group of patients with mild hepatic impairment in yellow and the group of patients with moderate hepatic impairment in red. Days 1, 3 and 4-6 of the study are shown in light, middle shaded and dark colour, as indicated in the legend. Note that only in one patient with moderate hepatic impairment has the threshold of 30 ms QTc prolongation been reached systematically (all these changes are below 35 ms prolongation). Group of subjects 3351-3359 (left part of the figure) contains patients with mild hepatic impairment, group of subjects 3360-3368 (middle part of the figure) contains patients with moderate hepatic impairment, and group of subjects 3355-3382 (right part of the figure) contains healthy individuals.

A scatter diagram of the changes in the individually optimized QTc intervals versus the ranolazine plasma concentrations and the mean (SEM) changes in the individually optimized QTc intervals per 1000 ng/mL ranolazine plasma concentration in each study participant are shown in Figures 21 and 22:

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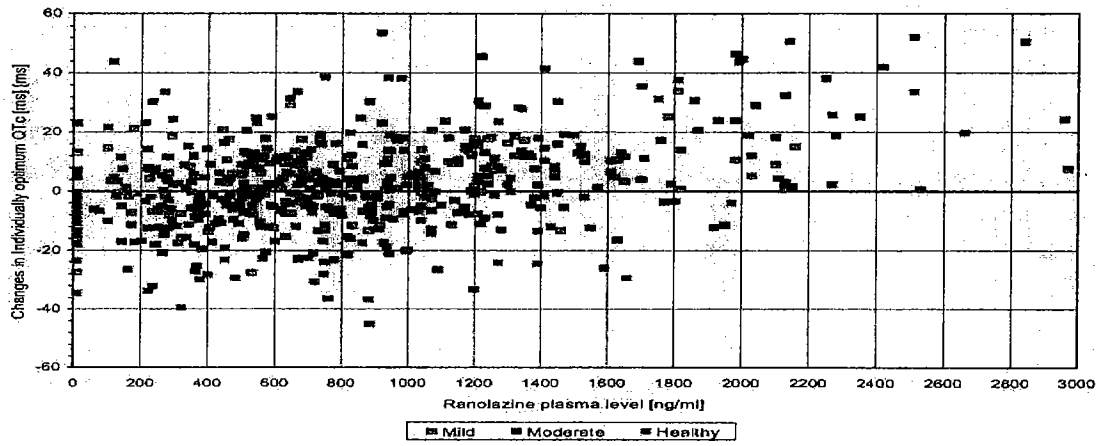

Figure 21. Scatter diagram of individual QTc changes versus ranolazine plasma levels.

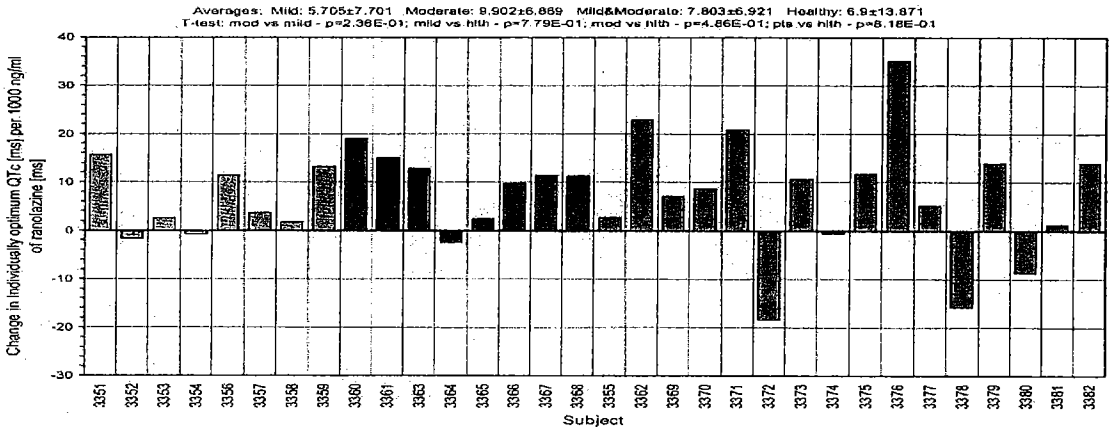

Figure 22. Individual changes in optimally corrected QTc interval per 1000 ng/ml of ranolazine plasma levels. Patients with mild hepatic impairment are shown in orange, patients with moderate hepatic impairment in red, and healthy subjects in green.

The salient findings on the change in the individually optimized QTc intervals included that they were largest in the patients with moderate hepatic impairment followed by the patients with mild hepatic impairment and the healthy subjects. The changes in QTc subsided on Days 4-6 values in the 3 study groups. All changes in QTc were below 60 msec and changes between 40 and 60 msec occurred with one exception in patients with moderate hepatic impairment. The one exception was a healthy volunteer who displayed a prolongation of the QTc interval of more than 40 msec at a low ranolazine plasma concentration suggesting that the ECG recording or interpretation was imprecise. For most of the subjects there appeared to be a correlation between change in QTc and ranolazine plasma concentrations. The serial changes in QTc and ranolazine plasma concentrations were not systematic in all subjects and a hysteresis in the relationship cannot be excluded.

A plot of the Pearson correlation coefficients obtained in the correlating QTc changes and ranolazine plasma concentrations are shown in Figure 25:

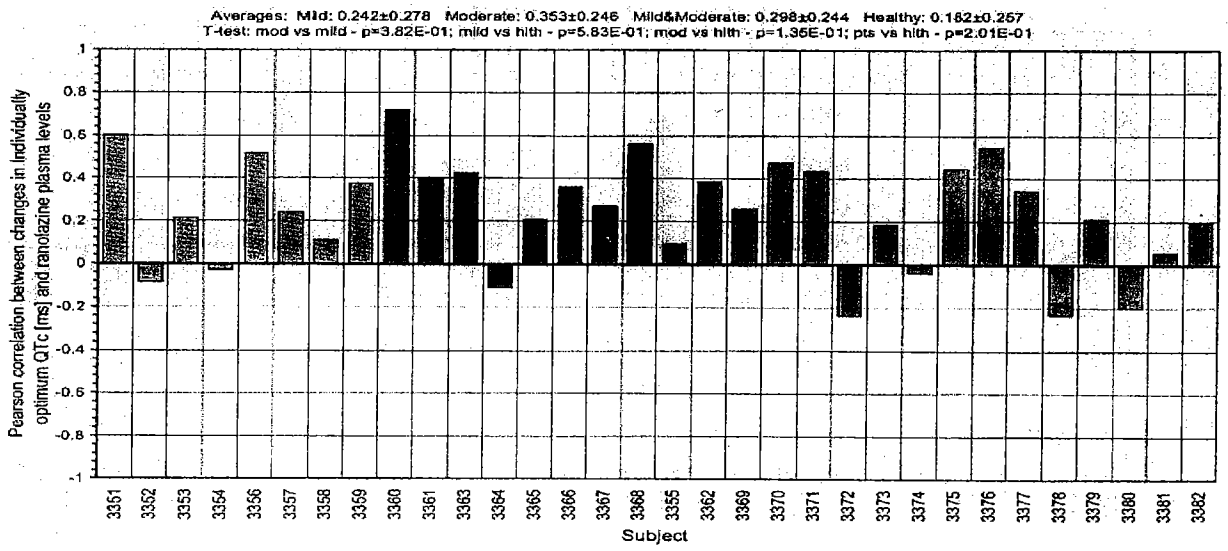

Figure 25. Pearson correlation coefficient between QTc changes and ranolazine plasma levels in individual study participants. Patients with mild hepatic impairment are shown in orange, patients with moderate hepatic impairment in red, and healthy subjects in green.

The Pearson correlation coefficients range between -0.022 and +0.72.

Analysis Based on Pooled QTc Corrections

A comparison of the QTc changes observed for the study groups when individually optimized and "pooled" optimized corrections were performed are shown in Table 2:

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QTc analysis	Moderate HI	Mild HI	Healthy subjects
Total pooled	10.17 ± 7.63	6.87 ± 7.61	6.97 ± 12.64
Healthy + HI pooled	9.79 ± 7.92	6.60 ± 7.49	7.04 ± 12.54
Group pooled	6.37 ± 10.74	8.59 ± 8.44	7.04 ± 12.54
Individual	9.90 ± 6.87	5.70 ± 7.70	6.90 ± 13.87

Table 2: Averaged QTc increases (in ms) per 1000 ng/ml of ranolazine plasma levels obtained with different QTc analyses (see Figures 22 and 32 – 34 for details). HI = hepatic impairment.

It can be seen that the difference in the values between healthy subjects and hepatic patients for the "pooled" optimized estimates for the QTc changes is larger than with the individually optimized estimates. The author has seen such a trend with other data.

Stability Analysis

Figures 38-40 show the mean (SEM) changes in the individually optimized QTc intervals with the lower and upper confidence limit of the correction in the upper and lower panel, respectively: A comparison of the results obtained in Figures 38-40 (corrected) and Figures 19 -21 (uncorrected) indicates only small differences:

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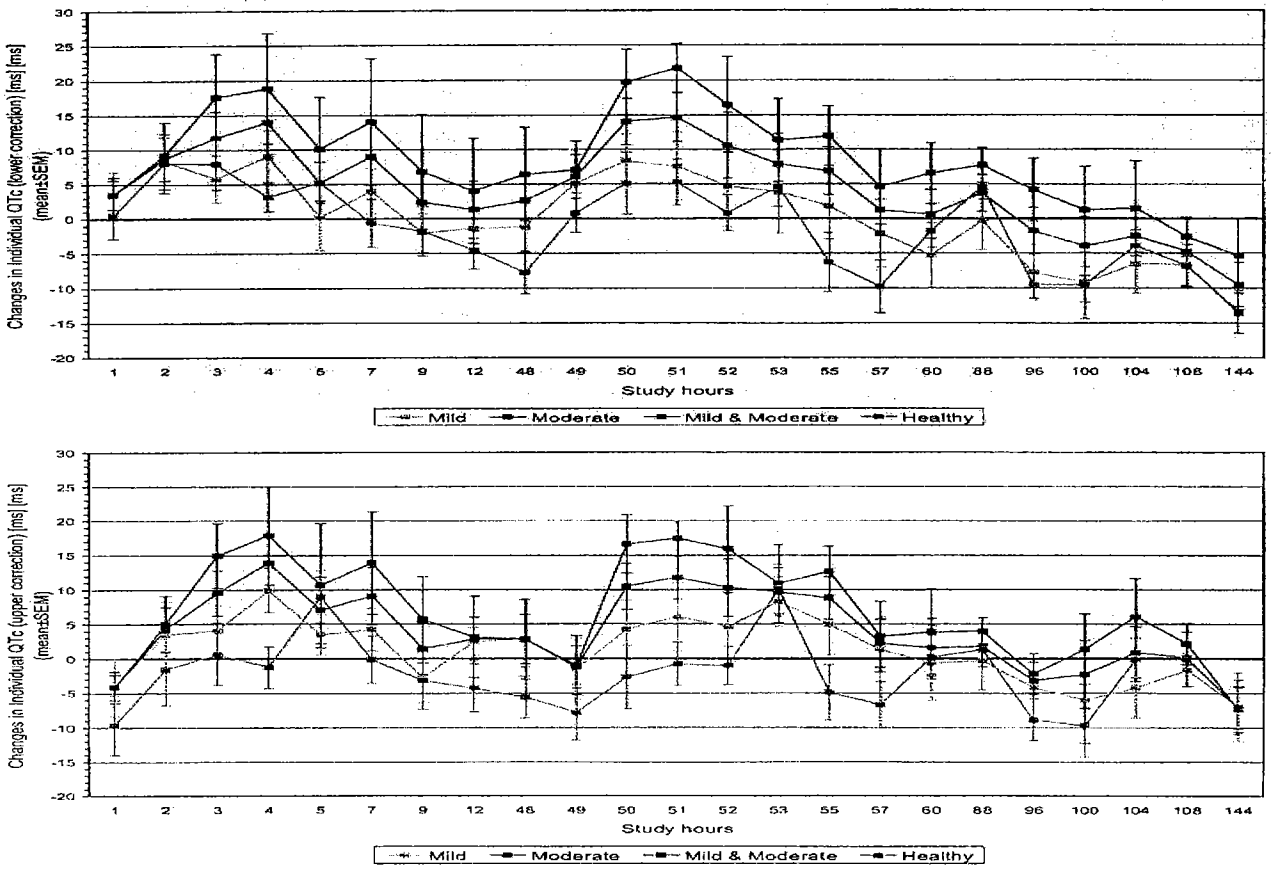

Figure 38: Differences between on-treatment and baseline values of study in individually corrected QTc intervals (lower and upper confidence limit of the correction in the upper and bottom panel, respectively) in individual on-treatment study points. Compare to Figure 19 and note that the differences are truly minimal.

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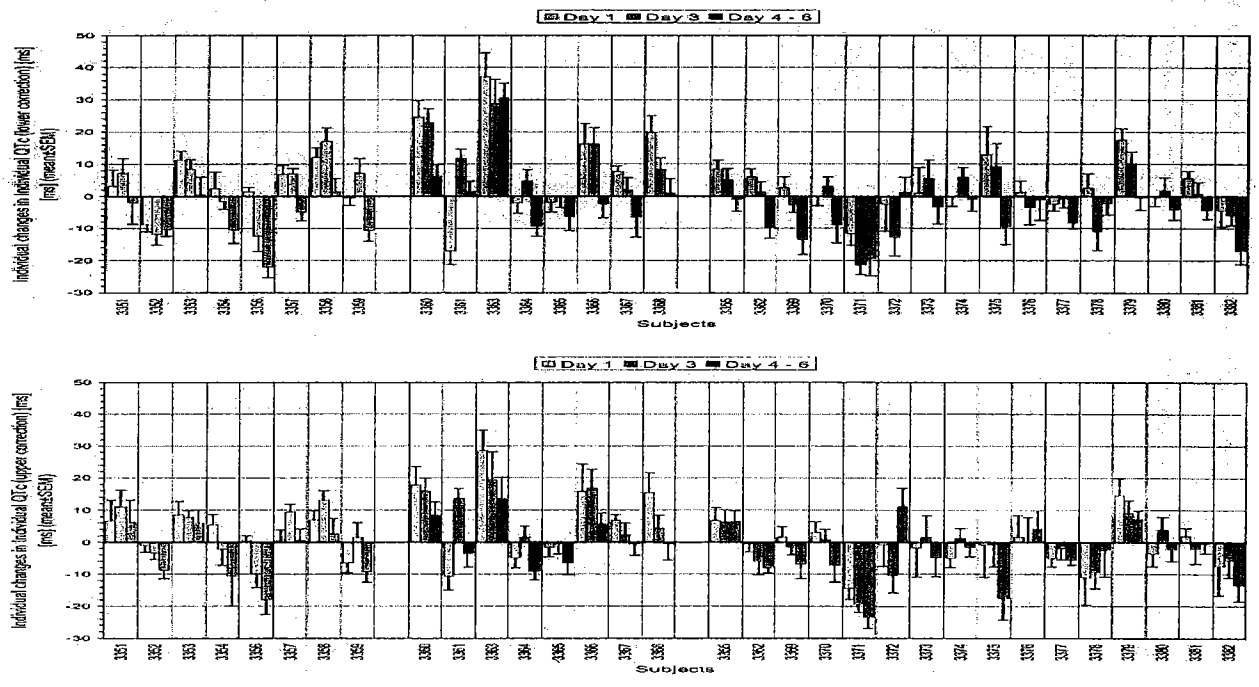

Figure 39: Individual changes in optimally corrected QTc value (lower and upper confidence limit of the correction in the upper and bottom panel, respectively) in separate study participants. Layout and colour coding as in Figure 20. Compare with Figure 20 and note that the differences are truly minimal.

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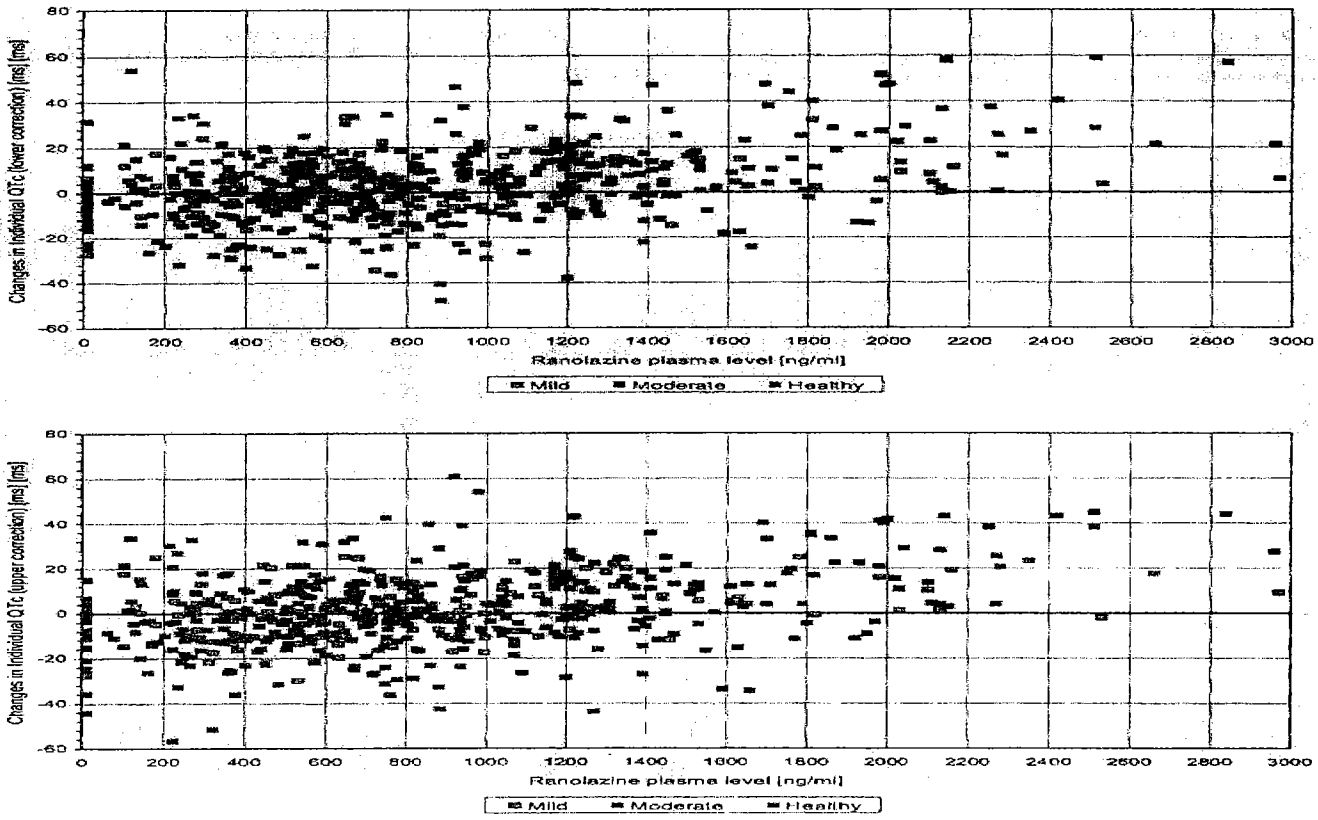


Figure 40. Scatter diagram of individual QTc changes (lower and upper confidence limit of the correction in the upper and bottom panel, respectively) versus ranolazine plasma levels. Compare with Figure 21 and note that neither of the confidence limits of the individual correction leads to any truly significant substantial outliers in terms of QTc prolongation in individual recordings of the study.

CONCLUSIONS

Study CVT 3018 was not designed to allow a detailed analysis of the QTc with the precision achievable in thorough QTc studies. The number of ECG recorded in the subjects participating in study CVT 3018 was not high The recordings were paper traced and thus the accuracy of the measurements was not as high as that from electronically stored data.

Despite these limitations the following conclusions can be drawn:

The difference in the QTc change between patients with mild hepatic impairment and healthy volunteers are not substantial. In both groups the individual mean increases were well below the upper limit of 20 msec as shown in Figure 19. This was despite the higher baseline QTc values in the patients with mild hepatic impairment compared to the healthy subjects. This finding suggests that the QTc prolongation in patients with mild hepatic impairment is as marginal as in healthy subjects.

The increase in QTc is more expressed in patients with moderate hepatic disease, although the baseline QTc interval in patients with mild and moderate hepatic disease were comparable as shown in Figure 2. Hepatic disease is known to increase the risk of drug induced QTc prolongation.

The range of concentrations was limited to very few observations above 1600 ng/mL. The correlation coefficient between QTc changes and concentrations of ranolazine in the healthy volunteers was generally low and variable. Extrapolations to changes in QTc at higher plasma concentrations should not be made. The changes in the QTc interval found in the present study should also not be compared with those obtained in other studies in which the study subjects received higher doses.

COMMENTS

The reanalysis of the data by the sponsor found no important difference in the QTc to ranolazine plasma concentration relationship between healthy subjects and patients with mild hepatic impairment. This was in contrast to the results of the analysis by the Agency which found a significant difference in the slope of the QTc to ranolazine plasma concentration relationship for patients with mild hepatic impairment and healthy subjects.

The reason for this discrepancy is not obvious. However, the following may be contributing factors:

The analysis by the Agency used data from 1827 subjects (327 healthy volunteers and 16 patients with and 1484 patients without overt hepatic impairment), whereas the sponsor's reanalysis used the data from CVT study 3018 only.

The analysis by the Agency used the maximum QT interval from all measurable leads, whereas the sponsor in the reanalysis used the median QT interval of all measurable leads. It is noteworthy that the sponsor in the original submission also had used the maximum QT intervals of all measurable leads.

If the correction of QT for RR was not optimal, the sponsor in the reanalysis replaced such data with by the mean correction parameter of that study group.

The sponsor's reanalysis report ought to clarify the following points:

Method of determining slope of the correlation between QTc and ranolazine plasma concentrations

The results of the two-sample two-tail t-test mentioned on p. 18 are not provided

It is unclear whether the use of independent data is appropriate for determining boundaries for the correlation coefficient r for the data of study CVT 3018. Are the independent data used comparable to those of study CVT 3018? For example did the independent data also show a dependency of the heart rate on drug concentration?

p. 13: It is unclear what is meant by the correction coefficients α_L and α_U

p. 18, third paragraph: It is unclear what is meant by "calculation of the outcome variables of the study was repeated ranging the averaged regression models from 2 to 6"

p.18: the first sentence of the last paragraph does not make sense:"The dependency on ranolazine plasma levels (both in terms of individual linear slopes and in terms of Pearson correlation coefficients) was statistically summarized and tested between different study groups using two-sample two-tail t-test assuming the difference of variabilities of the compared samples"

p.20: It is not clear what is meant by the label of the y axis of Figure 20 "individual changes of individually optimum QTc (ms) (ms) (mean±SEM)"

The majority of the references listed in the list of references 4 are not mentioned in the text

p.18: 1000 mg/nl should read 1000 ng/mL

6. STUDY CVT303.010-C: PHARMACOMETRIC REVIEW BY DR. A. BHATTARAM

Background

CV Therapeutics submitted re-analysis of assessments of changes in heart rate corrected QT intervals measured in electrocardiograms recorded during clinical study, CVT 3018. The analysis was performed by [ ] The primary reviewer analyzed the data originally submitted in NDA 21526 (2003) and concluded that subjects with mild and moderate impairment have larger increase in QT prolongation compared to normal subjects. The current submission however states that the degree of QT prolongation is similar in mild and normal subjects. The submission also concludes that subjects with moderate hepatic impairment show higher QT prolongation in comparison to mild and normal subjects. The aim of this review is to

1. Address the discrepancy between the sponsor's and the Agency's analysis.
2. Address any labeling issues for patients with either mild or moderate hepatic impairment.

The sponsor did not propose any specific dosing recommendations in patients with mild or moderate hepatic impairment based on benefit/risk ratio.

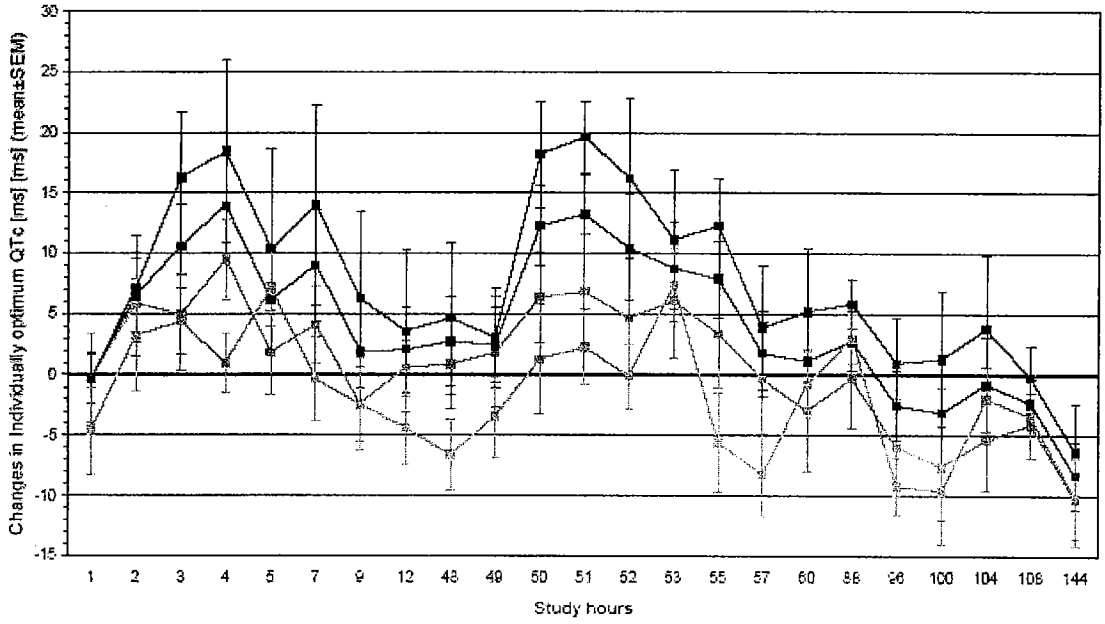
Differences between Sponsor's and Agency's Analysis

The following table highlights the differences in the analysis of data by the sponsor and the reviewer.

	Sponsor	Reviewer
Data	Used median of QT interval of all measurable leads for study CVT 3018	Used maximum QT interval of all measurable leads. (Note: This data was submitted by the sponsor originally in 2003). Analysis was done on maximum QT interval as it was submitted in 2003 using the entire database.
Model	Developed heart rate correction formula for each individual by fitting each individual's data to a family of 12 regression models.	Used a linear model (based on diagnostics) with mixed effects modeling to estimate parameters that would correct for changes in heart rate.

Sponsor's Analysis

As mentioned in the table above sponsor used a family of regression curves to optimize heart rate correction. The sponsor also used median value of the QT data collected on the 12 leads. The previous data submitted by the sponsor used the maximum of the 12 leads in the analysis. In cases where correction between QT and RR was not optimal, the sponsor replaced the data by the mean of the correction parameters of the study group. It is unclear what would be the impact of these factors on the overall conclusion. The absolute values of optimally corrected QTc intervals in individual time points of the study and their averages over the individual days of the study are shown in Figure 1 below:


Changes in Individually optimum QTc [ms] [ms] (mean±SEM)
30
25
20
15
10
5
0
-5
-10
-15
1
2
3
4
5
7
9
12
48
49
50
51
52
53
55
57
60
96
100
104
108
144
Study hours

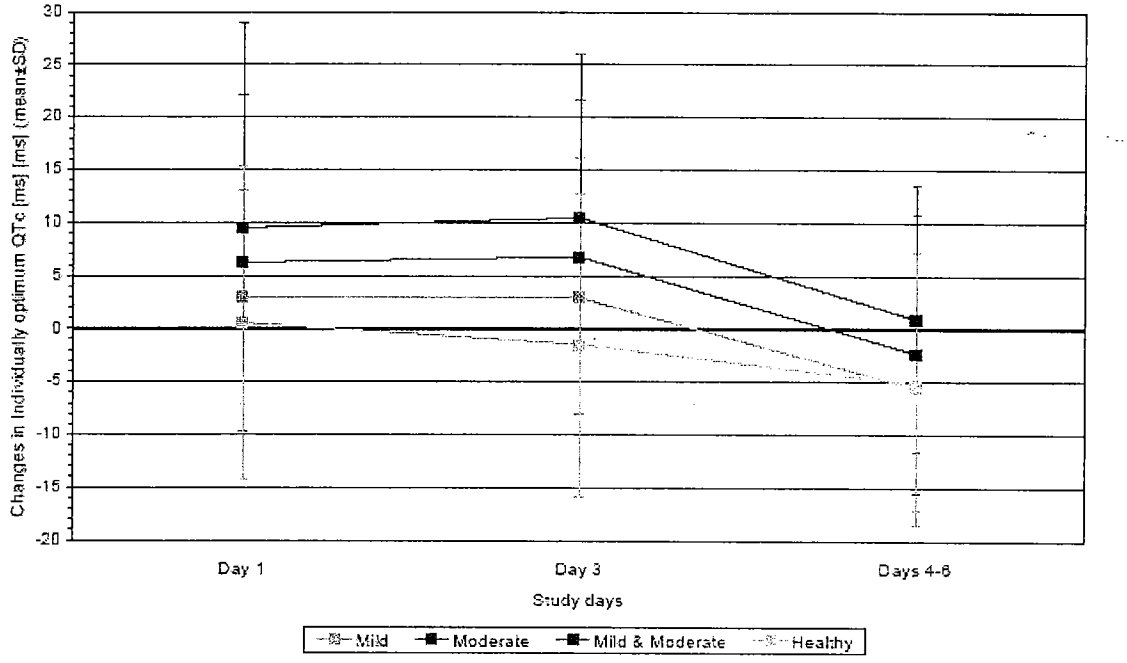

Changes in Individually optimum QTc [ms] [ms] (mean±SD)
30
25
20
15
10
5
0
-5
-10
-15
-20
Day 1
Day 3
Days 4-6
Study days
Mild
Moderate
Mild & Moderate
Healthy

Figure 1. Differences between on-treatment and baseline values of optimally corrected QTc intervals in individual on-treatment study points (top) and their averages over study days (bottom). The changes were calculated versus the readings on pre-dose Day -1, each on-treatment value was compared with the pre-dose value obtained at the same time of the day.

Reviewer's Analysis

Methodology

The data from study CVT 3018 was appended to database (all_qtc_sub2) used by sponsor for QTc analysis. A total of 17858 observations from 1827 individuals were used in the analysis.

A two-stage (1) Estimation of Correction factor followed by (2) Estimation of Concentration-QTc prolongation relation was used for describing the ΔQTc (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 jth QT interval of the ith patient, similarly α_i is the corrected QT and RR is the RR interval and βi is the exponent coefficient of the ith 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).

A linear model with and without threshold concentrations were fitted to the data.

Covariate Analysis

The significance of hepatic impairment was evaluated on the slope of concentration-QTc relationship using the model shown below:

H1=0

IF(HEP.EQ.0) H1=1

H2=0

IF(HEP.EQ.1) H2=1

H3=0

IF(HEP.EQ.2) H3=1

HEP1=H1*THETA(2)+H2*THETA(3)+H3*THETA(4)

TVIN=THETA(1)

TVSL=HEP1

TVPL=THETA(5)

Statistical 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.

The final parameter estimates are shown in Table 1.

Table 1. Summary of Covariate Analyis of Hepatic Status

Model	Slope (msec/1000 ng/mL)	OBJ	Δ OBJ
Base (No Covariates)		107605.25	
SLP~HEPATIC Normal Mild Moderate	 2.56 6.62 7.42	107579.00	-26.25
SLP~HEPATIC Normal Mild + Moderate	 2.56 7.10	107579.56	-25.69

Agreement between FDA and Sponsor's Analysis

Independent analyses by the sponsor and the FDA do suggest that moderate hepatic impairment do exhibit greater increases in QT prolongation. It is not known why patients with moderate hepatic impairment have greater QT prolongation.

Should ranolazine be administered in patients with mild or moderate hepatic impairment?

Based on the mixed effects analysis undertaken by the reviewer, it is not recommended to administer ranolazine in patients with mild or moderate hepatic impairment.

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DISSOLUTION

Dissolution Specifications

Based on dissolution results obtained with additional batches the sponsor proposes modifications of the dissolution specifications for the 500 mg ER tablets as follows:

Time (h)	Current Acceptance Criteria	Proposed Acceptance Criteria
0.5	[redacted]	same as current
4.0	[redacted]	[redacted]
12.0	[redacted]	delete
20.0	NLT [redacted]	same as current

Deletion of the 12 hour value ([redacted] dissolved) in the dissolution specifications proposed by the sponsor would result in accepting formulations with [redacted] dissolution at 5 hours. Drug delivery by such a formulation would profoundly alter the plasma concentration profile of ranolazine. Thus, the dissolution specifications recommended earlier by the Agency should be maintained.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21526 Resubmission	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	Dosage Form	SR tablets 500 mg
		Dosing Regimen	500 mg, 1000 mg bid
Date of Submission	7/26/05	Route of Administration	Oral
Estimated Due Date of OCPB Review	11/30/05	Sponsor	CVTherapeutics
PDUFA Due Date	1/26/06	Priority Classification	Standard
Division Due Date	11/30/05		

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:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	2	2	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:	X	1	1	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	X	1	1	
PD:				
Phase 2:				

Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	1	1	
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**5**	**5**	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable.

QBR questions (key issues to be considered)	**Relationship between QTc and ranolazine plasma concentrations in patients with mild hepatic impairment**
Other comments or information not included above	
Primary reviewer Signature and Date	**Peter Hinderling, 11/24/05**
Secondary reviewer Signature and Date	**Patrick Marroum ,11/24/05**

CC: NDA 21-526, HFD-850 (Lee), HFD-110 (Targum), HFD-860 (Marroum, Mehta, Hinderling), CDR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Peter Hinderling
11/28/2005 12:42:21 PM
BIOPHARMACEUTICS

Atul Bhattaram
11/29/2005 10:00:31 AM
BIOPHARMACEUTICS

Jogarao Gobburu
11/29/2005 12:44:29 PM
BIOPHARMACEUTICS

Patrick Marroum
11/30/2005 09:18:51 AM
BIOPHARMACEUTICS

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:

Condition	FDA Recommendation
Dissolution Medium	0.1N HCl
Paddle Speed	— rpm
USP Apparatus II	
Volume	[illegible] mL
Specifications	0.5 h: [illegible]
	4.0 h: [illegible]
	12.0 h: [illegible]
	20.0 h: NLT [illegible]

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 mean 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 1.5 fold 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 1.5 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 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 10^{th} and 90^{th} 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.

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 reviews. The 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 Cmax 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 1.6 and 2.3. 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 α1-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

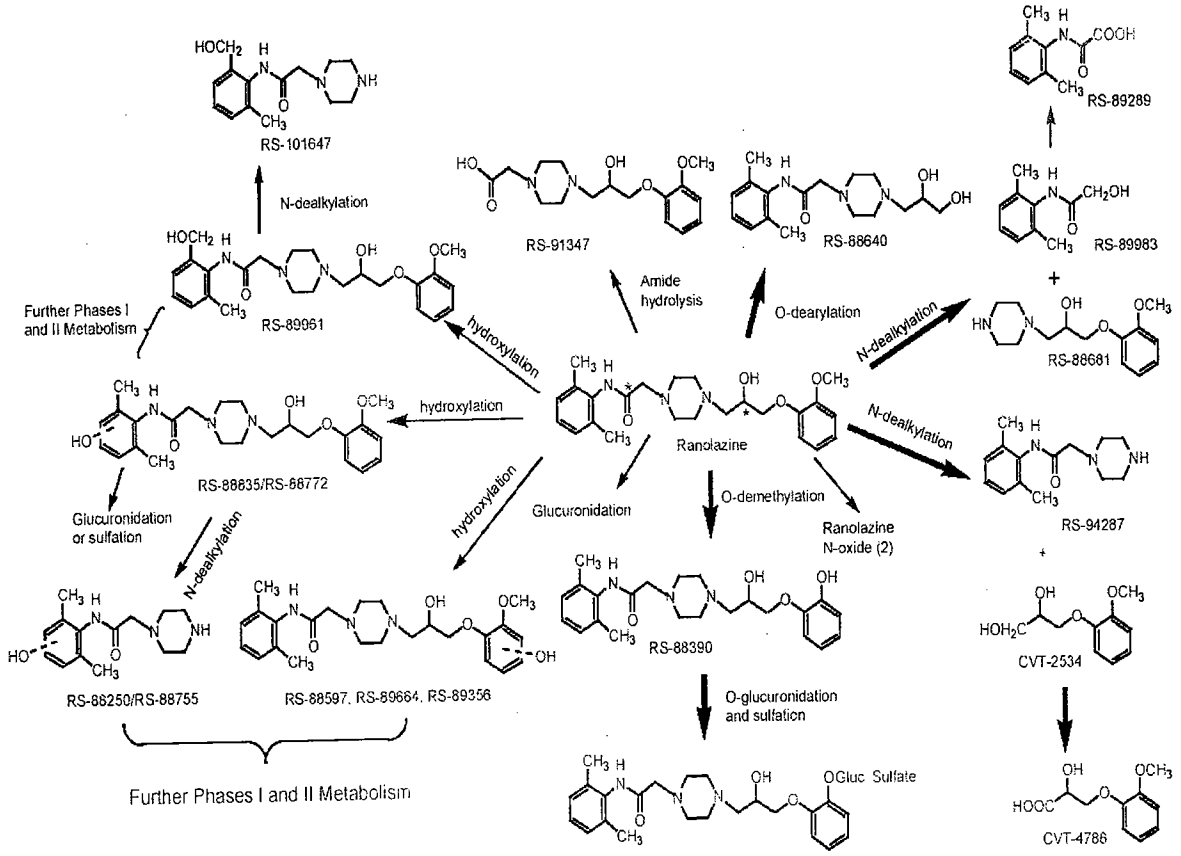
After administration of ^{14}C-ranolazine in aqueous solution total radioactivity declines with an apparent half-life of 40.9 hours and the recoveries in urine and feces amount to 73.13% and 24.46% of the dose, respectively. Only 3.13% of a 500 mg dose is recovered in urine as unchanged drug indicating 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 AUCs 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

The metabolites RS-88390 (CVT-2514), RS-88640 (CVT-2512) and RS-94287 (CVT-2738) have apparent half-lives in the range of 10 hours to 20 hours after oral administration. CVT-4786 is a product of RS-94287 (CVT-2738) and its reported apparent half life of 8 hours is probably underestimated. Three of the major circulating metabolites are also the major metabolites of ranolazine excreted in urine: The conjugate of RS-88390 (CVT-2514), RS-94287 (CVT-2738) and CVT-4786. Together they account for 31.51% of the dose. Additional, minor metabolites exist and the percentage of an oral dose of ranolazine excreted in urine as identified compounds is 46.46% corresponding to 63.5% of the total radioactivity excreted in urine.

The following scheme depicts the known metabolic pathways of ranolazine:



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.

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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

Regimen mg		**Ranolazine**			**DDI[a]**	**Clinical Significance**
Drug	**Ranolazine**	**dCmax,%[b]**	**dAUC,%[b]**	**Factor[c]**		
Ketoconazole 200 bid	SR 375 bid	157.1	222.5	3.2	yes	yes
Ketoconazole 200 bid	SR 1000 bid	216.0	264.2	3.6	yes	yes
Diltiazem 180 qd	SR1000 bid	90.1[d]	115.6[d]	2.2	yes	yes
		49.6[e]	51.9[d]	1.5	yes	yes
240 qd	SR 1000 bid	139.8[d]	137.9[d]	2.4	yes	yes
		88.6[e]	93.0[e]	1.9	yes	yes
360 qd	SR 1000 bid	181.0[d]	175.3[d]	2.8	yes	yes
		130.1[e]	138.7[d]	2.4	yes	yes
Diltiazem 60 tid	SR 1000 bid	49.8[d]	83.1[d]	1.8	yes	yes
		80.1[e]	89.9[e]	1.9	yes	yes
Verapamil 120 tid	SR 750 bid	92.3	116.6	2.2	yes	yes
Paroxetine 20 qd	SR 1000 bid	17.2	19.4	1.2	yes	no
Cimetidine 400 tid	IR 171 tid	12.2	25.0	1.2	yes	no
Simvastatin 80 qd	SR 1000 bid	13.9	6.0	1.1	no	no
Digoxin 0.125 qd	SR 750 bid	18.1	22.2	1.2	no	no

[a] Statistically significant drug-drug interaction [b] Increase in arithmetic mean Cmax and AUC of ranolazine in presence of other drug [c]. Factor derived from the greater of the respective ratios of the Cmax- or AUC values of ranolazine in presence and absence of the 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 Cmax is greater than on AUC. A similar time dependency of the effect on Cmax 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 Cmax 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

Regimen mg			**Drug**			**DDI[a]**	**Clinical Significance**
Ranolazine	**Drug**		**dCmax,%[b]**	**dAUC,%[b]**	**Factor[c]**		
SR 750 bid	0.125 qd	Digoxin[d]	68.1	88.4	1.9	yes	yes
SR 1000 bid	0.125 qd	Digoxin	45.6	59.5	1.6	yes	yes
IR 342 tid	0.250 qd	Digoxin	129.7	38.7	2.3	yes	yes
SR 1000 bid	60 tid	Diltiazem	5.3[e]	9.2[e]	1.1	yes	no
			12.4[f]	10.5[f]	1.1	yes	no
SR 1000 bid	80 qd	Simvastatin	75.3	86.3	1.9	yes	yes
		Simvastatin Acid	128.4	126.1	2.3		
		HMG CoA Red. Inhib.	97.3	76.1	2.0		
IR 342 tid	5[g]	Warfarin				yes	
		(+) Warfarin	-12.1	9.5	0.9	yes	possible
		(-) Warfarin	-10.6	7.4	0.9	yes	possible
		Prothrombin Time	42.4	20.1	1.4	yes	yes
SR 1000 bid		Dextromethorphan	na[h]	na[h]	na[h]	yes[i]	possible

[a] Statistically significant drug-drug interaction [b] Increase in arithmetic mean Cmax and AUC of ranolazine in presence of other drug [c] Factor derived from the greater of the respective ratios of the Cmax- or AUC values of ranolazine in presence and absence of the other drug [d] In CHF patients [e] After a single dose of ranolazine [f] After multiple doses of ranolazine [g] After a single dose [h] Not applicable [i] Dextrometorphan/dextrorphan ratio significantly increased

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 dextrometorphan/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 Cmax 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 Cmax 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 Cmax 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 cavorts). 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.

Biopharmaceutics

Bioequivalence of the clinical and to be marketed formulations was demonstrated for the 500 mg strength SR tablet. Based on the submitted data showing a proportionately similar composition and comparable dissolution behavior of the 375 mg and 500 mg tablets in 4 media the biowaiver requested by the sponsor is granted.
The dissolution specifications should be in accordance with the FDA recommendations as follows:

Condition	FDA Recommendation
Dissolution Medium	0.1N HCl
Paddle Speed	— rpm
USP Apparatus II	
Volume	— mL
Specifications	0.5 h: { }
	4.0 h:
	12.0 h:
	20.0 h: NLT ( ]

Issues not Addressed by the Sponsor

- The effective and safe dose range for ranolazine in the studied patient population is uncertain and unknown in patients with refractory angina pectoris
- 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 what the least effective concentration of ranolazine is (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 the population analysis of the relationship between ranolazine concentration and effect on ΔΔQTc resulted in imprecise estimates of the slope and consequently of the risk associated with the 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

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.

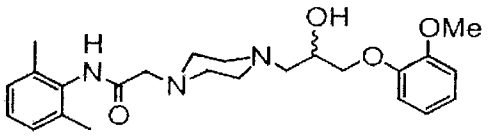
Appears This Way
On Original

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 (±)-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

Ranexa™ 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 (Type C), NF	[	
Microcrystalline Cellulose, NF		
Hydroxypropyl Methylcellulose JSP		
Sodium Hydroxide, NF		
Magnesium Stearate, NF		
Purified Water[a], USP	--	--
Tablet Core Weight (mg)	(	]
Film-Coating		
[ ) Light Blue	(	)
[ ) Orange	(	)
Carnauba Wax[b], NF	[	)
Purified Water[a], USP	--	--
Film-Coated Tablet Weight (mg)	**515.0**	**686.7**

The proposed manufacturers for drug substance and drug product for the commercial SR tablets are [

] , respectively. The 375 mg and 500 mg SR tablets will be packaged and labeled by [

]

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 (± 0.5) hours after evening dose) and additionally at morning peak (4 (±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. Precison 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-2714) 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 ΔQTc data and the corresponding plasma concentrations were used. ΔETT and ΔQTc values were obtained by subtracting the respective baseline values from ETT or QTc on drug or placebo. ΔΔETT and ΔΔQTc were obtained by subtracting the placebo value from ΔETT or ΔQTc.
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

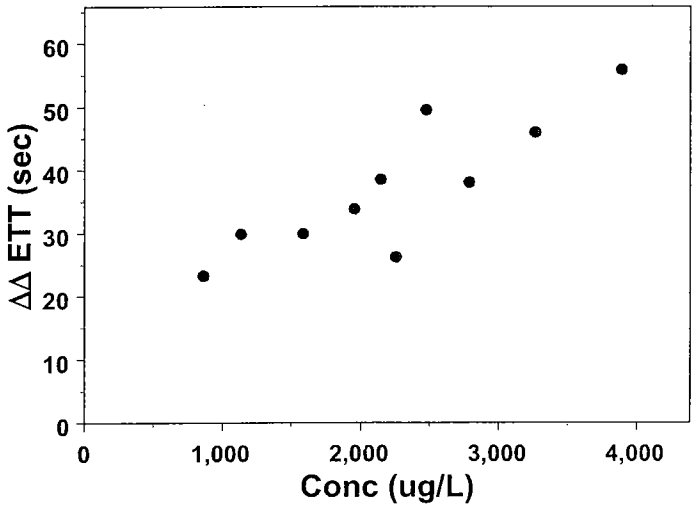
1.1 Ranolazine Plasma Concentration-ETT Relationship

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 ΔΔETT 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 ΔΔETT 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 ΔΔETT values for males and females are shown in Figure 2 and Table 1, respectively.

Figure 2. Pharmacometric Reviewers Model Predicted and Observed Mean ΔΔETT Values

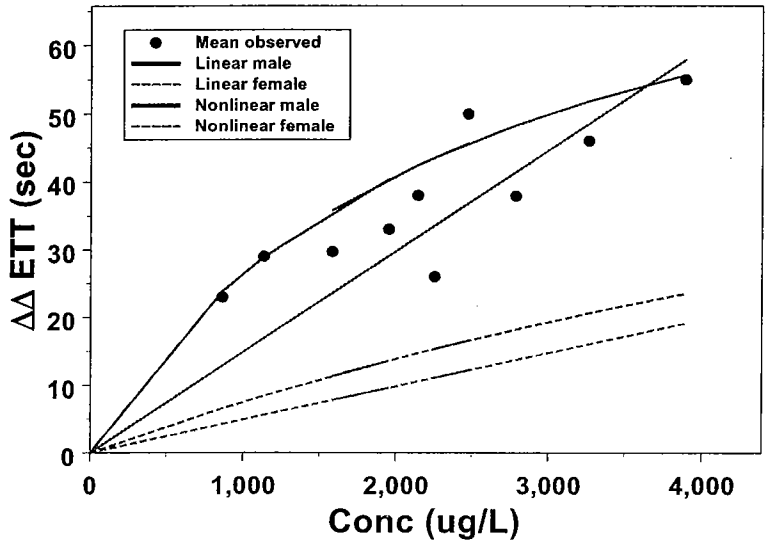


Table1. Reviewer's Final Model Predicted Peak and Trough Mean ΔΔETT(seconds)

	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 ΔΔETT 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 ΔΔETT Relevantly?

No.

ΔΔETT 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 ΔΔETT?

The factors are gender and ranolazine dose.

The time course of ranolazine's effect on ΔΔETT by ranolazine in males and females is shown in Figure 3:

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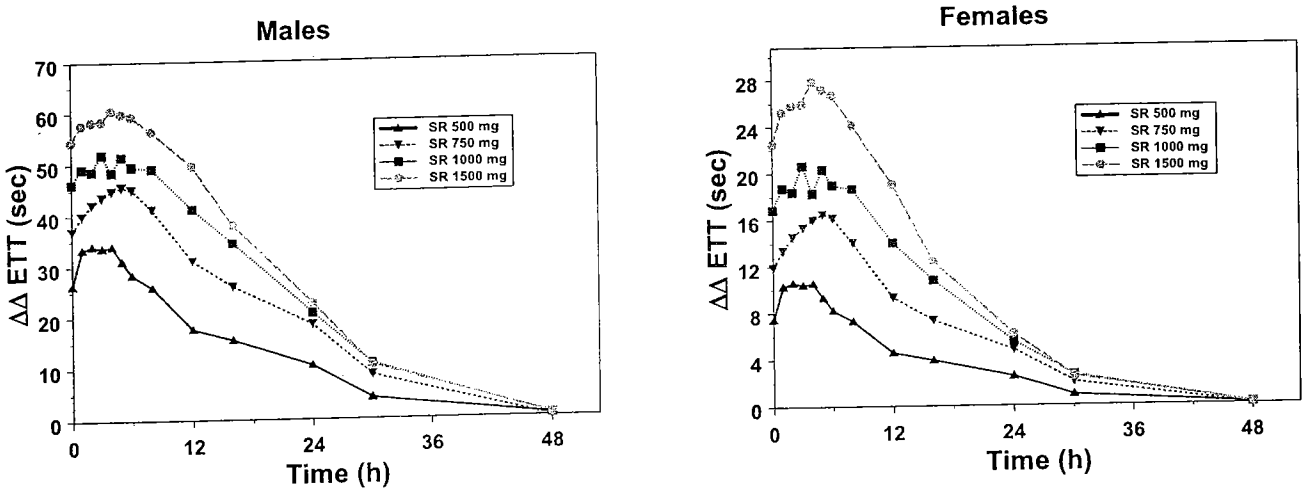
Figure 3. Model Predicted Time Course of ΔΔETT at Steady State for Ranolazine Doses Ranging between 500 mg to 1500 mg Administered every 12 Hours (Note the Difference in the Scale of the y-Axes in Males and Females)



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 ΔΔETT at all 4 dose levels is about 6 hours to 10 hours. The model predicted effect on ΔΔETT 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 ΔΔETT 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 ΔΔETT Values for 500 mg bid Regimens with Uneven Dose Intervals for Males (Left) and Females (Right)

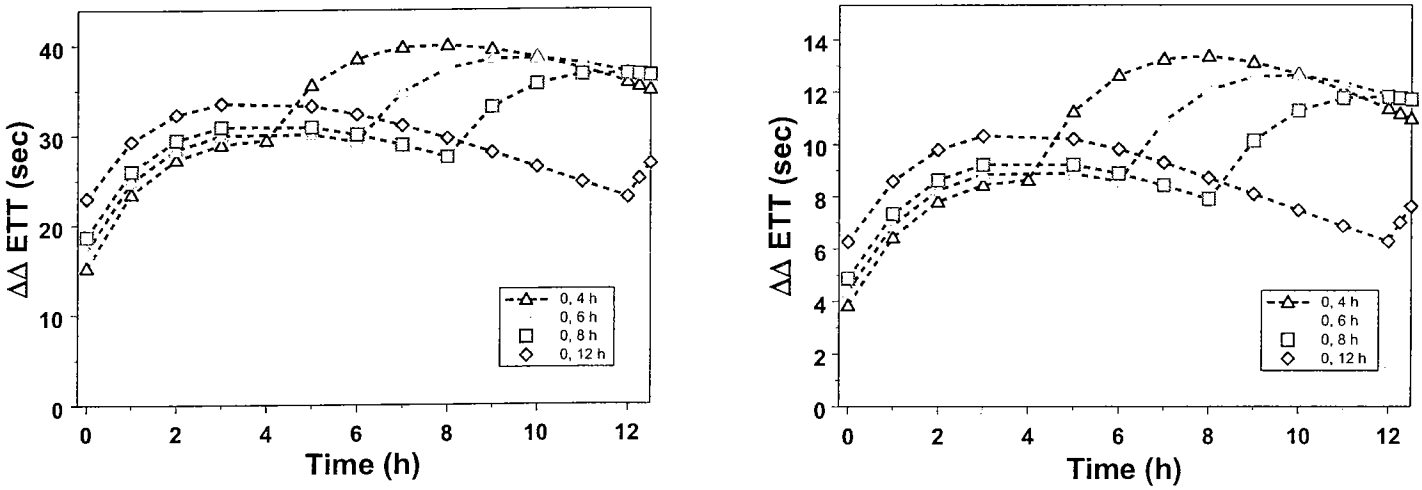
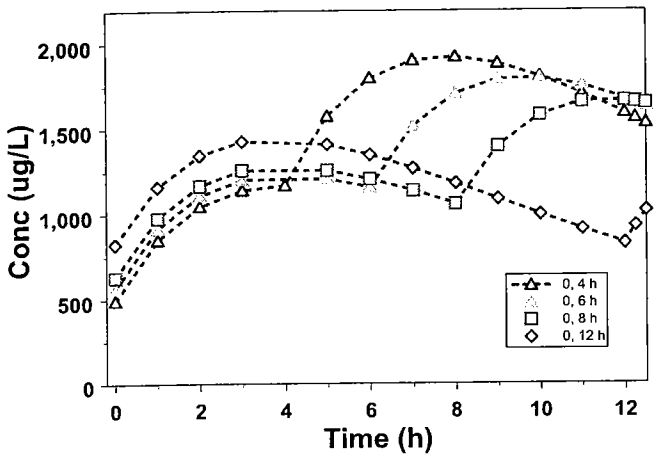


Figure 6. Simulation Predicted Mean Concentrations of Ranolazine for 500 mg bid Regimens with Uneven Dose Intervals



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 ΔΔETT?

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 ΔΔETT 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 to12 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 ΔETT Significantly?

No.

A significant correlation between drug concentration and ΔETT 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-ΔETT 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.

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2. Safety

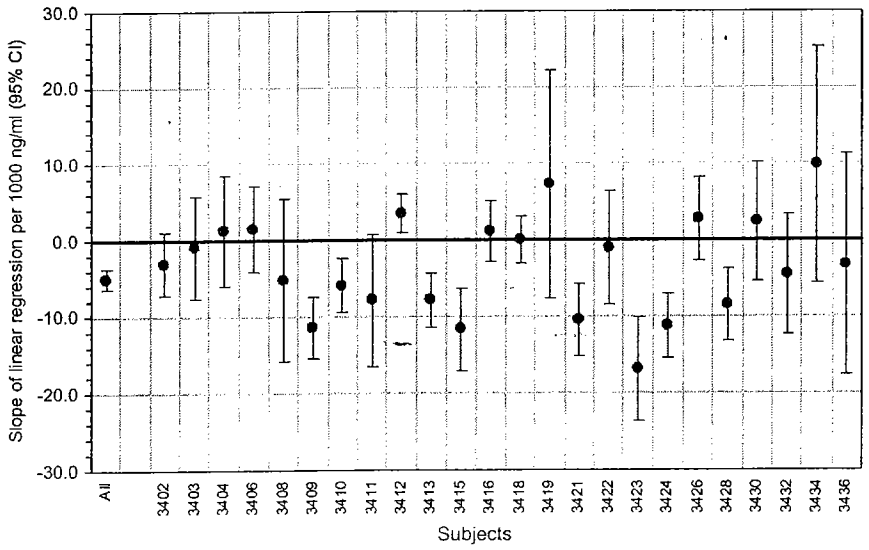
2.1. Plasma Concentration-QTc Effect Relationship

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 ΔRR on ranolazine concentrations:

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



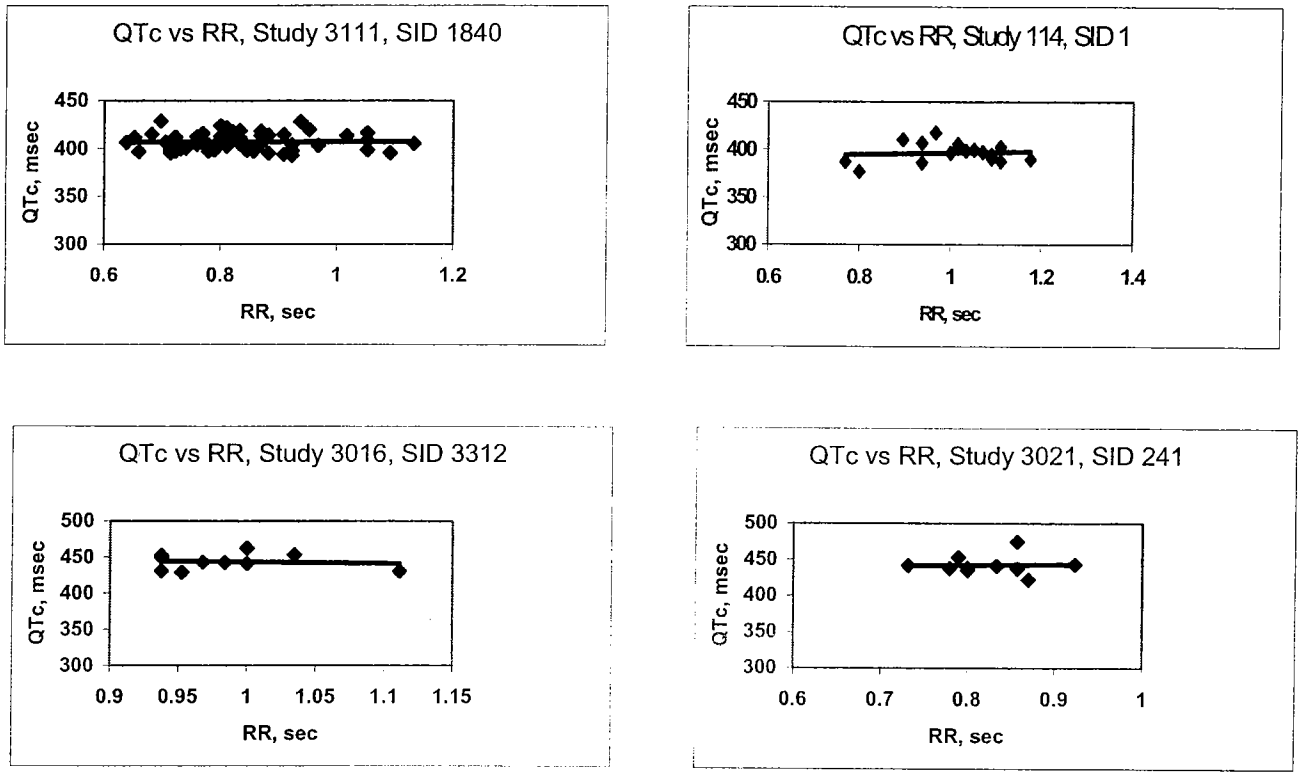
The average slope is -5 msec/1000 ng/mL indicating a negligible effect of ranolazine on heart rate.

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 $QTc = \alpha \bullet QT/RR^{\beta}$ 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

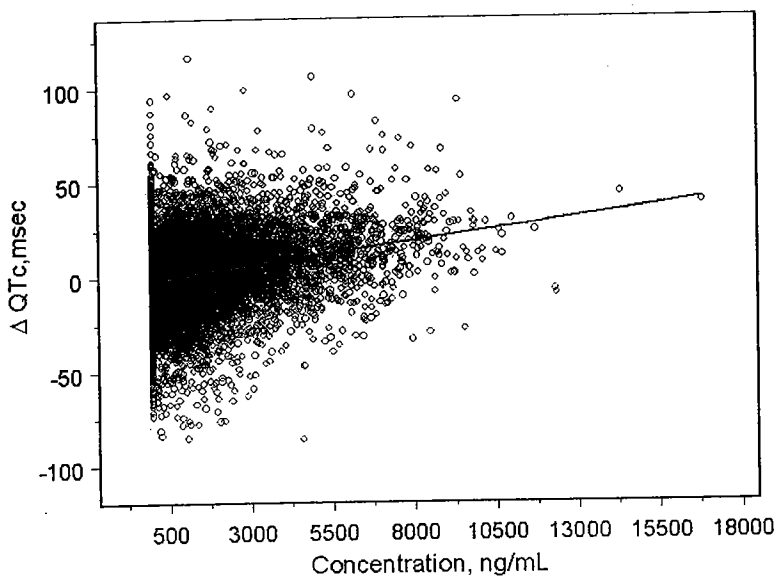


2.1.3. What are the Characteristics of the Relationship between Ranolazine and the Effect on QTc and what are the Factors affecting this Relationship?

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 ΔQTc 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-QTc 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 QTc 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 ΔΔQTc?

Because of the linear relationship between effect on ΔΔQTc and ranolazine concentration the time course of ΔΔQTc 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 ΔΔQTc 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.

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Figure 10. Linear Plot of the Time Course of ΔΔQTc at Steady State and after Cessation of Treatment at Doses of 500 mg to 1500 mg Ranolazine administered very 12 Hours to Healthy Male Volunteers

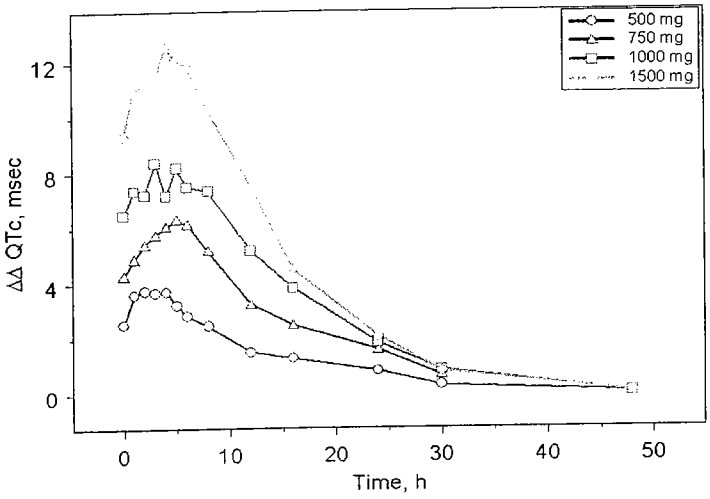

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Figure 10 indicates that t50 of ranolazine's effect on QTc is 6 hours to 8 hours and in the range of the apparent terminal half life of ranolazine.

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:

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

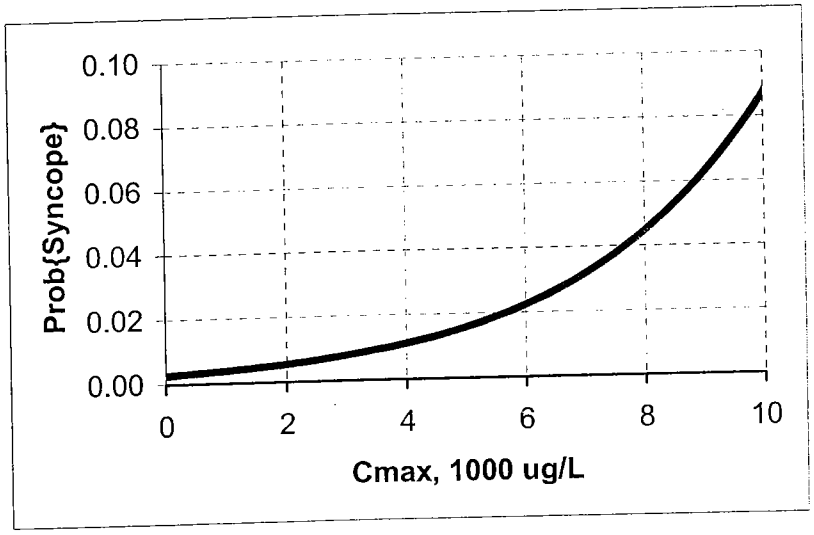
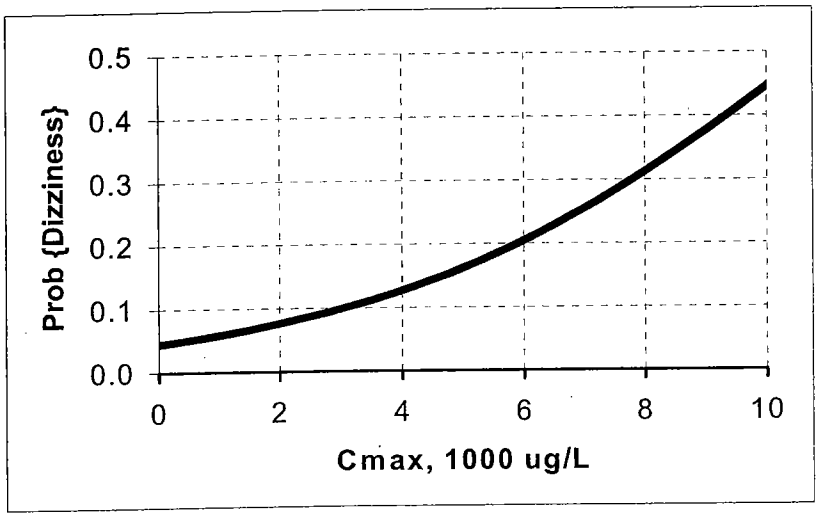


Figure 12. Linear Plot of the Probability of a Patient to incur Dizziness against Ranolazine Plasma Concentration



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.

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 ΔΔETT and ΔΔQTc 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-ΔΔETT 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 (Cmax, 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 ΔΔETT 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 Ranonalzine 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 Cmax and Cmin 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 Cmax values tended to be greater (+22 %) and the Cmin 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 Cmax and AUC when the dose is increased from 500 mg to 1500 mg is only 1.2 and 1.4 fold, 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 ^{14}C 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 tmax 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 α1-acid glycoprotein. The apparent red cell to plasma coefficient ranged between 0.620 and 0.879.

.

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 t1/2 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:

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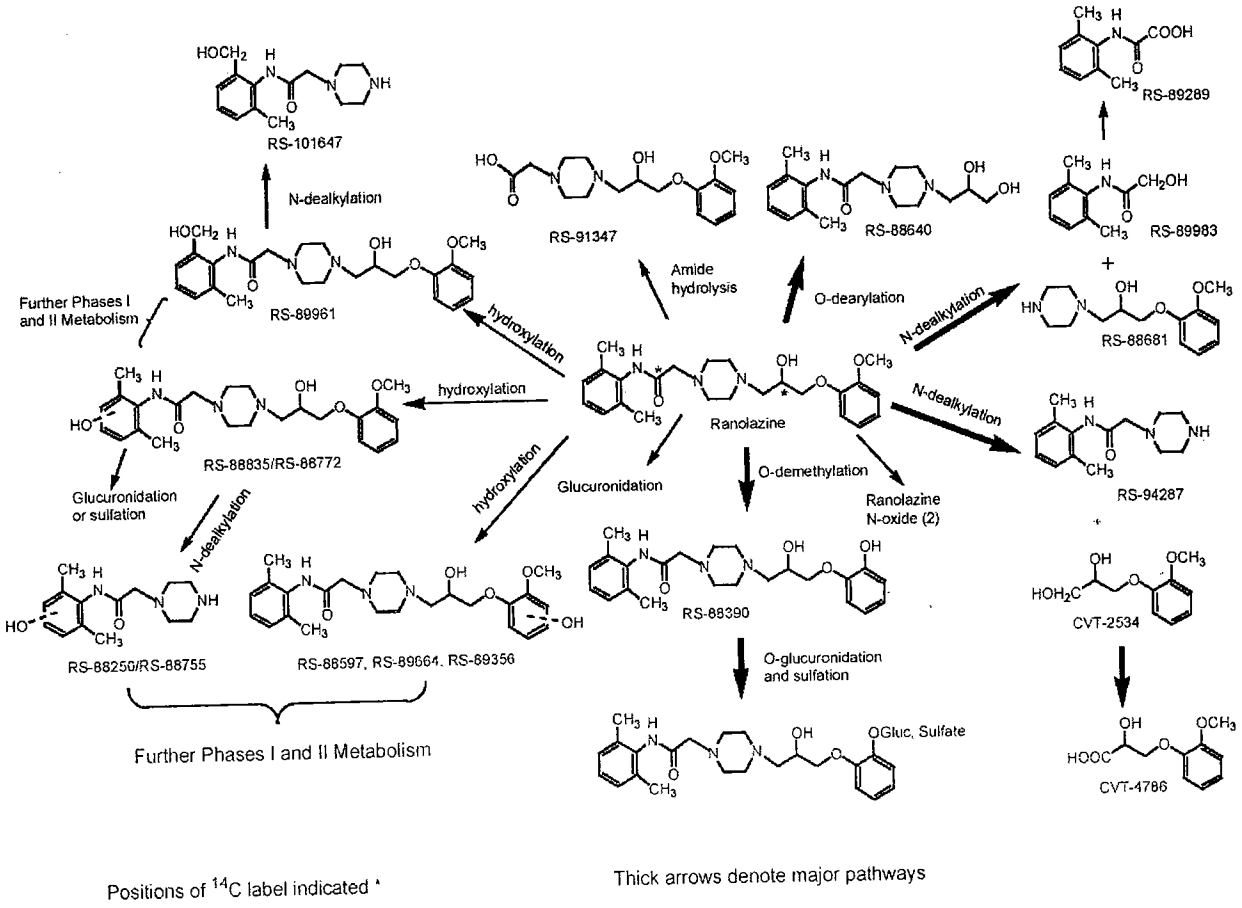

Based on information from in vitro metabolic and in vivo drug interaction studies the main enzymes catalyzing the metabolism of ranolazine include CYP 3A4, CYP 2D6 and in addition sulfatases and glucuronidases. The involvement of Phase 1 enzymes other than CYP 3A4 and CYP 2D6 cannot be excluded. The formation of RS-88390 (CVT-2514) and RS-94287 (CVT-2738) are most likely catalyzed by CYP 2D6 and 3A4, respectively. The results from in vitro metabolic and in vivo drug interaction studies with CYP 3A4 and CYP 2D6 inhibitors suggest that a large fraction of ranolazine is metabolized by CYP 3A4, whereas the contribution of CYP 2D6 to the metabolism of ranolazine is small.

Excretion

Renal clearance and the fraction of the dose excreted in urine as ranolazine and metabolites have not been determined in the target population.

Healthy Volunteers

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 Cmax 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 Cmax 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 in healthy volunteers.

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 Cmax 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 Cmax and AUC in patients with mild hepatic impairment were 27.9% and 10.9%, respectively, greater than in the control subjects. Median Cmax 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**		
	PK[a]	**PK-PD**	
		ETT[b]	**QTc[c]**
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	1.9	1.0	2.8
Renal Impairment			
Mild	1.5	1.0	1.0
Moderate	1.6	1.0	1.0
Severe[d]	1.7	1.0	1.0

[a] Factor derived from the greater of the respective ratios of the Cmax- and AUC values in presence and absence of covariate b Factor derived from ratio of effect in females relative to males in studies 3031 and 3033 [c] Factor derived from the relationship between plasma concentration and QTc [d] Diastolic blood pressure increase with 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

Other Drug	Daily Dose, mg		Factor[a]
	Drug	SR Ranolazine	
Typical Patient	0	1000-2000	1.0
Ketoconazole	400	750	3.2
	400	2000	3.6
Diltiazem	180 SR	2000	2.2
	240 SR	2000	2.4
	360 SR	2000	2.8
	180 IR	2000	1.8
Verapamil	120 SR	1500	2.2

a Factor derived from the greater of the respective ratios of Cmax-or AUC values of ranolazine in presence and absence of other drug

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 Cmax 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 Cmax and AUC on Day 8 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-Drug Interaction Studies with No Significant Impact on Ranolazine

Other Drug	**Daily Dose, mg**		**Factor[a]**
	Drug	**Ranolazine**	
Paroxetine	20	SR 2000	1.2
Cimetidine	1200	IR 325	1.2
Simvastatin	80	SR 2000	1.1
Digoxin	0.125	SR 2000	1.2

[a] Factor derived from the greater of the respective ratios of Cmax- or AUC values in presence and absence of other drug

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 2 D6 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 the impact of ranolazine on the PK and PD of other drugs was investigated are summarized in Table 7:

Table 7. Drug-Drug Interactions with Ranolazine Impacting the PK or PD of Other Drugs

Other Drug	Daily Dose, mg		Factor[a]	Clinical Significance
	Drug	Ranolazine		
Digoxin	0.125[b]	SR 1500	1.9	yes
	0.125	SR 2000	1.6	yes
	0.250	IR 1026	2.3	yes
Diltiazem	180 IR	SR 2000	1.1	no
Simvastatin	80	SR 2000	1.9	yes
Simvastatin Acid			2.3	yes
HMG CoA Red. Activity			2.0	yes
Warfarin	5[c]	IR 1026		
(+) Warfarin			0.88	possible
(-) Warfarin			0.89	possible
Prothrombin Time			1.4	yes
Dextrometorphan	30		na[d]	possible

[a] Factor derived from the greater of the respective ratios of Cmax- or AUC values of other drug in presence or absence of ranolazine [b] in patients with CHF [c] single dose
[d] Dextrometorphan/dextrorphan ratio statistically significantly increased

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/dextrorphan 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.

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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 performane 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 f 2 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 Biovailability of Ranolazine?

No.

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

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

Partly.

Because complete release of ranolazine from the SR tablets was only achieved in 0.1 N HCl buffer the sponsor selected 0.1 N HCl as dissolution medium. This is acceptable.
However, the proposed dissolution specifications should be in accordance with the FDA recommended acceptance criteria as follows:

Condition	FDA Recommendation
Dissolution Medium	0.1N HCl
Paddle Speed	— rpm
USP Apparatus II	
Volume	[ ] mL
Specifications	0.5 h:
	4.0 h:
	12.0 h:
	20.0 h: NLT [ ]

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.

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31 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

APPENDIX II

STUDY CVT 303.001-N DISTRIBUTION OF RANOLAZINE TO HUMAN BLOOD CELLS AND BINDING OF RANOLAZINE TO HUMAN PLASMA, HUMAN SERUM ALBUMIN, AND HUMAN α-1 ACID GLYCOPROTEIN IN VITRO BY AN ULTRAFILTRATION METHOD

Study ID: CVT 303.001-N
Volume: 49, ITEM 5

OBJECTIVES:

To determine binding of ranolazine to human plasma proteins, human serum albumin, and α-1 acid glycoprotein in vitro by ultrafiltration
To determine the partition of ranolazine to human blood cells in vitro

METHODS:

Plasma protein-, human serum albumin- and α-1 acid glycoprotein binding:

Plasma from 3 fasted, healthy male volunteers, and serum albumin and α-1 acid glycoprotein solutions were spiked with ^{14}C labeled (purity [redacted] and unlabeled ranolazine to achieve concentrations in the range of 250 ng/mL to 10'000 ng/mL. Ultrafiltration of aliquots of the spiked samples was performed at room temperature. Drug concentrations were measured in the samples prior to ultrafiltration and in the filtrates using liquid scintillation radiometry. The percentage of bound drug was calculated from % bound = [(Cp-Cf)/Cp]• 100, where Cp and Cf represent total drug concentration in the spiked sample and free concentration in the ultrafiltrate, respectively.

Blood Cell Distribution:

Blood samples from healthy male volunteers were spiked with ^{14}C labeled and unlabeled ranolazine to achieve concentrations in the range of 500 ng/mL to 8000 ng/mL. The partition experiments were performed at room temperature. Drug concentrations in whole blood and plasma were measured by liquid scintillation spectrometry. The red cell partitioning of ranolazine was computed from Cbc/Cp= ((Cb/Cp-1) + H))/H, where Cbc is the concentration in red blood cells, Cb is the concentration in whole blood and H represents the hematocrit.

ASSAY:

Ranolazine concentrations in plasma, albumin- and α1-acid glycoprotein solutions and thefiltrates were measured by LSC. Ranolazine in blood was measured afer hemolysis and extraction by LSC. Stability of ranolazine in plasma and blood during incubation was verified by HPLC-radiometry.

RESULTS:

The mean plasma protein binding of ranolazine ranged between 63.9% and 60.9% with a slight tendency to decrease with increasing concentrations. The mean values for the binding of ranolazine to serum albumin ranged between 29.5% and 31.5 % and was concentration independent. Compared to albumin the binding of ranolazine to α-1 acid glycoprotein was greater and the mean values showed a tendency to decrease from 62.1% at the 250 ng/mL level to 47.0% at the 10'000 ng/mL level.

Summary Data of Binding of Ranolazine to Human Plasma, Human Serum Albumin, and Human α-1 Acid Glycoprotein

Concentration of Ranolazine (µg/mL)	Human Plasma (n=3)	Human Serum Albumin (n=1)	Human α-1 Acid Glycoprotein (n=1)
*0.25	63.6 ± 0.53	29.5	62.1
0.5	63.9 ± 0.64	31.5	57.8
1.0	63.7 ± 0.62	30.2	57.9
2.0	62.7 ± 0.91	30.3	55.3
4.0	62.7 ± 0.67*	31.4	50.0
6.0	62.5 ± 0.55	31.0	51.4
8.0	62.0 ± 1.00	29.6	47.5
10.0	60.9 ± 1.49	31.1	47.0

The red cell to plasma partition coefficient ranged between 0.620 to 0.879.

Distribution of Ranolazine to Human Blood Cells

	Ranolazine Conc. (µg/mL)	Ratio of Cb/Cp	Ratio of Cbc/Cp
Mean	0.5	0.877	0.719
	1.0	0.835	0.620
	2.0	0.864	0.685
	4.0	0.878	0.719
	8.0	0.948	0.879

COMMENTS:

1. The binding of ranolazine to plasma proteins should have been conducted at 37 ° C.
2. The maintenance of pH 7.4 during ultrafiltration and the absence of membrane binding were not evaluated
3. The concentrations of albumin and α-1 glycoprotein in the respective solutions were not indicated
4. The plasma protein binding of ranolazine was not determined in the presence of the main metabolites
5. The blood to plasma concentration ratio should have been determined at 37° C

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STUDY CVT 303.009-N – IN VITRO METABOLISM OF RANOLAZINE BY HUMAN LIVER MICROSOMES AND IDENTIFICATION OF MAJOR HUMAN CYTOCHROM P450 ISOZYMES INVOLVED IN THE HEPATIC METABOLISM OF RANOLAZINE

Study ID: CVT 303.009-N
Volume: 41, ITEM 5

OBJECTIVES:

To determine Km and Vmax values of the metabolism of ranolazine to major metabolites and to conclusively determine the P450 isozymes responsible for the metabolism of ranolazine by human liver microsomes

METHODS:

Human liver microsomes with defined protein content, and total P450- and specific isozyme activities were used to study the metabolism of ranolazine to individual metabolites and determine Vmax and Km. cDNA-expressed CYP 3A4, CYP 2E1, CYP 2D6*1, CYP 2C19, CYP 1A2 and CYP 2B6 were also employed to determine the capacity of individual enzymes to metabolize ranolazine. The reactions were conducted at 37° C in 0.05 M pH 7.4 potassium phosphate buffer containing 5mM $MgCl_2$, 2mM NADPH, microsomal protein (0.25 and 0.75 mg/mL) and ranolazine (5-400 µM). The chemical inhibitors of CYP 3A4, ketoconazole and troleandomycin (50 µM) and of CYP 2D6, quinidine (10µM), were used. Specific antibodies for CYP 34A, 2C, 1A1/1A2 and 2D6 were also employed. The putative metabolites were identified and quantified. Standards for the metabolites were synthetized. Based on the results with human cDNA expressed P450 isozymes, immunological and chemical inhibition of the isozymes in microsomes and correlation analysis, the involved main isozymes were characterized and their relative contribution to the overall metabolism of ranolazine determined.

ASSAY:

The metabolites were measured by LC-MS using CVT-2506 as internal standard. Authentic standards for the metabolites were available. The linear range of the assay was 2.5 ng/mL to 1000 ng/mL ($R^2 \geq 0.99$)

RESULTS:

The mean Km values for the metabolism of ranolazine to the identified, individual metabolites ranged between 46.9 µM (20'050 ng/mL) and 77.7 µM (33'217 ng/mL) as shown in the following table:

APPARENT Km and Vmax VALUES FOR METABOLISM OF RANOLAZINE TO MAJOR METABOLITES BY HUMAN LIVER MICROSOMES

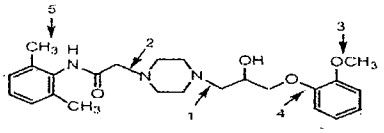
Kinetic Parameter	Exp. #	Metabolite ID RS-94287	RS-88390	RS-88681	RS-89961	RS-89983
Km (μM)	1					
	2					
	3					
	4					
	5					
	Mean	57.2	46.9	77.7	50.7	62.8
	SD	7.5	10.2	24.0	10.9	6.9
Vmax (pmoles/min/mg)	1					
	2					
	3					
	4					
	5					
	Mean	700	385	93.8	67.0	17.3
	SD	121	40	14.7	10.8	2.8

Experiment condition: 0.25 mg/mL microsomal protein for 10 min for initial rates of RS-94287, RS-88390, RS-88681, RS-89961.
Experiment condition: 0.75 mg/mL microsomal protein for 30 min for initial rate of RS-89983.
ND: Not determined.

The Vmax values ranged between 17.3 and 700 pM/min/mg. The Vmax values for RS-94387 (CVT-2738) and RS-88390 (CVT-2514) were greatest, 700 and 385pM/min/mg, respectively. The combined results obtained with the cDNA expressed isozymes, specific antibodies and chemical inhibitors of P450 isozymes and correlation analysis showed consistently that CYP3A4 and CYP2D6 are the main enzymes involved in the metabolism of ranolazine with relative contributions of about 78% and 15%, respectively.

The metabolism of ranolazine generated these major metabolites: RS-94287 (CVT-2738), RS-88681 (CVT-2513) and RS-89983 (CVT-2535) were formed by N-dealkylation of the piperazine nitrogens, RS-88390 (CVT-2514) by O-demethylation, RS-89961 (CVT-2551) by hydroxylation of a methyl group in the dimethylphenyl moiety and RS-88640 (CVT-2512) by O-dearylation. The following scheme shows the proposed metabolic pathways for ranolazine:

Proposed Primary Metabolic Pathways of Ranolazine



Pathway	Reaction	Primary Metabolite's
1	N-dealkylation at N4 nitrogen of piperazine	RS-94287 (CVT-2738), CVT-2534
2	N-dealkylation at N1 nitrogen of piperazine	RS-88681 (CVT-2513), RS-89983 (CVT-2535)
3	O-demethylation of methoxy group	RS-88390 (CVT-2514)
4	O-dearylation of the methoxyphenyl moiety	RS-88640 (CVT-2512)
5	Hydroxylation of methyl group on dimethylphenyl ring	RS-89961 (CVT-2551)

COMMENTS:

1. Information on the validation of the assay was not provided
2. The concentrations used in the inhibition experiments with ketoconazole, troleandomycin and quinidine exceeded 1μM so that isozymes other than CYP3A4 and CYP2D6 could have been inhibited
3. The involvement of CYP 2C9 was not tested
4. Addition of $MgCl_2$ to the reaction mixture can generate artifacts
5. The coefficient of variation about the mean Km values exceeded 20% for some of the metabolites
6. The potency of the antibodies used was not described
7. A possible Phase II metabolism of ranolazine was not investigated

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STUDY CVT 303.010-N -THE P170-GLYCOPROTEIN TRANSPORTER AS A POTENTIAL SITE OF RANOLAZINE/DIGOXIN DRUG INTERACTION

Study ID: CVT 303.010-N
Volume: 41, ITEM 5

OBJECTIVES:

To study the P-glycoprotein-mediated, bidirectional transport of ranolazine across monolayers of P-glycoprotein-overexpressing cells and to evaluate the effect of ranolazine on digoxin transport

METHODS:

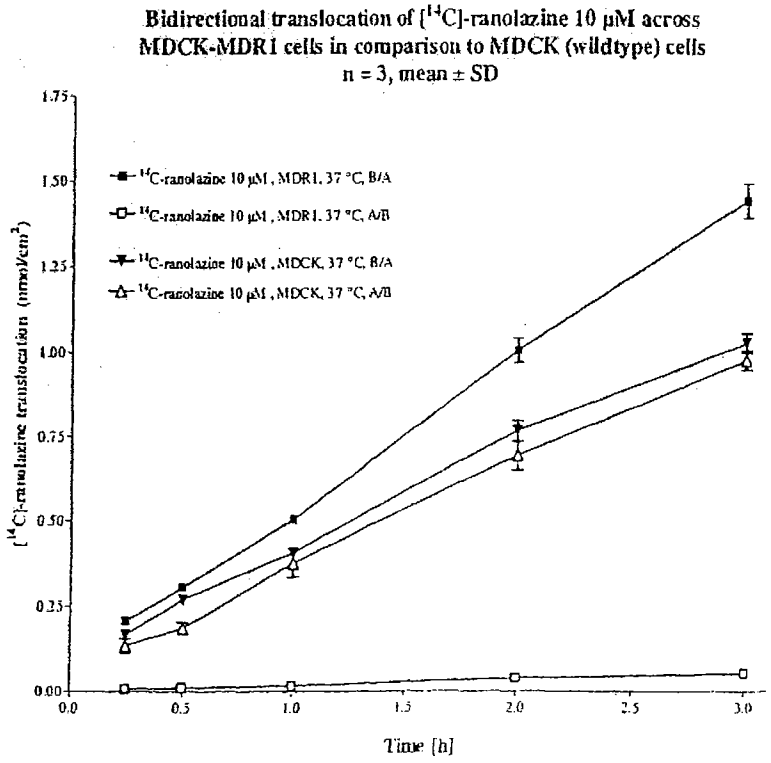
Monolayers of human P-glycoprotein-overexpressing, stably with the human MDR1-gene transfected Madin-Darby canine kidney cells (MDCK-MDR1) were used. Cell confluence and monolayer integrity were verified by microscopy and transepithelial resistance. Labeled mannitol was used as paracellular marker. The bi-directional transport of ^{14}C-labeled ranolazine (10μM) was measured at 4° and 37° C in MDCK-MDR1 cells and non-transfected MDRK cells. Km and Vmax for ranolazine's (10-1000 μM) baso-apical transport were determined in MDCK-MDR1 cells. The inhibition potential of ranolazine was tested using labeled digoxin (45 nM) as P-glycoprotein substrate. The impact of vinblastin, an established inhibitor of P-glycoprotein, on ranolazine transport was also studied. Drug concentrations were measured by liquid scintillation radiometry.

ASSAY:

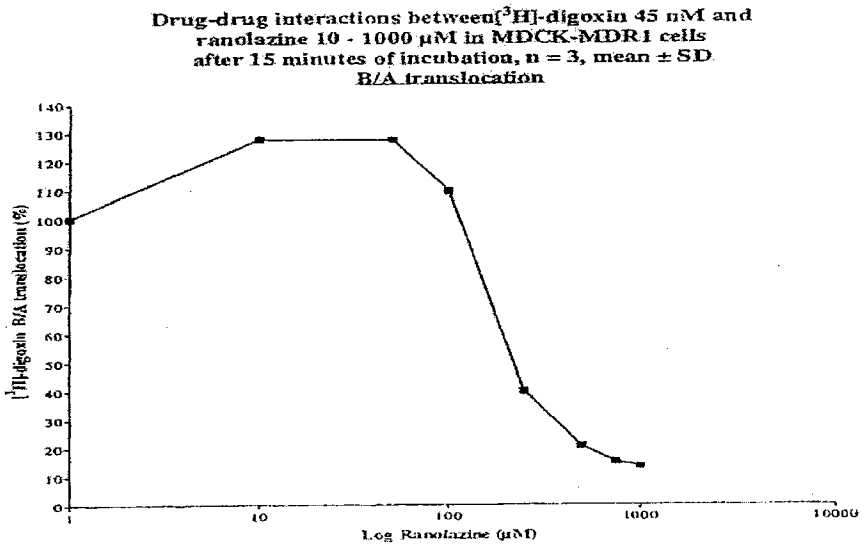
Labeled ranolazine, digoxin and mannitol were measured by liquid scitillation radiometry.

RESULTS:

Ranolazine was readily transported by P-glycoprotein as demonstrated by a 27 fold greater secretory basolateral to apical transport than absorptive apical to basolateral transport as shown by the following plot:



The secretory transport kinetics were characterized by K_m=84.6 (7.8) µM (36'167 ng/ml) and V_{max} =3.0 (0.5) nmol/cm^2/h. The transport of ranolazine was temperature dependent suggesting a carrier mediated mechanism and was completely inhibited by vinblastin. Ranolazine inhibited the transport of digoxin by P-glycoprotein with Ki =197 (75) µM (84'200ng/mL) as shown in the following figure:



COMMENTS:

1. No information on the purity of the labeled compounds and on the specifics of the assays were provided

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STUDY CVT 303.011-N –DETERMINATION OF THE POTENTIAL INHIBITORY EFFECTS OF COMMONLY PRESCRIBED DRUGS ON THE METABOLISM OF RANOLAZINE BY HUMAN LIVER MICROSOMES IN VITRO

Study ID: CVT 303.011-N
Volume: 41, ITEM 5

OBJECTIVES:

To assess effect of commonly prescribed drugs on the CYP mediated metabolism of ranolazine

METHODS:

Study CVT303.009-N indicated that the formation of RS-94287 (CVT-2738) and RS-88390 (CVT-2514) from ranolazine is catalyzed by CYP3A4 and CYP2D6, respectively. The potential inhibition of the metabolism of ranolazine was tested with 39 commonly prescribed drugs known to interact with CYP 3A4 or CYP 2D6. Human liver microsomes with known protein content, total P450 concentration and isozyme activities from 5 individuals were used. In screening experiments the percent inhibition of the formation of RS-94287 (CVT-2738) or RS-88390 (CVT-2514) was determined using microsomes from 5 individuals. In the definitive experiments the pooled microsomes were used and the IC50 was determined for drugs inhibiting the metabolism of ranolazine by more than 50%. The reaction mixture consisted of 0.05 M pH 7.4 potassium phosphate buffer, 5 mM $MgCl_2$, 0.20 mg/mL microsomal protein, 20 μM ranolazine dihydrochloride and the potential inhibitor. The inhibitor concentration was 250 μM in the screening experiments, and ranged from 0.38 μM to 250 μM in the definitive experiments. Mechanism based inhibitors were pre-incubated for 20 minutes. Controls containing no inhibitor were run in parallel. Ranolazine and metabolite standards were synthesized.

ASSAY:

The 2 metabolites were measured by LC/MS [redacted]
CVT 2506 was used as internal standard. The linear range of the assay was between 2.5 ng/mL to 500ng/mL ($R^2 \geq 0.99$).

RESULTS:

Drugs known to inhibit CYP3A4 inhibited the metabolism of ranolazine to RS-94287 (CVT-2738). Similarly, established inhibitors of CYP 2D6 inhibited the metabolism of ranolazine to RS-88390 (CVT-2514). The IC_{50} values of inhibitors for the CYP 3A4 mediated formation of RS-94287 (CVT-2738) ranged between 283 nM and >250 μM. The most potent in vitro

inhibitors with IC_{50}< 10 μM were ketoconazole, ergocristin, verapamil, diltiazem, troleandomycin, cyclosporine and terfenadine. The IC_{50} values of inhibitors of the CYP2D6 mediated metabolism of ranolazine to RS 88390 (CVT-2514) ranged between 79 nM and >250 μM. The most potent inhibitors with IC50 < 10 μM were quinidine, fluoxetine, amitryptiline, clozapine and dextrometorphan. Strong, intermediate and weak inhibitors of the two pathways are listed in the Table below:

IC_{50} Values of Commonly Prescribed Drugs on Metabolism of Ranolazine to RS-94287 and RS-88390 by Human Liver Microsomes

Drug	Drug Class	Known Interacting Cytochrome P450	IC_{50} (μM)[c] RS-94287 (CYP3A4)	IC_{50} (μM)[c] RS-88390 (CYP2D6)
Diltiazem	Calcium channel blockers	3A4	45.4	153
Diltiazem[a]	Calcium channel blockers	3A4	2.82	76.8
Fluoxetine	Serotonine reuptake inhibitors	3A4, 2D6	25.3	1.34
Amitriptyline	Tricyclic antidepressants	3A4, 2D6	95.0	5.75
Atenolol	Beta blocking agents	2D6	> 250	> 250
Metoprolol	Beta blocking agents	2D6	> 250	29.7
Propranolol	Beta blocking agents	2D6	51.7	19.3
Captopril	ACE inhibitors	2D6	> 250	> 250
Enalapril	ACE inhibitors	3A4	> 250	> 250
Furosemide	Diuretics	-	> 250	> 250
Clozapine	Sedative	3A4, 2D6	99.4	7.81
Dextromethorphan	Cough suppressants	2D6	166	9.77
Quinidine	Antiarrythmics	2D6	119	0.079
Nifedipine	Calcium channel blockers	3A4	66.6	100
Nitroglycerin[b]	Coronary Vasodilator	-	> 250	> 250
Lovastatin	HMG-CoA reductase inhibitors	3A4, 2D6	40.4	90.4
Simvastatin	HMG-CoA reductase inhibitors	3A4, 2D6	21.3	71.8
Cerivastatin[b]	HMG-CoA reductase inhibitors	3A4	124	> 250
Fluvastatin[b]	HMG-CoA reductase inhibitors	2C8/2C9	> 250	238
Pravastatin[b]	HMG-CoA reductase inhibitors	Not a 3A4 substrate	> 250	> 250
Atorvastatin[b]	HMG-CoA reductase inhibitors	3A4	> 250	> 250
Atorvastatin lactone	HMG-CoA reductase inhibitors	3A4	13.7	> 250
Sildenafil (Viagra)[b]	cGMP phosphodiesterase inhibitor	3A4, 2C9	16.0	176
Losartan	Angiotensin II receptor antagonists	-	> 250	> 250
Ergocristine	Ergot alkaloid	3A4	1.23	> 250
Terfenadine	Antihistaminics	3A4	7.38	14.0
Haloperidale	Neuroleptics	3A4, 2D6	> 250	68.0
Glibenclamide	Antidiabetic	3A4	> 250	> 250
Erythromycin	Macrolides	3A4	27.0	> 250
Amiodarone	Antiarrythmics	3A4, 2D6	> 250	65.6
Tamoxifen	Antiestrogen	3A4	51.2	77.5
Cyclosporine	Immunosuppressants	3A4	6.74	> 250
Omeprazole	Proton pump inhibitors	3A4, 2D6	> 250	158
Diazepam	Anxiolytic	3A4, 2C19	> 250	> 250
Verapamil[a]	Calcium channel blockers	3A4	2.13	46.9
Cimetidine[a]	H2-receptor	2D6 mainly	>250	108
Ketoconazole[a]	Antifungals	3A4, 2D6	0.283	13.8
Troleandomycin[a]	Macrolides	3A4	4.42	> 250
17 α-ethinyl estradiol[a]	Estrogen	3A4	13.9	17.6
Debrisoquine	Antihypertensive	2D6	> 250	> 250
Dexamethasone[a]	Corticosteroids	3A4	46.6	137

[a] Drug was pre-incubated with microsomes and NADPH (1 mM) for 20 minutes followed by addition of ranolazine and a fresh supply of NADPH.
[b] Compounds were extracted from commercial tablets and 100% recovery of active ingradient from the tablet was assumed.
[c] Rates of formation of RS-94287 and RS-88390 were determined in the presence of vehicle and 9 concentrations of interacting drugs at ranolazine concentration 20 μM using a pooled HLM from 5 liver donors and IC_{50} values were calculated by a formula listed in Methods.

Warfarin (250 μM) did not inhibit the metabolism of ranolazine but activated the formation of RS-94287 (CVT-2738).

COMMENTS:

1. Information on the validation of the assay was not provided
2. The use of $MgCl_2$ in the reaction mixture can lead to artifacts
3. It is not clear whether the IC_{50} values reported represent mean results from different experiments or the results from single experiments.

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STUDY CVT 303.018-N -EVALUATION OF DRUG-DRUG-INTERACTIONS BETWEEN RANOLAZINE AND HMG-COA REDUCTASE INHIBITORS IN VITRO

STUDY ID: CVT 303.018-N
VOLUME: 41, ITEM 5

OBJECTIVES:

To a) exclude possible drug-drug interactions with HMG-CoA inhibitors in vitro or b) if significant in vitro drug interactions were found, to identify and select the HMG-CoA reductase inhibitor most susceptible for a clinical ranolazine drug interaction study.

METHODS:

CYP P450 Interactions: Human microsomes with known protein content and isozyme activities of 5 different donors were used. The reactions were run at 37 ° C with 0.1M pH7.4 sodium-/potassium-phosphate buffer, microsomal protein (0.003-0.3 mg/mL) and statin (0.5-150 μM). The statins included atorvastatin, atorvastatin lactone, cerivastatin, lovastatin, pravastatin and simvastatin. The values for K_m, V_{max} and intrinsic clearance for each of the statins were obtained using 6 different concentrations. Incubation mixtures without microsomal proteins were used as controls. The IC_{50}-and K_i values for ranolazine were obtained with concentrations of ranolazine ranging between 0.1and 500 μM and using one concentration level of the statins that varied from 1.0 μM to 30 μM. The impact of pre-incubation on the inhibitory potency of ranolazine was also investigated.

Interactions with P-glycoprotein- mediated transport: Monolayers of MDR1 over-expressing Madin-Darby canine cells (MDCK-MDR1) and nontransfected MDCK as controls were used. Cell confluence and monolayer integrity were verified by microscopy, transepithelial resistance and by measuring the flux of ^{14}C-mannitol. The bi-directional transport of the statins (5 μM) in the presence and absence of ranolazine (0, 5, 50 or 500 μM) was evaluated at 37 ° C and the IC_{50} value determined. An established inhibitor of P-glycoprotein, GF120918A, was used as positive control. The statins were measured by HPLC/MS.

ASSAY:

The statins were assayed by a LC/MS/MS. The quantitation limits of the linear concentration curve for the different statins and metabolites were defined and the precision and accuracy determined form the QC samples were within ± 15%. There were exceptions as follows: the assays for 6'-exomethylene lovastatin and 5-hydroxy fluvastatin could not be validated because of insufficient quantities and for 6'β-hydroxy simvastatin 2 values were outside of the ±15% limit. Due to a lack of authentic statin metabolites standards metabolites were obtained by semi-preparative HPLC/UV.

RESULTS:

Ranolazine is a weak inhibitor of the metabolism of statins with an $IC_{50} \geq 46$ μM and $K_i \geq 20$ μM (≥8'600 ng/mL) as shown in the following table:

Half-maximal inhibition concentrations (IC_{50}) and inhibition constants (K_i) for the inhibition of the CYP-dependent metabolism of the statins by ranolazine.

Drug	IC_{50} [μM]	K_i [μM]
Atorvastatin		
ortho-hydroxy atorvastatin	50.9 ± 7.5	35.6 ± 5.3
para-hydroxy atorvastatin	45.7 ± 11.7	23.0 ± 5.3
Atorvastatin lactone		
ortho-hydroxy atorvastatin lactone	72.2± 19.2	32.4 ± 12.4
para-hydroxy atorvastatin lactone	66.5± 16.5	22.7± 12.1
Cerivastatin		
hydroxy cerivastatin (M-23)	147.0 ± 65.8	71.4 ± 32.0
desmethyl cerivastatin (M-1)	105.1 ± 46.8	70.8 ± 31.5
Fluvastatin		
5-hydroxy fluvastatin	155 ± 133	58.5± 36.0
Lovastatin		
6'β-hydroxy lovastatin	62.2 ± 29.0	24.9 ± 11.6
6'-exomethylene lovastatin	146.4 ± 99.8	90.1 ± 61.4
Simvastatin		
6'β-hydroxy simvastatin	54.0 ± 22.2	29.7 ± 12.1
6'-exomethylene simvastatin	150.5 ± 82.9	75.3 ± 41.5

Data is presented as means ± standard deviations (n=5 different microsomal preparations).

Ranolazine (concentrations from 0.1μM to 500μM) were used to determine the IC_{50}. The results indicate that ranolazine is a weak inhibitor of the metabolism of the statins with IC_{50} values ≥46 μM and inhibition constants (K_i) > 20 μM.

The IC50 values for the inhibition of P-glycoprotein's transport of the statins by ranolazine were > 19 μM (8123 ng/mL). Most sensitive to the inhibition by ranolazine were lovastatin and simvastatin as shown in the following table:

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Half-maximal inhibition concentrations (IC_{50}) of the inhibition of the p-glycoprotein-mediated transport of HMG-CoA reductase inhibitors across MDCK-MDR1 cell monolayers by ranolazine.

	Ranolazine IC_{50} [μM]	
	(B to A) / (A to B)	(B to A) – (A to B)
Atorvastatin	57 ± 16.5	89.5 ± 15.9
Cerivastatin	56.6 ± 2.8	234.1 ± 75.6
Fluvastatin	n.d.*	290.7 ± 121.2
Lovastatin	19.5 ± 19.1	75.6 ± 36.2
Simvastatin	32.2 ± 10.9	39.5 ± 5.4

Data is presented as mean ± standard deviation. The IC_{50} values were calculated using the WinNonlin program (version 2.1 professional, Pharsight, Mountain View, CA). IC_{50}- calculations were based on the following ranolazine concentrations: 0, 5, 50, and 500 μM (n=3/ concentration).
* Abbreviation: n.d.: not determined. The permeation of fluvastatin from apical-to-basal (A-to-B) declined over the observation period, resulting in a negative slope (see Figure 14C).

Ranolazine has the potential to inhibit the metabolism and the P-glycoprotein transport of statins. Among the statins lovastatin and simvastatin were most and pravastatin least susceptible to be impacted by coadministered ranolazine.

COMMENTS:

1. Validation of the assay for 6'-exomethylene lovastatin and 5-hydroxy fluvastatin was not achieved and the precision and accuracy acceptance limit was exceeded for 6'β-hydroxy simvastatin
2. A control experiment with a probe inhibitor was not performed.

STUDY CVT 303.020-N- DETERMINATION OF THE INHIBITORY EFFECTS OF RANOLAZINE, RS-88390 and RS-94287 ON THE METABOLISM OF HUMAN CYTOCHROME P450 3A4 and P450 2D6 MODEL SUBSTRATES BY HUMAN LIVER MICROSOMES and RECOMBINANT CYP450 3A4

Study ID: CVT 303.020-N
Volume: 42, ITEM 5

OBJECTIVES:

To determine the effect of ranolazine and its 2 major metabolites, RS-94287 (CVT-2738) and RS-88390 (CVT-2514) on the activity of CYP450 3A4 and CYP450 2D6 using pooled human liver microsomes and/or recombinant enzymes

METHODS:

Three well established model substrates for CYP 3A4, testosterone, midazolam and nifedipine and two well characterized substrates for CYP 2D6, dextrometorphan and bufuralol, were used to determine the inhibitory potential of ranolazine and two of its major metabolites. The respective IC_{50} values were estimated by using pooled human liver microsomes from male and female donors with the substrates at a concentration close to the Km value and the potential inhibitors at 7 different concentrations ranging from 10 to 1000μM. The data analysis used plots of the rate of the metabolite formation versus the log of the concentration of the potential inhibitor. If significant inhibition occurred Ki values were determined using microsomes and recombinant CYP 3A4. With liver microsomes the determination of Ki used 5 concentrations of ranolazine and 2 concentrations of the substrates, midazolam and testosterone. With recombinant CYP 3A4 also 5 concentrations of ranolazine were used, and the substrates were testosterone and nifedipine. CYP 450 specific inhibitors were used as positive controls. All assays were conducted at 37°C in 0.1M potassium phosphate buffer at pH 7.4 with a NADPH regenerating system. The protein concentration was 0.25 mg/mL or 0.50 mg/mL.
Ranolazine and metabolite standards as well as probe substrates and their metabolite standards were available.

ASSAY:

The analytes were measured by LC/MS/MS.

RESULTS:

RS-94287 (CVT-2738) had no impact on CYP 3A4 activity (10-1000 μM). Ranolazine and RS-88390 (CVT-2514) inhibited CYP3A4 with all 3 substrates (IC50 ranolazine: 28.2 μM to 185 μM (12'055 ng/mL – 79'088 ng/mL), IC_{50} RS-88390 (CVT-2514): 13 μM- 174 μM (5369 ng/mL-71'862 ng/mL). However, extent and underlying mechanism varied. Similar results were obtained with recombinant CYP 3A4. In the studies with the microsomes ranolazine and RS-88390 (CVT-2514) were weak inhibitors of CYP 2D6 with either substrate used. RS- 94287 (CVT-2514) showed no inhibitory potential regarding CYP 2D6.

Summary Table of IC_{50} and K_i Results for CYP450 3A4 and CYP450 2D6 Activity

			Human Liver Microsomes		Recombinant CYP450 3A4	
Compound	CYP450	Substrate	IC_{50} (μM) (Mean ± SE)	K_i (μM)	K_i (μM)	Apparent Inhibition Mechanism
Ranolazine	3A4	Testosterone	185*	117	43.9	Competitive
		Nifedipine	28.2 ± 11.3	ND	ND	Mixed
		Midazolam	101 ± 16.7	90	----	Competitive
RS-88390	3A4	Testosterone	172 ± 23.7	174*	29.3	Competitive
		Nifedipine	8.24 ± 5.38	13	ND	Mixed
		Midazolam	85.7 ± 11.1	104	----	Competitive
RS-94287	3A4	Testosterone	No Inhibition	----	----	----
		Nifedipine	No Inhibition	----	----	----
		Midazolam	No Inhibition	----	----	----
Ranolazine	2D6	Dextromethorphan	241 ± 19.2	----	----	----
		Bufuralol	324 ± 158	----	----	----
RS-88390	2D6	Dextromethorphan	236 ± 31.9	----	----	----
		Bufuralol	171 ± 68.3	----	----	----
RS-94287	2D6	Dextromethorphan	No Inhibition	----	----	----
		Bufuralol	No Inhibition	----	----	----

IC_{50} calculated using nonlinear regressiou and Grafit 4.06 software (Erithacus Software Limited, 1989-1998)
K_i calculated from linear transformation of data using Excel97 software (Microsoft Corporation)
*= average of two determinations #1: 148 ± 105 μM and #2: ; 222 ± 33.1 μM
---- = not done
ND = not determined; non-linear fit
* $R^2 < 0.970$ for Dixon Plot 1/v fit at 50 μM Testosterone Concentration

COMMENTS:

1. It is unclear whether the K_i value using cDNA enzymes represents a mean value or the value obtained in a single experiment
2. The Ki and IC_{50} values obtained for midazolam with microsomes are similar, even though the postulated inhibition type is competitive and the substrate concentration was ~ Km
3. The variation (SEM) about IC_{50} exceeded 50 % in some instances
3. Information on the validation of the assay methods used was not provided

STUDY 303.022-N-DETERMINATION OF THE POTENTIAL INHIBITORY EFFECTS OF MAJOR RANOLAZINE METABOLITES RS-88390, RS-94287, RS-88640, and CVT-4786 ON THE METABOLISM OF RANOLAZINE BY HUMAN LIVER MICROSOMES *IN VITRO*

Study ID: CVT 303.022-N
Volume: 42, ITEM 5

OBJECTIVES:

To determine the potential inhibitory effects of four major Phase I metabolites of ranolazine: RS-88390 (CVT-2514), RS-94287 (CVT-2738), RS-88640 (CVT-2512), and CVT-4786 on the metabolism of ranolazine in vitro by human liver microsomes.

METHODS:

Human liver microsomes with defined total protein content and total P450 concentrations from a pool of 21 individual donors were used. The reaction mixture consisted of 0.05 M pH 7.4 phosphate buffer, 5 mM $MgCl_2$, microsomal protein (0.5 mg/mL) and ranolazine (20 µM), metabolite (15.6 µM-1000 µM) and NADPH (1 µM). The experiments were conducted at 37° C. The concentration to reach 50% inhibition (IC50) on the rate of ranolazine metabolism were determined for each metabolite. Ketoconazole (0.039 µM- 5 µM), an established inhibitor of CYP 3A4, served as positive control. Ranolazine and metabolite standards were synthesized.

ASSAY:

The ranolazine concentrations in the samples were analyzed by [redacted] and using d3-ranolazine as internal standard. The limits of the calibration curves were 2.5 µM and 25 µM (R^2>0.99).

RESULTS:

RS-88390 (CVT-2514) inhibited weakly the metabolism of ranolazine with an IC_{50}=99.6 µM (41'135ng/mL). The other metabolites did not interfere with the metabolism of ranolazine as shown in the following table:

Compound	Inhibitor Concentrations	IC_{50} (Mean ± SD, n=3)
RS-88390	15.6 – 1000 µM	99.6 ± 5.75 µM
RS-94287	62.5 – 1000 µM	> 1000 µM
RS-88640	15.6 – 1000 µM	> 1000 µM
CVT-4786	62.5 – 1000 µM	> 1000 µM
Ketoconazole	0.039 – 5 µM	0.824 ± 0.162 µM*

*Mean ±SD of 6 determinations.

COMMENTS:

1. Addition of $MgCl_2$ to the reaction mixture can lead to artifacts

2. No information on the validation of the assay method was provided

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STUDY CVT 303.005-MET- COMPARISON OF IN VITRO METABOLISM OF RANOLAZINE IN MOUSE, RAT, DOG AND HUMAN LIVER MICROSOMES

Study ID: CVT 303.005MET
Volume: 40, ITEM 5

OBJECTIVES:

To compare 1.The *in vitro* metabolism of ranolazine in liver microsomes prepared from humans and the principle animal species employed in the safety assessment of ranolazine, namely CD-1 mice, Sprague-Dawley rats and beagle dogs and 2. The *In vitro* and *in vivo* metabolism of ranolazine in these four species.

METHODS:

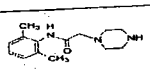
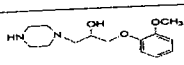
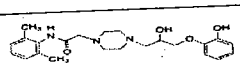
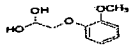
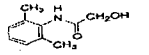
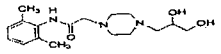
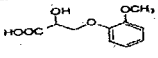
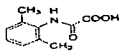
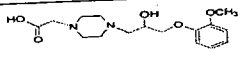
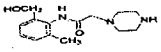
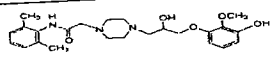
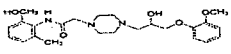
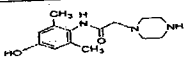
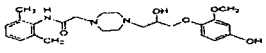
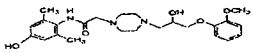
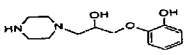
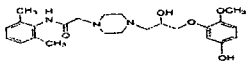
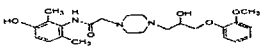
Liver microsomes with known protein contents and total P450 activities from male CD-1 mice, Sprague Dawley rats, beagle dogs and humans were used. The reactions were run at 37° C in 0.05M pH 7.4 potassium phosphate buffer, 5 mM $MgCl_2$, microsomal protein (0.20 mg/mL), ranolazine (20 μM) and NADPH (1mM). ^{14}C-labeled (purity —) and cold ranolazine were used. Disappearance of ranolazine and appearance of the metabolites were determined from the initial maximum rates measured between 2 time points.

ASSAY:

Standards for ranolazine and the metabolites were synthetized. A LC/MS method was used to measure the concentrations of ranolazine and the metabolites. CVT-2506 was used as internal standard. The limits of the linear calibration curve were 2.5 ng/mL and 500 ng/mL (R^2> 0.99). Separately selected samples were subjected to radio-chromatographic analysis. The detector for measuring radioactivity. metabolite identification

RESULTS:

With the exception of RS-89664 that was not detected in the dog, all 4 species produced the same 18 metabolites depicted in the following table:

 RS-94287 (CVT-2738) (Lot SN-01-65)	 RS-88681 (CVT-2513) (Lot GN289-44PR)	 RS-88390 (CVT-2514) (Lot 390-21)
 CVT-2534 (Lot 253-68-1)	 RS-89983 (CVT-2535) (Lot 253-72B-1)	 RS-88640 (CVT-2512) (Lot 390-20)
 CVT-4786 (Lot SAR-114-8-1)	 RS-89289 (CVT-2537) (Lot 253-72B-3)	 RS-91347 (CVT-3369) (Lot 315-77)
 RS-101647 (CVT-3248) (Lot 315-60)	 RS-89664 (CVT-5029) (Lot JE-90-26)	 RS-89961 (CVT-2551) (Lot 253-78-3)
 RS-88755 (CVT-3389) (Lot unknown)	 RS-88597 (CVT-5030) (Lot MC-18-68)	 RS-88772 (CVT-3388) (Lot 315-85)
 Desmethyl RS-88681 (CVT-3247) (Lot 315-57)	 RS-89356 (CVT-5031) (Lot RJ-91-11)	 RS-88835 (CVT-5028) (Lot SMH-8732)

However, quantitative differences among the 4 species were evident with respect to the total metabolic rates of ranolazine and the individual rates to the metabolites as shown in the following table:

Route/Metabolites	Maximal Rates of Metabolism of Ranolazine and Formation of Metabolites (pmole/min/mg microsomal protein) [a]			
	Mouse	Rat	Dog	Human
Total metabolism				
Ranolazine	894	753	491	589
N-dealkylation at the N4 piperazine nitrogen				
RS-94287	145 [b]	102	60.6	160
CVT-2534	65.8	78.6	31.9	99.5
CVT-4786	10.5	4.43	7.46	33.7
N-dealkylation at the N1 piperazine nitrogen				
RS-88681	441	150	81.7	17.3
RS-89983	59.3	29.7	11.7	5.4
RS-89289	5.14	3.41	3.24	6.91
Hydroxylation at the dimethylphenyl ring				
RS-89961	88.5	30.0	21.5	17.1
RS-88772	12.6	3.71	7.58	8.67
RS-88835	48.6	23.2	85.4	7.00
Hydroxylation at the methoxyphenyl ring				
RS-88597	17.6	25.3	128	18.6
RS-89664	2.10	1.47	ND [c]	1.58
RS-89356	10.9	16.2	53.7	9.57
O-Demethylation				
RS-88390	19.1	39.7	50.6	110
O-Dearylation				
RS-88640	1.31	2.43	2.70	5.05
Amide bond cleavage				
RS-91347	2.04	2.14	1.47	1.09
Downstream metabolites				
Desmethyl RS-88681	6.35	28.4	0.794	1.17
RS-88755	2.00	13.2	0.447	0.886
RS-101647	2.04	1.53	0.307	0.882

[a] Values represent the overall metabolism (disappearance of ranolazine in incubate) and formation (appearance) of various metabolites.

[b] Values in bold represent the top five metabolites for each species.

[c] ND denotes not detected

COMMENTS:

1. The use of $MgCl_2$ in the reaction mixture can lead to artifacts.
2. Information on the validation of the assay methods used was not provided.
3. It is unclear what the results reported represent: Means or results from a single experiment.

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STUDY CVT 3019 - A STUDY TO INVESTIGATE THE ABSORPTION, METABOLISM AND EXCRETION OF [^{14}C]- RANOLAZINE FOLLOWING A SINGLE ORAL ADMINISTRATION TO HEALTHY MALE VOLUNTEERS

TECHNICAL REPORT CVT 303.001-MET-METABOLIC PROFILES OF RANOLAZINE FOLLOWING ORAL ADMINISTRATION OF A SINGLE 500-MG DOSE OF [14C]-RANOLAZINE TO HEALTHY MALE VOLUNTEERS

STUDY INVESTIGATOR AND SITE: [

]

Report No: CVT 3019, CVT303.001-MET
Volume No.: 34,35, ITEM 6, Volume 40, ITEM 5

OBJECTIVES:

To define the absorption and excretion kinetics of ranolazine and related metabolites in man following oral administration and to investigate the profile of the metabolites present in plasma and excreta

FORMULATIONS:

Ranolazine oral solution (50 mL aqueous solution containing 500 mg [^{14}C]- ranolazine with specific activity of 0.071 μCi/μmol, labelled twice in the carbonyl- and propyl moieties
^{14}C-Ranolazine (Batch No. CFQ 11807, [ ]
Unlabelled ranolazine (Batch No. OM900021185)

STUDY DESIGN:

This was an open label, non-randomized, single center trial involving 4 healthy male volunteers receiving a single oral dose of [^{14}C]- ranolazine. The subjects fasted overnight until 4 hours after drug administration. Immediately after taking the solution containing the drug the volunteers drank 200 mL of tap water.

ASSAY:

The determination of total radioactivity in plasma, urine and feces was performed by [redacted] The determination of the metabolic profiles in plasma, urine and feces and the identification of the metabolites were carried out by CV Therapeutics, Palo Alto, CA. Plasma and urine aliquots were measured by radiometry after mixing with liquid scintillation fluid. Feces samples and whole blood samples were combusted using a sample oxidizer and the resultant $^{14}CO_2$ was collected by absorption in CO_2 absorbing fluid and after addition of scintillation fluid measured by radiometry.

The quantification of ranolazine and the metabolites in plasma, urine and feces used LC/MS or LC/MS/MS. A radiochromatographic analysis of the feces was also performed. The LC/MS/MS method[redacted] CVT-2506 as internal standard. Standards of ranolazine and the metabolites were synthetized.

Blood Sample Collection:

Blood samples were taken prior to and 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours postdose.
Urine samples were collected prior to and from 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours postdose.
Feces samples were collected prior to and 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours postdose.

RESULTS:

Four healthy male volunteers were enrolled and completed the study. Their average age was 39.3 years and they were all of Caucasian origin.

PK:

The mean (SD) recovery of total radioactivity in urine and feces combined was 97.59 (1.63)% and the individual recoveries in urine and feces were 73.13 (2.57) % and 24.46 (1.27)%, respectively.
The following two tables list the pharmacokinetic parameters in plasma and urine for ranolazine and the major metabolites:

Pharmacokinetics of Total Radioactivity, Ranolazine, and Metabolites in Healthy Male Volunteers Following a Single 500-mg Oral Dose of [^{14}C]-Ranolazine

(Study CVT-3019)
(Mean ± SD, N = 4)

Analyte ID	Cmax (μgEquiv/mL or μg/mL)	Tmax (hr)	$AUC_{0-\infty}$ (μgEquiv·hr/mL or μg·hr/mL) (% AUC for	$T_{1/2}$ (hr)
Total ^{14}C	11.75 ± 2.41	0.50 ± 0.00	58.1 ± 14.4	40.9 ± 3.7
Ranolazine	4.51 ± 2.18	0.50 ± 0.00	7.67 ± 3.80 (100)	1.64 ± 0.53
RS-88390	0.558 ± 0.448	1.0 ± 0.58	2.82 ± 0.80 (36.8)	13.4 ± 4.55
RS-94287	0.444 ± 0.050	0.50 ± 0.00	3.15 ± 1.27 (41.1)	5.11 ± 0.89 (n=3)
RS-88640	0.083 ± 0.065	2.50 ± 2.61	0.91 ± 0.55 (11.9)	9.06 ± 1.36 (n=3)
CVT-4786	2.17 ± 0.85	0.50 ± 0.00	3.09 ± 1.37 (40.3)	2.23 ± 0.53
RS-89961	0.164 ± 0.036	0.50 ± 0.00	0.68 ± 0.40 (8.9)	3.00 ± 0.31 (n=3)
RS-88597	0.118 ± 0.052	0.50 ± 0.00	0.18 ± 0.06 (2.3)	2.25 ± 0.68
RS-88681	0.048 ± 0.004	0.50 ± 0.00	0.37 ± 0.20 (4.8)	10.1 ± 1.42 (n=3)
CVT-2534	0.047 ± 0.019	0.50 ± 0.00	0.08 ± 0.06 (1.0)	1.84 ± 0.74
RS-89983	0.045 ± 0.008	1.38 ± 1.75	0.26 ± 0.15 (3.4)	4.20 ± 0.60 (n=3)
RS-89289	0.078 ± 0.013	0.56 ± 0.13	0.16 ± 0.05 (2.1)	2.59 ± 0.57
RS-101647	0.018 ± 0.005	2.06 ± 2.63	0.13 ± 0.04 (1.7)	8.63 ± 2.07 (n=3)
RS-88772	0.062 ± 0.009	0.50 ± 0.00	0.20 ± 0.07 (2.6)	6.23 ± 2.00
RS-89356	0.034 ± 0.011	0.50 ± 0.00	0.03 ± 0.01 (0.4)	0.80 ± 0.24
RS-88835	0.015 ± 0.005	0.56 ± 0.13	0.03 ± 0.04 (0.4)	5.72 (n=2)
RS-88390 Conjugate*	0.813 ± 0.374	2.25 ± 2.60	4.55 ± 0.93 (59.3)	7.77 ± 5.19
Ranolazine Glucuronide*	0.891 ± 0.244	0.69 ± 0.24	1.46 ± 0.82 (19.0)	0.13 (n=1)
RS-88597 Conjugate*	0.192 ± 0.047	0.81 ± 0.13	1.02 ± 0.22 (13.3)	4.49 ± 1.91
RS-89664 Conjugate*	0.053 ± 0.008	1.63 ± 1.59	0.49 ± 0.17 (6.4)	9.14 ± 4.69
RS-89961 Conjugate*	0.112 ± 0.038	3.25 ± 3.57	0.35 ± 0.24 (4.6)	NC
RS-89356 Conjugate*	0.079 ± 0.020	0.56 ± 0.13	0.36 ± 0.06 (4.7)	3.09 ± 1.38
RS-88835 Conjugate*	0.061 ± 0.018	1.00 ± 0.71	0.27 ± 0.18 (3.5)	2.63 ± 1.99 (n=3)

PK data were provided by [redacted]. NC: Not calculated.

*Concentrations of conjugates were estimated from the differences before and after β-glucuronidase hydrolysis.

The hydrolying enzyme used contained both β-glucuronidase and sulfatase.

The following metabolites were either not detected or at levels that were below the quantification limit of the assay: Conjugates of RS-88640 (CVT-2512), RS-88772 (CVT-3388), desmethyl RS-88681 (CVT-3247), CVT-2534, RS-89983 (CVT-2535), RS-89289 (CVT-2537), RS-101647 (CVT-3248) and RS-88755 (CVT-3389).

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Metabolites of Ranolazine RS Number (CVT Number)	Plasma $AUC_{(0-t)}$ (μg.hr/mL) (% AUC for ranolazine)[a]	Urine % Dose[c]
Phase I Metabolites		
Ranolazine (RS-43285, CVT-303)	7.67 (100)	3.13
RS-94287 (CVT-2738, Ran 2)	3.15 (41.1)	11.6
CVT-4786 (Acid of CVT-2534)	3.09 (40.3)	11.5
RS-88390 (CVT-2514)	2.82 (36.8)	0.22
RS-88640 (CVT-2512)	0.91 (11.9)	1.79
RS-89961 (CVT-2551)	0.68 (8.9)	0.46
RS-88681 (CVT-2513)	0.42 (5.5)	0.00
RS-89983 (CVT-2535)	0.26 (3.4)	0.00
RS-88772 (CVT-3388)	0.20 (2.6)	0.00
RS-88597 (CVT-5030)	0.18 (2.3)	0.72
RS-89289 (CVT-2537)	0.16 (2.1)	0.85
RS-101647 (CVT-3248)	0.13 (1.7)	0.00
CVT-2534	0.08 (1.0)	0.00
RS-88835 (CVT-5028)	0.03 (0.4)	0.00
RS-89356 (CVT-5031)	0.03 (0.4)	0.00
Phase II Metabolites		
RS-88390 (CVT-2514) Conjugate[b]	4.55 (59.3)	8.41
Ranolazine (CVT-303) Glucuronide	1.46 (19.0)	1.76
RS-88597 (CVT-5030) Conjugate	1.02 (13.3)	0.82
RS-89664 (CVT-5029) Conjugate	0.49 (6.4)	Trace
RS-89356 (CVT-5031) Conjugate	0.36 (4.7)	0.62
RS-89961 (CVT-2551) Conjugate	0.35 (4.6)	1.30
RS-88835 (CVT-5028) Conjugate	0.27 (3.5)	0.00
RS-88640 (CVT-2512) Glucuronide	0.00 (0.0)	2.83
RS-89983 (CVT-2535) Conjugate	0.00 (0.0)	0.45

[a]Values represent % AUC of ranolazine based on μg.hr/mL. Ranolazine plasma AUC was set at 100%.
[b]Units for conjugates are expressed as μg of the corresponding Phase I metabolite equivalent.hr/mL.
[c]Values represent % of the dose administered to the human subjects.
The following metabolites were either not detected or at levels that were below the quantification limit of the assay: RS-91347 (CVT-3369), desmethyl RS-88681 (CVT-3247), RS-88755 (CVT-3389) and conjugates of RS-88772 (CVT-3388), desmethyl RS-88681 (CVT-3247), CVT-2534, RS-89289 (CVT-2537), RS-101647 (CVT-3248) and RS-88755 (CVT-3389).

Total radioactivity and ranolazine in plasma declined with mean apparent half-lives of 40.9 hours and 1.64 hours, respectively. Seven (7) metabolites had AUC values relative to ranolazine between 59.6% and 11.9%: RS-88390 (CVT-2514) conjugate, RS-94287 (CVT-2738), CVT-4786, RS-88390 (CVT-2514), ranolazine glucuronide, RS- 88597 (CVT-5030) and RS-88640 (CVT-2512). Among the major circulating metabolites RS-88390 (CVT-2514) displayed the longest mean half-life with 13.4 hours. All the measured major metabolites peaked between 0.5 and 3.25 hours post dose. RS-94287 (CVT-2738), CVT-4786 and RS-88390 (CVT-2514) conjugate were the major metabolites recovered in urine representing 11.6%, 11.5% and 8.41%, respectively of the dose. In the feces the amount of unchanged ranolazine (4%) was low. RS-88640 (CVT-2512) and a number of minor metabolites were detected in the feces.

The following scheme depicts the major metabolic routes of ranolazine:

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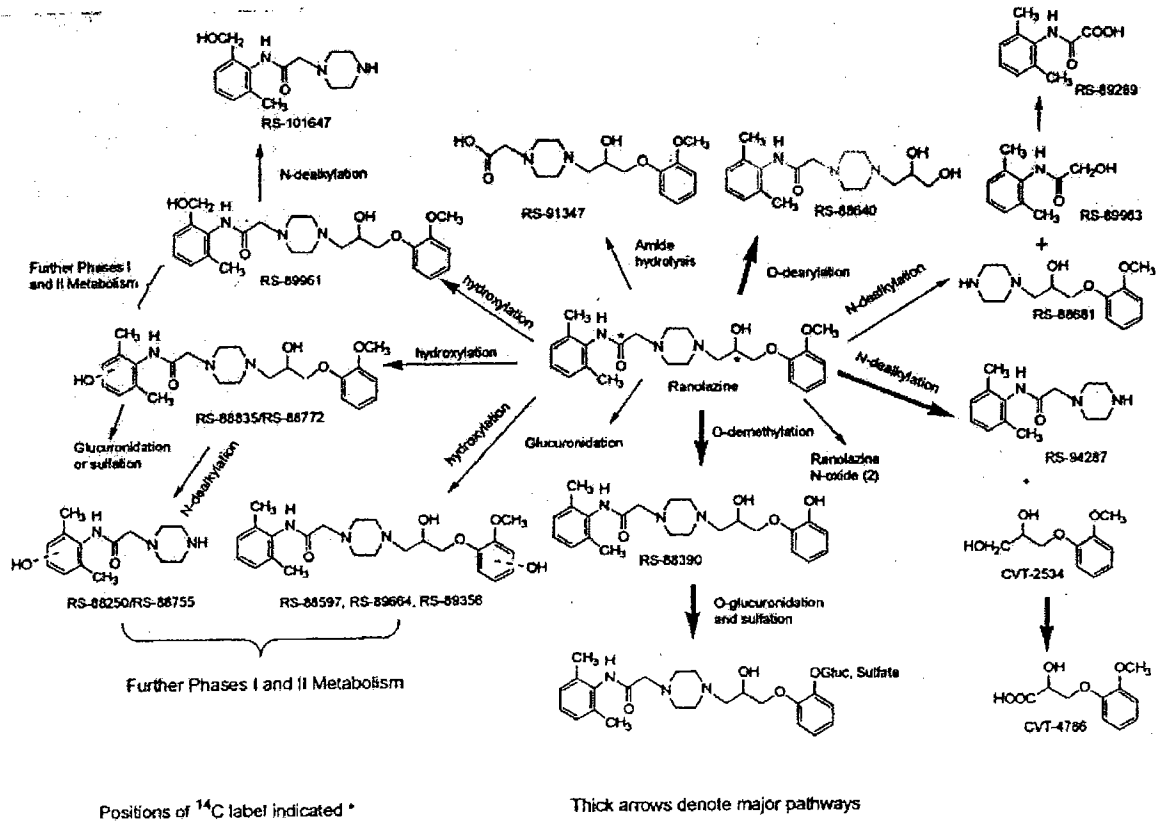

RS-88390 (CVT-2514) conjugate was the product of O-demethylation at the methoxyphenyl ring followed by sulfation and glucuronidation. N4-demethylation at the piperazine ring produced RS-94287 (CVT-2738) and CVT-4786. RS-88640 (CVT-2512) and RS-88597 (CVT-5030) were the result of O-dearylation and hydroxylation, respectively.

CONCLUSIONS:

The recovery of the administered radioactivity is essentially complete. Total radioactivity decays with an apparent mean half-life of 40.9 hours, and the major fraction is excreted in urine. The terminal half-life of ranolazine administered in solution is 1.64 hours. The major circulating metabolites are RS-88390 (CVT-2514)-Conjugate, RS-94287 (CVT- 2738), CVT-4786 and RS-88390 (CVT-2514) exhibiting average plasma concentrations that are between 36.8% and 59.3% of ranolazine. Of the identified metabolites RS-88390 (CVT-2514) exhibits the longest half-life with 13.4 hours.

COMMENTS:

1. No specifics are provided regarding calibration, LOQ, precision and accuracy of the assay methods used.

2. The 2D6 metabolizer status of the subjects investigated was not determined.
3. The metabolites in the feces were not quantified.
4. The half-life of total radioactivity in plasma (40.9 hours) was considerably longer than that of RS-88930 (CVT-2514) the metabolite with the longest half-life (13.4 hours). The measured major metabolites peaked early (Tmax 0.5-3.25 hours). The existence of a more slowly generated and /or eliminated, unidentified metabolite(s) cannot be excluded.

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STUDY CVT303.006C - SUMARY REPORT- PHARMACOKINETICS OF ADDITIONAL RANOLAZINE METABOLITES
ORAL DOSE STEADY- STATE PHARMACOKINETICS OF RANOLAZINE ADDITIONAL METABOLITES (#8) IN HEALTHY SUBJECTS, RENALLY IMPAIRED SUBJECTS AND FOLLOWING CO-ADMINISTRATION OF KETOCONAZOLE AND PAROXETINE

Report No.: CVT 303.006-C
Volume No.: 284, ITEM 6

OBJECTIVES:

To evaluate the pharmacokinetics of eight additional metabolites in plasma after multiple oral (bid) doses of ranolazine SR tablets that were measured in healthy subjects (CVT 3015), in renally (CVT 3016) and hepatically (CVT 3018) impaired subjects and in subjects receiving co-administration of ketoconazole (CVT 301-10) or paroxetine (CVT 3013). These metabolites were measured using non-GLP methods after the parent drug and the metabolites (RS-88640 (CVT-2512), RS-88930CVT-2514) and RS-94387 (CVT 2738) had been determined with validated methodology at an earlier time point.

METHODS:

The metabolite plasma concentration data were subjected to a non-compartmental analysis. AUC0-12, Cmax and t1/2 were computed.

RESULTS:

CVT 3015:Three of the metabolites displayed greater than dose proportionate kinetics. The deviation from linearity for mean AUC0-12 at the 1000 mg dose level ranged between 40.9% and 78.5% for RS-89961 (CVT- 2551), RS-88772 & 88835, and RS-88597 (CV-5030). The AUC0-12 values increased approximately dose proportionately for the metabolites RS-89289 (CVT- 2537) and RS-89983 (CVT-2535), CVT-4786, and RS-88681 (CVT-2513). Among the 8 metabolites CVT-4786 showed the largest AUC(0-12) value. The Cmax values showed the same trends. The half-lives of the metabolites ranged between 6.65 hours (CVT-4786) and 17.2 hours (RS-89289 (CVT- 2537). The half- lives of the metabolites RS-101647 (CVT-3248) and RS-88772 & 88835 tended to increase with increasing dose.

CVT 3016 : Except for RS-89983 (CVT- 2535) all other metabolites displayed a creatinine clearance dependent increase in AUC0-12 and Cmax. The increase in mean AUC0-12 of the latter metabolites in patients with severe renal impairment compared to matched healthy volunteers ranged from 92.6% to 76.0%. RS-101647 (CVT-3248) and RS-88681 (CVT-2513) showed important increases in mean t1/2 from 13.6 hours to 78.4 hours and 14.0 hours to 35.4 hours, respectively, whereas the mean t1/2 for the other 6 metabolites remained unchanged.
CVT 3018: In patients with mild or moderate liver impairment the mean AUC0-12 and Cmax decreased relative to matched healthy volunteers for 6 metabolites (RS-89289 (CVT-2537), CVT-4786, RS-88681 (CVT- 2513), RS-101647 (CVT-3248), RS-89961 (CVT- 2551) and RS-88772 & RS-88835. The decreases in AUC0-12 ranged between 12.8%and 52.6%. The exposure

measures were unchanged for RS-88597 (CVT-5030). RS-89983 showed an increase in AUC0-12 of 54.6% but only in patients with moderate liver impairment. The changes in Cmax paralleled those of the AUC0-12 values. For none of the metabolites the mean t1/2 changed importantly in patients with liver impairment.

CVT 301-10: In healthy male volunteers the co-administration of ketoconazole to ranolazine reduced the mean AUC0-12 and Cmax values of RS-101647 (CVT-3248), RS-89289 (CVT-2537), CVT-4788, RS-89983 (CVT-2535) and RS-88681 (2513). The AUC0-12 of these metabolites in the presence of ketoconazole was between 17.6% and 46.7% smaller than in the absence of ketoconazole. After co-administration of ketoconazole the mean AUC0-12 increased for RS-88597 (CVT-5030) by 219.2%, RS-89961 (CVT-2551) by 181.8%and RS-88772 & 88835 by 23.0%.

CVT 301-13: In healthy male volunteers the co-administration of paroxetine to ranolazine increased the mean AUC0-12 and Cmax values for 7 of the 8 ranolazine metabolites and decreased the corresponding values in 1 metabolite, RS-88597 (CVT-5030). The mean AUC0-12 of RS-88597 (CVT-5030) in the presence of paroxetine was 32.0% smaller compared to in the absence of paroxetine. The increase in the mean values of AUC0-12 for the 7 metabolites (RS-88597 (CVT-5030), RS-88772 & 88835, RS-88681 (CVT-2513), CVT-4786, RS-89289 (CVT-2537), RS-101647 (CVT-3248) and RS 89961 (CVT-2551) after co-administration of paroxetine ranged between 23.7% and 78.1%.

CONCLUSION:

Three of the 8 additionally measured metabolites show more than dose proportionate pharmacokinetics similar to the parent drug after administration of multiple doses ranging between 500 mg bid to1500 mg bid. Renal impairment increases the exposure to 7 of the 8 metabolites. The increase in exposure is related to the degree of renal impairment. Renal impairment decreases renal and/or non-renal elimination of these metabolites. Mild or moderate liver impairment decreases the exposure to 6 of the metabolites, suggesting a decrease in the activity of the enzymes involved in the formation of these metabolites. RS-89983 in moderate liver impairment shows an increase in exposure of 54.6%. However, the AUC0-12 value of 558 ng/mL•h is considerably smaller than the corresponding values in healthy volunteers receiving paroxetin 20 mg qd and ranolazine 1000 mg bid (1368 ng/mL•h) or 1500 mg ranolazine bid alone (973 ng/mL•h). Co-administration of ketoconazole and paroxetin with ranolazine change the exposure in opposite directions for 6 of the 8 metabolites metabolites suggesting involvement of different enzymes in the generation and/or elimination of these metabolites. The co-administration of either drug with ranolazine increases the exposure for 2 metabolites, RS-89961 (CVT- 2551) and RS-88772 & 88835 suggesting involvement of enzymes other than CYP3A4 or 2D6 in the formation and/or elimination of these metabolites.

COMMENTS:

1. Non GLP-assay methods were used.

STUDY CVT 3015 - A THREE WAY CROSSOVER STUDY TO DETERMINE THE SINGLE DOSE AND STEADY-STATE PHARMACOKINETICS OF RANOLAZINE AT DOSES OF 500 MG, 1000 MG, and 1500 MG IN HEALTHY VOLUNTEERS

STUDY INVESTIGATOR AND SITE: [

]

Report No.: CVT 3015
Volume No.: 14-17, ITEM 6

OBJECTIVES:

To determine the single dose and steady state (following four days of bid dosing) pharmacokinetics of ranolazine SR and estimate dose proportionality

FORMULATIONS:

SR tablets containing 500 mg ranolazine (Lot No. 9G2714A)

STUDY DESIGN:

This was an open-label, multiple dose, randomized, three-way crossover pharmacokinetic study. Twelve subjects were to be enrolled. Each subject was randomized to one of six sequences:

Sequence	Session 1	Session 2	Session 3
1	500 mg	1000 mg	1500 mg
2	500 mg	1500 mg	1000 mg
3	1000 mg	500 mg	1500 mg
4	1000 mg	1500 mg	500 mg
5	1500 mg	500 mg	1000 mg
6	1500 mg	1000 mg	500 mg

The subjects received at each dose level a single dose of ranolazine on Day 1, bid dosing on Days 2-5 and a single dose on Day 6. There was a minimum wash-out of 6 days between dosing sessions. The ranolazine doses were administered orally with 200mL of tap water with the volunteers in the sitting position. The subjects were institutionalized for the duration of the treatments.

ASSAY:

All samples were analyzed at CV Therapeutics, Palo Alto, CA. Ranolazine and the metabolites RS-88390 (CVT-2514), RS-88640 (CVT-2512) and RS-94287 (CVT-2738) were determined by a validated LC/MS/MS method [redacted] d3-ranolazine was used as internal standard. The respective calibration ranges were 50 ng/mL to 10'000ng/mL for ranolazine and 10 ng/ml to 2000 ng/mL for the metabolites. The calibration curves were linear (1/X weighted) with $R^2 \geq 0.990$. The mean inter-run accuracy (percent relative error) and precision (CV, %) of the method for the 4 analytes were within ±15%.

Bood Sample Collection:

Day 1: Pre a.m.dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, 24 post-dose
Days 2-5: Pre a.m.dose
Day 6: Pre a.m. dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48 post-dose

PK and Statistical Analysis:

Cmax, AUC(0-12), AUC, tmax, t1/2, Cl/f and tlag were determined for ranolazine and the metabolites using compartment model independent methods. Geometric means, the within coefficient of variation and between coefficient of variation with the logarithmically transformed data were computed for Cmax and AUC computed. AUC and Cmax were analyzed separately for dose proportionality using analysis of variance techniques. An estimate of dose proportionality and a 95 % confidence interval was constructed.

Safety:

A 12 Lead and a Lead II ECG were obtained at the following times:
Screening
Days 1 and 6: Pre-dose, and 2, 4 and 12 hours after dosing, 4 hours pa on Days 2-5 and Days 2-5: 4 hours post-dose
Discharge (48 hours post final administration).
QT intervals, QT dispersion, QRS duration, T wave amplitude and morphology were measured and QTc intervals determined. The ECG analyses were performed at St. Louis University Core ECG Laboratory. Subjects showing an increase from baseline in QTc exceeding 30% or a QTc ≥500msec at any time point of the study were withdrawn.

Vital signs were measured at scheduled times throughout the study.

RESULTS:

Fourteen (14) subjects were enrolled in the study and 13 completed all 3 sessions. One subject withdrew after completing sessions 1 and 2 for personal reasons. The mean age of the volunteers was 44.6 (20-76) years. All were of Caucasian origin.

PK:

The following 13 tables list AUC, Cmax and t1/2el parameters for ranolazine and its main metabolites RS-88640 (CVT-2512), RS-88390 (CVT-2514) and RS-94287 (CVT-2738):

Ranolazine Pharmacokinetic Parameter Estimates
AUC(0-inf) (ng.h/mL)
Summary Statistics: PK Dataset

Dose of Ranolazine / Study Day		Mean	Geometric Mean	Median	SD	CV (%)	Min	Max	N
500MG	DAY 1	9614.7	8553.3	8443.5	5489.9	52.4			12
1000MG	DAY 1	21075.4	18311.1	17275.0	13622.4	56.1			13
1500MG	DAY 1	33779.1	28997.6	27377.0	22059.5	59.2			12

Ranolazine Pharmacokinetic Parameter Estimates
AUC(0-12) (ng.h/mL)
Summary Statistics: PK Dataset

Dose of Ranolazine / Study Day		Mean	Geometric Mean	Median	SD	CV (%)	Min	Max	N
500MG	DAY 6	13720.2	11691.0	12494.0	8288.3	67.0			13
1000MG	DAY 6	32901.6	30291.0	29330.0	15541.3	42.2			14
1500MG	DAY 6	56133.8	50062.4	49972.5	29270.4	52.2			14

Ranolazine Pharmacokinetic Parameter Estimates
Cmax(obs) (ng/mL)
Summary Statistics: PK Dataset

Dose of Ranolazine / Study Day		Mean	Geometric Mean	Median	SD	CV (%)	Min	Max	N
500MG	DAY 1	1081.23	981.74	1070.00	491.45	49.1			13
	DAY 6	1766.31	1521.79	1720.00	1040.96	63.9			13
1000MG	DAY 1	1955.14	1723.21	1640.00	1136.09	54.0			14
	DAY 6	3825.00	3589.06	3870.00	1512.82	37.8			14
1500MG	DAY 1	2720.71	2505.21	2960.00	1046.31	46.9			14
	DAY 6	6215.71	5702.63	5710.00	2661.78	45.7			14

Ranolazine Pharmacokinetic Parameter Estimates
$T_{½}el$ (h)
Summary Statistics: PK Dataset

Dose of Ranolazine / Study Day		Mean	Median	SD	Min	Max	N
500MG	DAY 1	4.515	4.445	2.303			12
	DAY 6	6.824	5.775	4.178			12
1000MG	DAY 1	5.498	6.180	2.028			13
	DAY 6	6.649	6.075	2.573			14
1500MG	DAY 1	7.277	5.435	4.917			12
	DAY 6	7.340	6.680	2.333			14

RS-88640 Pharmacokinetic Parameter Estimates
AUC(0-12) Absolute and Relative Values
Summary Statistics: PK Dataset

Dose of Ranolazine / Study Day		Absolute Value (ng.h/mL)						Relative Value (%)					
		Mean	Median	SD	Min	Max	N	Mean	Median	SD	Min	Max	N
500MG	DAY 6	1599.5	1099.0	1174.8	214	3877	13	18.95	8.40	23.11			13
1000MG	DAY 6	2385.6	2092.0	1407.2	313	5044	14	8.94	7.50	6.73			14
1500MG	DAY 6	2737.7	2577.5	1623.1	509	5990	14	6.49	5.15	5.90			14

RS-88640 Pharmacokinetic Parameter Estimates
Cmax(obs) (ng/mL)
Summary Statistics: PK Dataset

Dose of Ranolazine / Study Day		Mean	Median	SD	Min	Max	N
500MG	DAY 6	160.05	111.00	119.97			13
1000MG	DAY 6	231.30	208.50	135.34			14
1500MG	DAY 6	275.24	237.50	190.53			14

RS-88640 Pharmacokinetic Parameter Estimates
$T_{\frac{1}{2}}el$ (h)
Summary Statistics: PK Dataset

Dose of Ranolazine / Study Day		Mean	Median	SD	Min	Max	N
500MG	DAY 6	21.043	20.740	7.150			12
1000MG	DAY 6	24.434	22.785	8.828			14
1500MG	DAY 6	27.452	27.280	9.228			13

RS-94287 Pharmacokinetic Parameter Estimates
AUC(0-12) Absolute and Relative Values
Summary Statistics: PK Dataset

Dose of Ranolazine / Study Day		Absolute Value (ng.h/mL)						Relative Value (%)					
		Mean	Median	SD	Min	Max	N	Mean	Median	SD	Min	Max	N
500MG	DAY 6	3711.5	3460.0	1125.0	2297	5760	13	34.06	30.10	16.62			13
1000MG	DAY 6	8043.8	7407.5	2394.7	5199	14636	14	27.69	25.30	10.63			14
1500MG	DAY 6	13867.7	13176.5	4553.4	8878	25245	14	28.81	27.95	11.28			14

RS-94287 Pharmacokinetic Parameter Estimates
Cmax(obs) (ng/mL)
Summary Statistics: PK Dataset

Dose of Ranolazine / Study Day		Mean	Median	SD	Min	Max	N
500MG	DAY 6	376.92	373.00	111.78			13
1000MG	DAY 6	769.50	717.50	238.89			14
1500MG	DAY 6	1294.64	1215.00	405.77			14

RS-94287 Pharmacokinetic Parameter Estimates
$T_{\frac{1}{2}}el$ (h)
Summary Statistics: PK Dataset

Dose of Ranolazine / Study Day		Mean	Median	SD	Min	Max	N
500MG	DAY 6	9.584	8.340	2.826			13
1000MG	DAY 6	10.090	9.230	2.883			14
1500MG	DAY 6	10.803	9.385	3.503			14

RS-88390 Pharmacokinetic Parameter Estimates
AUC(0-12) Absolute and Relative Values
Summary Statistics: PK Dataset

Dose of Ranolazine / Study Day		Absolute Value (ng.h/mL)						Relative Value (%)					
		Mean	Median	SD	Min	Max	N	Mean	Median	SD	Min	Max	N
500MG	DAY 6	4527.5	4726.0	2462.3	423	8532	13	46.11	33.30	39.22			13
1000MG	DAY 6	8868.8	7004.0	5189.7	1445	17864	14	32.27	24.20	23.67			14
1500MG	DAY 6	11587.8	10566.0	6708.3	2463	22468	14	27.04	16.00	23.53			14

RS-88390 Pharmacokinetic Parameter Estimates
Cmax(obs) (ng/mL)
Summary Statistics: PK Dataset

Dose of Ranolazine / Study Day		Mean	Median	SD	Min	Max	N
500MG	DAY 6	498.33	542.00	262.90			13
1000MG	DAY 6	913.36	785.00	543.78			14
1500MG	DAY 6	1170.07	1075.00	715.95			14

RS-88390 Pharmacokinetic Parameter Estimates
$T_{\frac{1}{2}}el$ (h)
Summary Statistics: PK Dataset

Dose of Ranolazine / Study Day		Mean	Median	SD	Min	Max	N
500MG	DAY 6	10.044	10.430	3.126			13
1000MG	DAY 6	11.990	12.290	3.599			13
1500MG	DAY 6	15.834	15.970	5.249			14

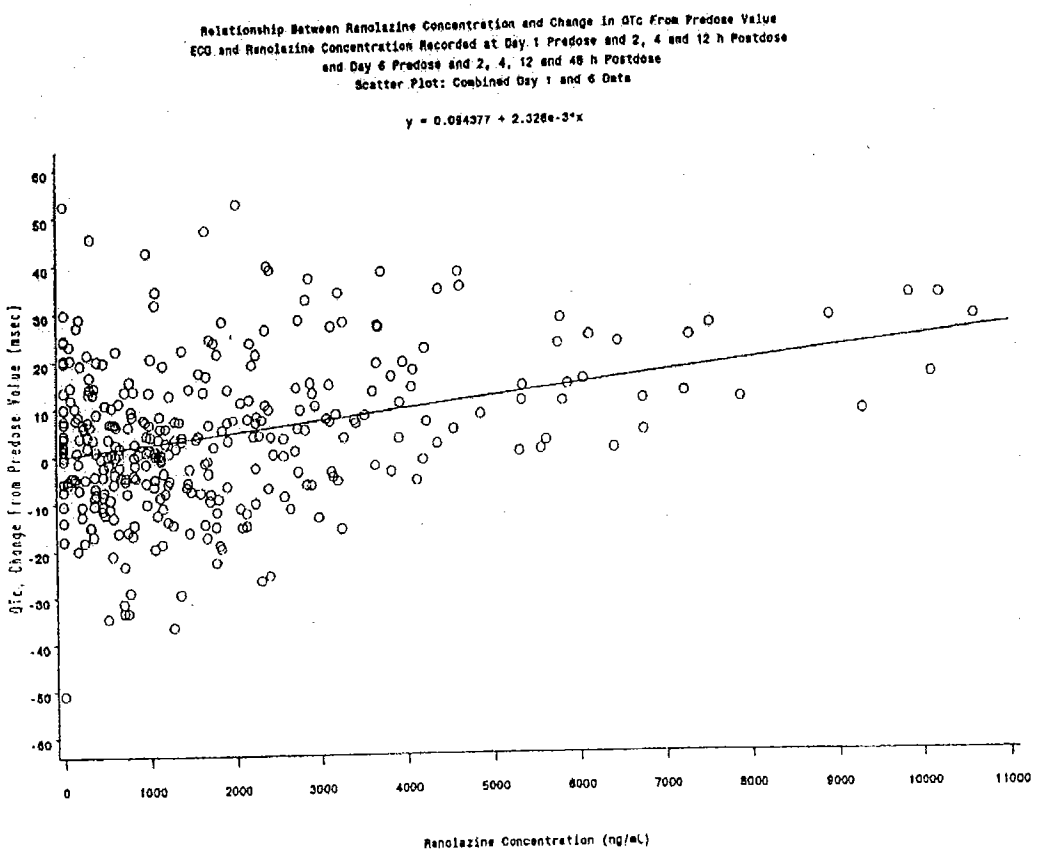
A comparison of the geometric and arithmetic mean AUC(0-τ) and Cmax values at the 3 dose levels for ranolazine on Day 6 indicated a more than dose proportionate increase for ranolazine. The geometric mean values for AUC(0-τ) expressed as multiples of the value obtained at the 500 mg bid dose level were 2.59 and 4.28 , respectively, for 1000 mg bid and 1500 mg bid. The corresponding multiples for Cmax were 2.36 and 3.75, respectively, for 1000 mg and 1500 mg bid. The arithmetic mean values for AUC(0-τ) expressed as multiples of the value obtained at the 500 mg bid level were 2.40 and 4.09, respectively for the 1000 mg and 1500 mg bid levels. The corresponding multiples for Cmax were 2.17 and 3.52 for the 1000 mg and 1500 mg bid levels.

The respective ratios of the geometric means of AUC(0-12) on Day 6 to AUC(0-∞) on Day 1 at the 500 mg, 1000 mg and 1500 mg dose levels were for ranolazine 1.37, 1.65 and 1.73, respectively . The corresponsing ratios of the Cmax values on Day 6 and Day 1 were 1.55, 2.08 and 2.28. The ratios of the arithmetic means of AUC(0-12) to AUC(0-∞) were 1.43, 1.56 and 1.66 at the 500 mg bid, 1000 mg bid and 1500 mg bid dose levels, respectively. The corresponsing ratios of the arithmetic Cmax values on Day 6 and Day 1 were 1.63, 1.96 and 2.29, respectively. All ratios exceeded 1.0 indicating some accumulation with the bid dose regimens. The ratios increased with increasing dose confirming that the pharmacokinetics of ranolazine are nonlinear.
The inter-subject variation for AUC(0-τ) and Cmax ranged between 42.2% and 67.0% and 37.8% and 63.9%, respectively. The intra-subject variation for AUC(0-τ) and Cmax of ranolazine was 22.3% and 27.7%, respectively. Maximum concentrations of ranolazine were observed on average between 2 and 5 hours after multiple dose administration and the mean apparent terminal half-life of ranolazine ranged between 6.65 hours and 7.34 hours.

The median AUC(0-τ) values for RS-94287 (CVT-2738), RS 88390 (CVT-2514) and RS- 88640 (CVT-2512) relative to ranolazine at the 500 mg bid dose level were 30.1%, 33.3% and 8.4%, respectively. At the 1500 mg dose level the AUC(0-τ) of the metabolites relative to ranolazine was similar (28.0%) only for RS-94287 (CVT-2738). For RS-88390 (CVT-2514) and RS-88640 (CVT-2512) the respective relative exposures decreased to 16.0% and 5.2 %, respectively, indicating that the formation of these metabolites decreased dose dependently as a result of saturation or product inhibition. Compared to ranolazine the apparent half-lives of the 3 metabolites were greater. RS-88640 (CVT-2512) had the longest half life (21.04-27.45 hours), followed by RS-88390 (CVT-2514) (10.04-15.83 hours) and RS-94287 (CVT-2738) (9.58-10.80 hours). The inter-subject variation of AUC(0-τ) and Cmax for RS-88640 (CVT-2512) ranged between 58.5% -75.0% and for RS-88390 (CVT-2514) between 52.8.% and 61.2%. The corresponding values for RS-94287 (CVT-2738) ranged between 29.7% and 32.8 % and were the smallest among the 4 analytes.

SAFETY:

There was a linear relationship between change from the baseline QTc value and the plasma concentrations of ranolazine as shown in the following figure:



The data show significant scatter. The predicted increase in QTc from baseline is 2.3 msec/1000 ng/mL ranolazine. No subject developed changes in QTc to meet the withdrawal criteria of a > 30% increase from baseline or an absolute value of ≥ 500msec.

A 75 years old subject experienced a single episode of syncope approximately 4.5 hours after dosing at the 1500 mg bid dose level on Day 6 of the treatment. The event lasted for 2 min. The subject then experienced dizziness. ECGs recorded 8 min after onset of syncope and at the 24 hour time point showed sinus rhythm and no clinically significant changes. The QTc interval was 428 msec in the ECG taken 8 min after onset of the syncope. The QTc interval of the baseline ECG taken at Day 1 of the same session was 416 msec. The subject was well following the resolution of the syncope and dizziness and returned to complete Session 3 (500 mg). Both syncope and dizziness were assessed as possibly drug related.

The T-wave amplitude was dose dependently decreased. No consistent change in the duration of QRS was found. A dose dependent decrease of the systolic and diastolic blood pressure relative to baseline was noted. The respective mean maximum decrease in systolic blood pressure with

the 1500 mg treatment was 10.8 mmHg (1500 mg, Day 6 at 4 hours post-dose). The mean maximum decrease of the diastolic blood pressure was 8.4 mmHg (1000 mg, Day 6 at 2 hours pst-dose) at the 1000 mg level.

CONCLUSIONS:

The pharmacokinetics of ranolazine are more than dose proportionate. Ranolazine is a drug with high intersubject variability. The exposures to the individual metabolites RS-94287 (CVT-2738), RS-88390 (CVT-2514) and RS-88640 (CVT-2512) relative to ranolazine range between 28.0-30.1%, 16.0 - 33.3%, and 5.2-8.4%, respectively. At the higher dose levels the exposure to RS-88390 (CVT-2514 and RS-88640 (CVT-2512) decrease relative to ranolazine. The exposure to RS-94287 (CVT 2734) relative to ranolazine is not dose dependent. The metabolites display longer half-lives than ranolazine. The increase of the pre-dose QTc is linearly related to the plasma concentration of ranolazine. The predicted mean increase in QTc from baseline is 2.3 msec/1000 ng/mL ranolazine. A significant decrease in systolic and diastolic blood pressure are noted at the 1500 mg and 1000 mg dose level. A possibly drug related syncope followed by dizziness was observed in a 76 year old subject who received multiple doses of 1500 mg bid about 4.5 hours following drug administration.

COMMENTS:

1. No female subjects were enrolled in this pharmacokinetic and tolerability study.
2. A justification for weighting the concentrations of the calibration standards by 1/X hould be given.
3. Baseline ECGs should have been measured for a period of 24 hours in order to determine time specific QTc interval changes.
4. The type of heart rate correction algorithm applied and a justification for its use should have been provided in the report.
5. Attainment of steady-state for ranolazine was not evaluated statistically.
6. AUC(0-12) on Day 1 and the accumulation factor were not provided.
7. The estimates for the terminal half lives for RS-94287 (CVT-2738) and RS-88640 (CVT-2512) after multiple dose administration in the present study were considerably longer than the estimates after single dose administration in study CVT 3019.
8. The relationship between QTc and the plasma concentrations of ranolazine was not explored
9. The a.m. and p.m. trough values on Day 6 were not analyzed for a possible circadian rhythm.

STUDY RAN0114 (CL 6876) - AN ASCENDING MULTIPLE DOSE STUDY TO ASSESS THE PHARMACOKINETICS AND TOLERABILITY OF SUSTAINED RELEASE RANOLAZINE IN HEALTHY MALE VOLUNTEERS

STUDY INVESTIGATOR AND SITE: [

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Report No: RANS0114 (CL 6876)
Volume No.: 225, 226, ITEM 6

OBJECTIVES:

To assess the safety, tolerability, hemodynamic and pharmacokinetic profile of multiple oral doses of sustained release ranolazine at 500 mg, 750 mg and 1000 mg twice daily (bid) in young male subjects.

FORMULATIONS:

500 mg SR tablets (Lot No. CT1123SC1215A, CT1123SC121B)
750 mg SR tablets (Lot No.CT1123SCV1213A)
Matching placebo tablets (Lot No. CT1123SC1211A and CT1123SC1211A)

STUDY DESIGN:

This was a double-blind, four-way crossover study with three ascending doses of ranolazine SR with a randomized placebo phase using a double dummy technique.
Nine healthy male subjects were enrolled in the study. The volunteers received the ranolazine dose in ascending order and the placebo phase was randomly assigned.The volunteers received drug or placebo bid on Days 1-4 and a single morning dose on Day 5 of each treatment phase. The tablets were taken with 150 mL water. A washout of at least 6 days was maintained between the different treatments. The subjects were institutionalized from the evening before Day 1 until the morning of Day 6, returning by taxi for the 30 hours and 48 hours post-dose assessments. Based on previous information 8 subjects were sufficient to detect with 80% power changes in erect systolic and diastolic blood pressure of 11.2 mmHg and 9.6 mmHg, respectively.

TREATMENT CODE

Subject	Phase 1	Phase 2	Phase 3	Phase 4
AM001	Placebo	500 mg	750 mg	1000 mg
EM002	500 mg	750 mg	Placebo	1000 mg
JA003	500 mg	750 mg	1000 mg	Placebo
BD004	500 mg	Placebo	750 mg	1000 mg
TC005	Placebo	500 mg	750 mg	1000 mg
BG006	500 mg	-	-	-
NS007	500 mg	-	-	-
MQ008	500 mg	750 mg	Placebo	1000 mg
FM103	500 mg	750 mg	1000 mg	Placebo

ASSAY:

Plasma concentrations of ranolazine were measured by a specific HPLC method with fluorimetric detection [redacted]. The LOQ was set at 10ng/mL.

Blood Sample Collection

Day 1: Predose, 5 and 12 hours pa
Days 2-4: Predose a.m.
Day 5: Predose, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 30 and 48 hours pa

PK and Statistical Analyis:

Cmax, tmax, $AUC_{96\text{-}108h}$, C_{96h}, C_{108h} and Cave ($AUC_{96\text{-}108h}$/12h) and degree of fluctuation (Cmax-Cmin/Cave) were obtained by routine methods. Cmax, $AUC_{96\text{-}108h}$, C_{96h}, C_{108h} and degree of fluctuation were tested for linearity and dose proportionality. Linearity was assesed ussing a mixed effects analysis of variance (ANOVA) model. The test for linearity consisted of fitting linear and quadratic constants to the treatment means.
Dose proportionality was assesed using ln transformed parameters. An analysis of covariance was fitted, with log dose as a covariate and subject and residual as random effects. The test for dose proportionality was performed by testing whether the coefficient of log dose was significantly different from 1. Day 5 degree of fluctuation was analyzed by a mixed effects ANOVA model with treatment as fixed effect and subject and the residual as random effects. The analysis was performed with untransformed and log transformed data. Attainment of steady state was tested by fitting an analysis of covariance to C_{48}, C_{72} and C_{96}, with time from the first steady state sample as a covariate and subject and residual as random effects. The test for steady state was performed by testing whether the coefficient for time was significantly different from zero. The tests for linearity, dose proportionality and steady state were made using two-sided t-tests employing estimates of variability from the ANOVA models. Confidence intervals (90%

and 95%) were calculated for the linear and quadratic estimates and the linear regression coeffeicients for log dose and time. Comparisons of the degree of fluctuation between the different treatments on Day 5 were made. Confidence intervals (95% and 90%) were calculated for the treatment comparisons.

Safety:

A twelve lead ECG was recorded at the following times:
Pre-dose, 4 and 12 hours post-dose.
The standard intervals as measured by the machines were used.
Supine and erect systolic and diastolic blood pressure and heart rate were measured at the following times:
Days 1-5: Pre-dose and 2, 4, 6, 8 and 12 hours post-dose.

RESULTS:

Seven (7) of the 9 enrolled subjects completed the study. A first subject withdrew for personal reasons. A second subject displayed a prolonged PR interval assessed to be possibly drug related. A third individual withdrew temporarily on Day 5 during treatment with 750 mg ranolazine. A fourth subject receiving the 1000 mg treatment displayed a lower than predicted C_{72h} value and a C_{96h} value below LOQ. The values obtained at the 1000 mg dose level for this subject were not included in the computation of the mean. The mean values for the pharmacokinetic parameters of ranolazine are listed in the following table:

MEAN RANOLAZINE PHARMACOKINETIC PARAMETERS AFTER MULTIPLE ORAL DOSING AT 500 mg, 750 mg AND 1000 mg RANOLAZINE SR TWICE DAILY

Parameter	Dose		
	500 mg SR bid	750 mg SR bid	1000 mg SR bid
C_{max} (ng/ml)	1760 ± 715	2710 ± 657	3660 ± 1090
t_{max} (h)	2.00 ± 1.15	4.33 ± 1.62	4.17 ± 2.48
C_{108h} (ng/ml)	585 ± 340	1260 ± 501	2020 ± 723
C_{min} (ng/ml)	585 ± 340	1260 ± 501	1960 ± 812
$AUC_{96-108h}$ (ng.h/ml)	13200 ± 5180	24100 ± 5540	33300 ± 10600
C_{ave} (ng/ml)	1100 ± 433	2010 ± 463	2770 ± 890
Degree of fluctuation	1.12 ± 0.313*	0.746 ± 0.269	0.640 ± 0.139

Values are given as Mean ± SD in terms of ranolazine base.
n=6 except for 500 mg where n=7.
* Statistically significantly different from the values at 750 and 1000 mg dose levels, using untransformed data; $p<0.05$.

The values for C_{48}, C_{72} and C_{96} were not statistically significantly different from each other.The plasma concentrations of ranolazine increased more than dose proportional: There was a surplus of 26.1% and 4.0% in arithmetic mean AUC $_{96-108h}$ and Cmax at the 1000 mg dose level

compared to the 500 mg dose level. Steady state concentrations of ranolazine were reached after 3 days of bid dosing. Maximum plasma concentrations on Day 5 occurred from 2 hours to 4 hours post-dose. The mean trough concentrations in the morning of Day 5 (C_{96h}) were at the 500 mg, 750 mg and 1000 mg dose levels 68.9%, 32.5% and 25.2% respectively, greater than in the evening (C_{108h}), indicating a diurnal variation. The degree of fluctuation decreased with increasing dose: The arithmetic mean Cmax and Cmin values deviated from the average concentration by 112% at the 500 mg dose level, but only by 64% at the 1000 mg dose level.

SAFETY:

The mean (SD) apparent QTc intervals 4 hours and 12 hours post-dose on Day 5 of the treatment with 750 mg ranolazine were 17.3 (4.8) msec and 18.9 (4.8) msec, respectively, greater than with placebo. The respective values with the 1000 mg treatment were 26.7 (4.9) msec and 20.8 (4.9) msec.
One subject showed an increase of LDH of 100 IU/l accompanied by a simultaneous increase in bilirubin from 11 μM to 22 μM during the treatment with 750mg ranolazine. The treatments with 500 mg and 1000 mg ranolazine in the subject were uneventful.

CONCLUSIONS:

The pharmacokinetics of ranolazine are more than dose proportional. Steady state is reached after 3 days of a bid treatment. There is evidence for diurnal variation with greater trough levels in the morning than in the evening. The apparent mean maximum QTc interval increase relative to placebo at the 750 mg and 1000 mg dose levels is 17.3 msec and 26.7 msec, respectively.

COMMENTS:

1. The assay and validation reports are missing. No data on accuracy and precision are reported.
2. No females were enrolled in the study.
3. Baseline QTc values should have been determined over a period of 24 hours in order to estimate the time specific changes in QTc.
4. The QT intervals should have been evaluated by a blinded Cardiologist and a justification for the applied heart correction algorithm provided in the report
5. The relationship between QTc and the plasma concentrations of ranolazine were not explored
6. QTc prolongation was not a concern in the calculation of statistical power.
7. Results on the cross validation of the HPLC assay with fluorimetric detection used in the present study and the LC/MS/MS assay used in other studies was no provided.

STUDY RANS0117 (CL 6905) - AN ASCENDING MULTIPLE DOSING STUDY TO ASSESS THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SUSTAINED RELEASE RANOLAZINE ADMINISTERED THREE TIMES DAILY IN HEALTHY MALE SUBJECTS

STUDY INVESTIGATOR AND SITE: [redacted]

Report No.: RAN0117 (CL 6905)
Volume No.: 227-229, ITEM 6

OBJECTIVES:

To assess the safety, tolerability and pharmacokinetic profiles of multiple oral doses of sustained release ranolazine (ranolazine SR) at 500 mg, 750 mg and 1000 mg three times daily (tid) in young healthy male subjects

FORMULATIONS:

500 mg SR tablets (Lot No. CT 1136SC1215A)
750 mg SR tablets (Lot No. CT1136SC1213A)
Matching placebo tablets (respective Lot Nos. CT1136SC1211A and CT1136SC1212A)

STUDY DESIGN:

This was a double blind, four-way crossover study with three ascending doses of ranolazine and a randomized placebo phase using a double dummy technique. The volunteers received the ranolazine doses in ascending order and the placebo phase was randomly assigned as shown in the following scheme:

TREATMENT CODE

Subject	Phase 1	Phase 2	Phase 3	Phase 4
DF001	500 mg	Placebo	750 mg	-
AS002	500 mg	750 mg	1000 mg	Placebo
IA003	Placebo	500 mg	-	-
DM004	500 mg	750 mg	Placebo	1000 mg
DS005	500 mg	750 mg	1000 mg	Placebo
MH006	500 mg	Placebo	750 mg	1000 mg
AH007	500 mg	750 mg	Placebo	1000 mg
EH008	Placebo	500 mg	-	-
AC101	500 mg	Placebo	750 mg	1000 mg
PG103	500 mg	750 mg	Placebo	1000 mg
SD104	Placebo	500 mg	750 mg	1000 mg

The volunteers received drug or placebo bid on Days 1-4 and a single dose in the morning of Day 5. The tablets were taken with 150mL water. A washout of at least 6 days was maintained between the different treatments. The subjects were institutionalized from the evening before Day 1 until the morning of Day 6 of each treatment phase, returning by taxi for the 30 hours and 48 hours post dose assessments. The number of subjects enrolled was selected based on previous information predicting that the inclusion of 8 subjects was sufficient to detect with 80% power changes in erect systolic and diastolic blood pressure of 12.2 mmHg and 7.0 mmHg, respectively.

ASSAY:

Plasma concentrations of ranolazine were measured by a HPLC method with fluorimetric detection [redacted] The LOQ was set at 10 ng/mL.

Blood Sample Collection

Day 1: Pre-dose, 5 hours and 8 hours post-dose
Days 2-4: Pre-dose am.
Day 5: Pre-dose, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 30 and 48 hours post-dose

PK and Statistical Analysis:

Cmax, tmax, AUC $_{96\text{-}108h}$, C_{96h}, C_{104h}, Cave (AUC $_{96\text{-}104}$/8h) and degree of fluctuation (Cmax-Cmin/Cave) were obtained by standard methods. Day 5 Cmax, $AUC_{96\text{-}104h}$, C_{96h}, and C_{104h} were tested for linearity and dose proportionality and C_{48h}, C_{72h} and C_{96h} for attainment of steady-state. The impact of dose on the degree of fluctuation was also evaluated. Day 5 AUC $_{96\text{-}104h}$, Cmax, C_{96h} and C_{104h} were tested for linearity and dose proportionality. Lineariy was assesed using mixed effects analysis of variance (ANOVA) model with treatment as fixed effect and subjects and the residual as random effects. Linear and quadratic contrasts of the treatment means were fitted to test for linearity. Ninety and 95% confidence intervals were calculated for the linear and quadratic estimates. Dose proportionality was assesed using log (base e) transformed parameters. An analysis of covariance model was fitted, with log dose as covariate and subject and residual as random effects. The test for dose proportionality was performed by establishing whether the coefficient of log dose was significantly different from 1. Confidence intervals (90% and 95%) were calculated for the linear regression coefficient for log dose.
Day 5 degree of fluctuation was analyzed using fixed effects ANOVA model with treatment as fixed effect and subject and residual as random effects. The analysis used both untransformed and log transformed data. Following the ANOVA treatment comparisons were performed via two-sided t-tests using estimates of variability from the ANOVA model. Confidence intervals (90% and 95%) for the treatment comparisons were calculated. An analysis of covariance model was fitted to C_{48h}, C_{72h}, and C_{96h} data to test whether steady state was attained. The time from the first steady state sample was used as covariate and subject and the residual as random effects. The test for steady-state was perfomed by testing whether the coefficient for time was

significantly different from zero. Confidence intervals (90% and 95%) were calculated for the linear regression coefficient for time.

Safety Parameters

A 12 lead ECG was recorded at the following times:
Day 1-5: Pre-dose, 5 and 8 hours post-dose
The standard intervals as measured by the machine were used.
Supine and erect systolic and diastolic blood pressure and heart rate were measured at the following times:
Days 1-5: Pre-dose and 1, 3, 5, 13 hours post-dose.

RESULTS:

Only 6 of the 11 subjects enrolled completed all the study phases. Eight subjects initially entered the study and 4 subjects withdrew, 3 for personal reasons and 1 because of an adverse event (indigestion). The 3 subjects who withdrew for personal reasons were replaced. One of the latter subjects missed the last 2 doses in Phase 3, but returned for Phase 4. The mean age of the 6 evaluable subjects was 26.0 years. All were of Caucasian origin.

PK:

Six (6) subjects were available for full pharmacokinetic analysis. The salient findings are listed in the following table:

MEAN DAY 5 RANOLAZINE PHARMACOKINETIC PARAMETERS FOLLOWING MULTIPLE ORAL ADMINISTRATION AT 500, 750 AND 1000 mg RANOLAZINE SR tid

Parameter	500 mg SR tid (n=6)	750 mg SR tid (n=6)	1000 mg SR tid (n=6)
C_{max} (ng/ml)	1990 ± 629	3690 ± 1260	5290 ± 1760
t_{max} (h)	3.67 ± 1.51	3.33 ± 1.97	2.42 ± 1.50
C_{96h} (ng/ml)	1290 ± 383	2800 ± 811	4360 ± 1250
C_{104h} (ng/ml)	1090 ± 453	2330 ± 1460	3330 ± 935
C_{min} (ng/ml)	989 ± 257	2010 ± 819	3290 ± 976
$AUC_{96-104h}$ (ng.h/ml)	11900 ± 3710	23700 ± 9250	33700 ± 9570
C_{ave} (ng/ml)	1490 ± 464	2960 ± 1160	4210 ± 1200
Degree of fluctuation	0.659 ± 0.118*	0.606 ± 0.183	0.457 ± 0.112

Values are given as Mean ± SD
Degree of Fluctuation statistically compared between doses: * Statistically significantly different from the value at 1000 mg dose level, using log-transformed data; $p<0.05$.

The pharmacokinetics of ranolazine were more than dose proportional: There was a surplus increase in arithmetic mean $AUC_{96-104h}$ and Cmax of 41.6% and 32.9%, respectively, at the 1000 mg dose level compared to the 500 mg dose level. Steady-state was reached by Day 3 with the 750 mg treatment and by Day 4 with the 1000mg treatment. With the 500 mg treatment steady-

state was not attained by Day 4. Peak concentrations of ranolazine were observed 2.5 to 4 hours after drug administration. The arithmetic mean trough concentrations in the morning of Day 5 (C_{96h}) were at the 500mg, 750 mg and 1000 mg dose levels 18.3%, 20.2 % and 30.9% greater than the evening trough concentrations (C_{104h}) indicating a diurnal variation. The degree of fluctuation decreased with increasing dose: The Cmax and Cmin values deviated from the average concentration by 65.9% at the 500 mg dose level compared to 45.7 % at the 1000 mg dose level. Mean tmax ranged between 2.42 hours and 3.67 hours.

SAFETY:

The mean QTc interval values under active treatment became greater than under placebo on Days 4 and 5. There were statistically significant increases of the mean apparent QTc interval compared to placebo with the 750 mg treatment 5 hours post-dose on Day 5 (+15.2msec) and with the 1000 mg treatment predose (+12.2msec) and 5 hours post dose (+17.0msec) on Day 5. A statistically significant correlation existed between QTc and the plasma concentrations of ranolazine. One subject displayed QTc values of 503 msec (8 hours post-dose on Day 4 of the 500 mg treatment) and 524 msec (5 hours postdose on Day 4 of the 750 mg treatment). A retrospective evaluation of the ECGs showed dose related morphological changes in the T-wave.

The PR intervals on Days 4 and 5 during active treatment tended to become greater than during placebo. Statistically significant increases of the PR interval relative to placebo were found on Day 5 at few times of the treatments with 750mg and 1000mg ranolazine.

CONCLUSIONS:

The pharmacokinetics of ranolazine are not dose proportional. There is a surplus increase in AUC and Cmax with increasing dose. Steady state is reached after ≤ 4 days of treatment at the 750 mg and 1000 mg dose levels. The pharmacokinetics of ranolazine are subject to diurnal rhythm with greater morning than evening through concentrations. The QTc interval is correlated with the plasma concentrations of ranolazine. The respective mean (se) increase of the apparent QTc interval relative to placebo on Day 5 is +15.2 (5.7) msec and +17.0 (5.9) msec with the 750 mg and 1000 mg doses.

COMMENTS:

1. The assay and validation reports are missing. No estimates for the accuracy and precision of the method were provided.
2. No females were enrolled in the study.
3. Baseline ECG should have been measured over a 24 hour interval to determine time specific increases in the QTc interval.
4. The QT intervals should have been evaluated by a blinded Cardiologist and a justification for the applied heart rate correction algorithm to compute QTc should have been provided.
5. QTc prolongation was not a concern in the calculation of statistical power.

6. No data on the crossvalidation of the HPLC assay with fluorimetric detection used in the presence study and the LC/MS/MS assay used in other studies were provided.

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STUDY RAN0201 (CL 6922) -A STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF RANOLAZINE SR 1500 AND 2000 MG ADMINISTERED TWICE DAILY IN YOUNG, HEALTHY MALE SUBJECTS

STUDY INVESTIGATOR AND SITE: [

]

Report No.: RAN01201 (CL 6922)
Volume No.: 235, 236, ITEM 6

OBJECTIVES:

To assess the safety, tolerability and pharmacokinetic profiles of multiple oral doses of ranolazine SR at 1500 mg and 2000 mg, administered twice daily (bid) to healthy young male subjects

FORMULATIONS:

500 mg SR tablets (Lot No. CT1146SC1215B)
750 mgSR tablets (Lot No. CT1146SC1213A)
Matching placebo tablets (respective Lot Nos. CT1146SC1211A and CT1146SC1212A)

STUDY DESIGN:

This was a double-blind, three-way crossover study with ascending doses of ranolazine SR and a randomized placebo phase using a double dummy technique. The doses of ranolazine were given in ascending order and the placebo phase was randomly assigned. As shown in the following scheme:

TREATMENT CODE

Subject	Phase 1	Phase 2	Phase 3
KJ001	1500 mg	2000 mg	Placebo
PR002	1500 mg	Placebo	2000 mg
GR003	Placebo	1500 mg	2000 mg
JM004	1500 mg	2000 mg	Placebo
RS005	Placebo	1500 mg	2000 mg
AM006	1500 mg	Placebo	2000 mg
GF007	1500 mg	Placebo	2000 mg
RD008	1500 mg	2000 mg	Placebo

The volunteers received ranolazine or placebo bid on Days 1-4 and a single dose on Day 5 of each treatment phase. The tablets were taken with 150 mL water. A washout of at least 6 days was maintained between the treatments. The subjects were institutionalized from the evening before Day1 until the morning of Day 6 of each treatment phase, returning by taxi for the 30 hours and 48 hours post dose assessments. The number of subjects enrolled was selected based on previous information predicting that the inclusion of 8 subjects was sufficient to detect with 80% power changes in erect systolic and diastolic blood pressure of 10.9 mmHg and 9.8 mmHg, respectively.

ASSAY:

Racemic ranolazine plasma concentrations were determined by a HPLC method[C fluorimetric detection [L J The individual enantiomers (+)R and (-)S ranolazine were measured on Day 5 of the 1500mg treatment using HPLC with fluorometric detection [L J. The respective LOQ of the racemic and the enantioselective assays was 10ng/mL and 100ng/mL. The precision (CV%) of the racemic assay was ≤ 22.2% and the recovery ranged between 98.2% and 103%. The precision of (+) R ranolazine was ≤ 15.0% and the accuracy ranged between 103% and 115%. The precision for the (-) S ranolazine was ≤ 23.0% and the recovery ranged between 95.0% and 106%.

Blood Sample Collection

Day 1: Pre-dose, 5 and 12 hours post-dose
Days 2-4: Pre-dose a.m.
Day 5: Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 30, 48 hours post-dose

PK and Statistical Analysis:

Cmax, tmax, Cmin, C_{96h}, C_{108h}, $AUC_{96\text{-}108h}$, Cave ($AUC_{96\text{-}108}$/12h), and the degree of fluctuation (Cmax-Cmin)/Cave for racemic ranolazine were determined by standard methods. The same parameters were also determined for (+) R and (-) S ranolazine at the 1500 mg dose level. The morning trough levels of racemic ranolazine measured on Days 3-5 (C_{48h}, C_{72h} and C_{96h}) were tested for attainment of steady state. An analysis of covariance was fitted to these plasma concentrations with time from the first steady state sample as a covariate and subject and the residual as random effects. The test for steady state was performed by testing whether the coefficient for time was significantly different from zero. The untransformed and log transformed data were used. The tests for steady state were made using two-sided t-tests using estimates of variability from the ANOVA models. Confidence intervals (90% and 95%) were calculated for the linear regression coefficients for time. An additional analysis used a mixed effects ANOVA model with day as fixed effect and subject and residual as random effects. The untransfomed and log transformed data were used. Confidence intervals (90% and 95%) were calculated. No adjustments for multiple comparisons were made.

The hemodynamic and ECG parameters obtained for the Day 1 pre-dose treatment means and on Day 5 were compared across treatments using a mixed effects ANOVA model.
The fixed effects were treatment, phase, time and time by treatment. The fixed effects of carryover, phase by treatment and phase by time were tested for and removed from the model. The random effects were subject, subject within treatment and phase, and the residual. The phase, treatment, carryover and phase by treatment effects were tested against the subject within phase and treatment and all other fixed effects were tested against the residual. Following the ANOVA, the effects of the two doses of ranolazine were compared with the effects of placebo. All treatment comparisons were performed via two-sided t-tests using estimates of variability from the ANOVA model. Confidence intervals (90% and 95%) for the diffeence between treatment means were calculated. No adjustments for multiple comparisons were made.

Safety Parameters

Supine and erect systolic and diastolic blood pressures were measured on Days 1-5. A 12 Lead ECG was recorded on Days 1-4 pre-dose, 4 and 12 hours post-dose on Days 1-4. On Day 5 the ECG recordings were performed pre-dose, 2, 4, 6, 8, 12 and 24hours pa. The standard intervals as measured by the machine were used. The ECG recording were reviewed by a Syntex Cardiologist for changes in T-wave morphology.

RESULTS:

Eight (8) subjects entered and completed the study. The mean age of the subjects was 26.8 years. Seven of the subjects were of Caucasian origin and 1 was of Mongoloid race.

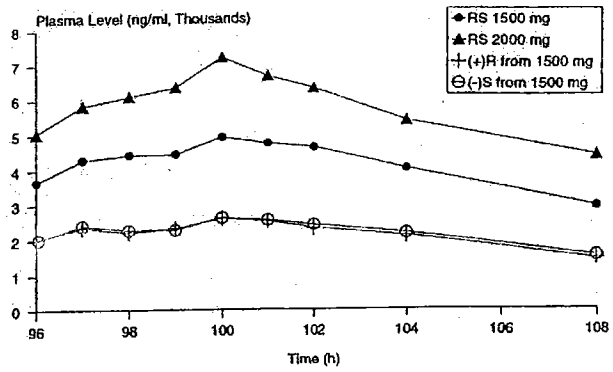
PK:

The salient pharmacokinetic findings are listed and depicted in the following table and figure:

SUMMARY OF RS, (+)R AND (-)S RANOLAZINE PHARMACOKINETIC PARAMETERS

Parameter	1500 mg SR bid			2000 mg SR bid
	RS ranolazine	(+)R ranolazine	(-)S ranolazine	RS ranolazine
C_{max} (ng/ml)	5284 ± 2434	2909 ± 1308	2944 ± 1426	7281 ± 2700
C_{min} (ng/ml)	2932 ± 1918	1436 ± 1046	1514 ± 1201	4149 ± 2228
t_{max} (h)	4.00*	4.00*	4.00*	4.00*
C_{96h} (ng/ml)	3656 ± 1477	2009 ± 1137	2399 ± 1205	5042 ± 1797
C_{108h} (ng/ml)	2942 ± 1937	1447 ± 1071	1541 ± 1260	4398 ± 2396
$AUC_{96-108h}$ (ng.h/ml)	49516 ± 23945	25731 ± 13385	26407 ± 14849	68459 ± 25842
C_{ave} (ng/ml)	4126 ± 1995	2144 ± 1115	2201 ± 1237	5705 ± 2153
Degree of fluctuation	0.664 ± 0.336	0.833 ± 0.402	0.824 ± 0.443	0.591 ± 0.240

Values are given as Mean ± SD, except for * = Median t_{max}



Day 5 96-108h Mean Plasma RS, (+)R and (-)S Ranolazine Levels (n=8)

Steady-state concentrations of racemic ranolazine were reached on Day 4. Median tmax was observed at 4 hours post dose at both dose levels. The mean trough concentrations of racemic ranolazine in the morning of Day 5 (C_{96h}) at the 1500 mg and 2000 mg dose levels were 24.3% and 14.6% greater, respectively, than the evening trough concentrations (C_{108h}) indicating a diurnal rhythm. The degree of fluctuation of the mean maximum and minimum concentrations about the average concentration was 66.4% at the 1500 mg dose level and 59.1% at the 2000 mg dose level.
The $AUC_{96\text{-}108h}$ and Cmax values for the 2 enantiomers were similar, indicating no stereoselective pharmacokinetics for ranolazine. The median peak concentrations of (+)R and (-)S ranolazine occurred 4 hours pa. Both enantiomers showed greater trough levels in the morning than in the evening in agreement with the findings for racemic ranolazine. The intersubject variation in $AUC_{96\text{-}108h}$ and Cmax for the enantiomers and racemic ranolazine was similar and ranged between 45.0% and 56.2 % at the 1500 mg dose level.

SAFETY:

Relative to placebo the mean erect systolic and diastolic blood pressure values changed statistically significantly by -11.9 mmHg and -6.6 mmHg, respectively, 4 hours after 1500 mg ranolazine on Day 5. At the 2000 mg dose level the erect diastolic blood pressure was decreased by 6.6mmHg 4 hours post-dose on Day 5. A statistically significant change in the orthostatic systolic blood pressure of -9.8 mmHg relative to placebo was noted 4 hours after 1500 mg ranolazine on Day 5. A similar change in the orthostatic systolic blood pressure of -8.4 mmHg was observed 6 hours after 2000 mg on Day 5. Because of lightheadedness measurements of the erect blood pressure could not be completed on Day 5 in the time interval between 2 hours and 6 hours post-dose in 3 individuals at the 1500 mg dose level and in 2 individuals at the 2000 mg dose level.

The mean QTc interval data are listed in the following table:

MEAN ECG DATA
QT_c Interval (msec)

Day	Time Post-Dose	Treatment								
		Placebo			1500 mg SR			2000 mg SR		
		n	mean	se	n	mean	se	n	mean	se
1	Pre-dose	8	392.9	2.8	8	396.4	4.0	8	405.8	6.3
	4 h	8	398.1	6.7	8	393.8	7.5	8	396.0	4.2
	12 h	8	400.1	4.9	8	397.8	5.8	8	411.8	5.8
2	Pre-dose	8	389.6	3.1	8	398.3	4.8	8	410.4	7.3
	4 h	8	397.1	6.5	8	406.4	5.9	8	406.8	7.3
	12 h	8	395.4	4.9	8	401.6	5.9	8	412.6	7.7
3	Pre-dose	8	403.1	3.6	8	402.6	2.2	8	409.8	8.1
	4 h	8	397.4	8.0	8	403.8	5.5	8	409.3	5.1
	12 h	8	397.3	3.8	8	404.8	6.2	8	411.8	6.8
4	Pre-dose	8	389.4	5.0	8	411.0	5.7	8	412.3	6.8
	4 h	8	400.1	9.4	8	406.1	7.0	8	418.5	7.3
	12 h	8	398.5	6.4	8	410.4	5.0	8	415.9	5.1
5	Pre-dose	8	397.1	8.1	8	409.4	6.3	8	417.5	4.8
	2 h	8	394.3	5.4	8	407.0	7.0	8	417.5	7.0
	4 h	8	388.9	5.0	8	405.6	6.6	8	418.9	5.5
	6 h	8	400.9	6.6	8	414.9	6.7	8	416.9	6.3
	8 h	8	391.1	5.7	8	407.8	7.0	8	414.0	6.0
	12 h	8	403.1	6.8	8	412.6	6.1	8	417.9	6.7
	24 h	8	396.1	4.8	8	403.4	4.6	8	404.6	6.5

Key:
n = number of subjects
mean = raw (unadjusted) mean
se = standard error of the mean

The least square mean QTc intervals and differences between the treatments are shown in the following table:

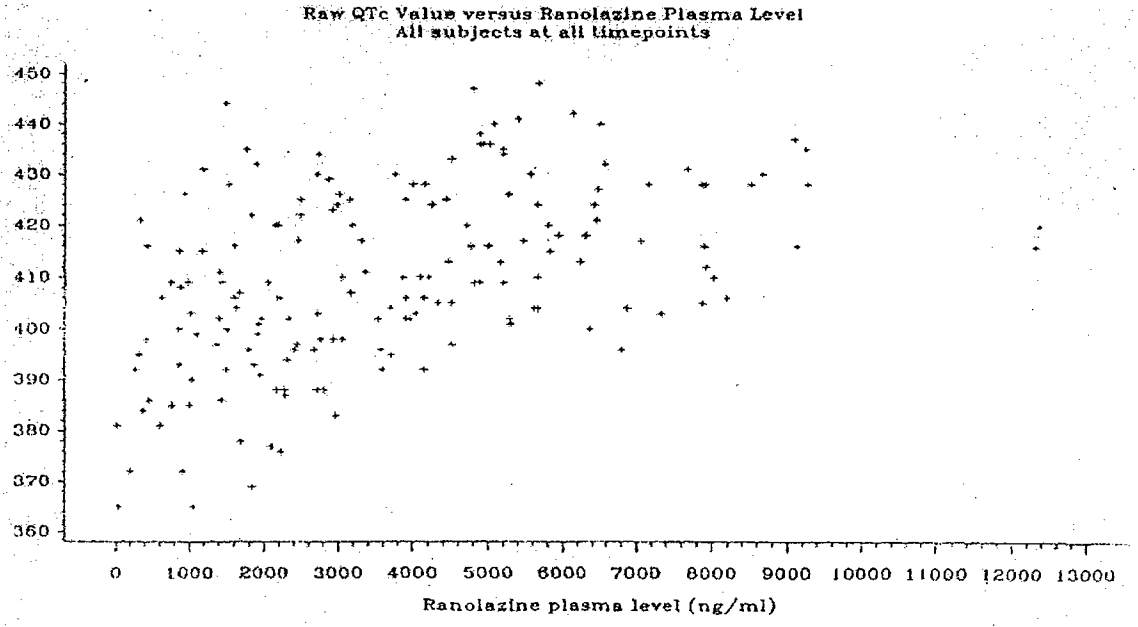
QT_c Interval (msec)
Mean Values and Treatment Comparisons : Day 5

Treatment		Time						
		Pre-dose	2 h	4 h	6 h	8 h	12 h	24 h
1500 mg SR	mean	412.6	410.2	408.9	418.1	410.9	416.8	406.6
	se	6.3	6.3	6.3	6.3	6.3	6.3	6.3
	n	8	8	8	8	8	8	8
2000 mg SR	mean	415.0	415.0	416.4	414.4	411.5	415.4	402.1
	se	6.3	6.3	6.3	6.3	6.3	6.3	6.3
	n	8	8	8	8	8	8	8
Placebo	mean	396.4	393.6	388.2	400.2	390.4	402.4	395.4
	se	6.2	6.2	6.2	6.2	6.2	6.2	6.2
	n	8	8	8	8	8	8	8
1500 mg SR - Placebo	mean difference	16.1**	16.6**	20.6***	17.9**	20.5***	13.4*	11.1*
	sed	5.4	5.4	5.4	5.4	5.4	5.4	5.4
	P	0.004	0.003	<0.001	0.001	<0.001	0.015	0.043
	95% CI	(5.4,26.9)	(5.9,27.4)	(9.9,31.4)	(7.1,28.6)	(9.7,31.2)	(2.6,24.1)	(0.4,21.9)
2000 mg SR - Placebo	mean difference	18.6***	21.4***	28.2***	14.2**	21.1***	12.9*	6.7
	sed	5.2	5.2	5.2	5.2	5.2	5.2	5.2
	P	<0.001	<0.001	<0.001	0.007	<0.001	0.014	0.201
	95% CI	(8.3,28.9)	(11.1,31.8)	(17.9,38.5)	(3.9,24.5)	(10.8,31.4)	(2.6,23.3)	(-3.6,17.0)

Key:
mean = least square mean
se = standard error of least square mean
n = number of subjects
mean difference = least square mean difference
sed = standard error of least square mean difference
P = probability - * = p<0.05, ** = p<0.01, *** = p<0.001
95% C.I. = 95% Confidence Interval for mean difference

A statistically significant increase in the apparent QTc interval relative to placebo was observed at the 1500 mg dose level on Day 5 lasting from pre-dose to 24 hours after the last dose with an apprent mean (se) maximum value of +20.6 (5.4) msec at 4 hours. At the 2000 mg dose level relative to placebo there was a statistically significant increase in the apparent QTc interval at at all time points except at 24 hours after the last dose. The apparent mean (se) maximum increase in QTc occurred at 4 hours and was +28.2 (5.2) msec. The data showed considerable scatter.

There was a statistically significant correlation between QTc interval duration and plasma concentrations of ranolazine as shown in the following figure:



The QTc data showed significant scatter. Dose related changes in T-wave morphology with abnormalities in 5 subjects at the 1500 mg dose level and in 7 subjects at the 2000 mg dose level were seen.

CONCLUSIONS:

The pharmacokinetics of ranolazine are not stereospecific. The racemic and individual enantiomer data indicate the presence of a diurnal rhythm of the pharmacokinetics of ranolazine. The intersubject variation of racemic ranolazine and the enantiomers is similarly large. Ranolazine decreases the blood pressure statistically significantly at the 1500 mg and 2000 mg

dose levels. The mean maximum increase in apparent QTc relative to placebo is 20.6 msec and 28.2 msec at the 1500 mg and 2000 mg dose levels, respectively. There exists a statistically significant correlation between QTc interval duration and plasma concentration of ranolazine. Ranolazine alters the morphology of the T wave at the 1500 mg and 2000 mg dose levels

COMMENTS:

1. No information on the calibration curve standards, the criteria use for setting the LOQ values and the accuracy of the method for measuring racemic ranolazine and the enantiomers was provided in the report. The respective values for the precision of the methods measuring racemic (+) R and (-) S ranolazine exceeded the limits of ± 15%.
2. Baseline QT interval determinations over a period of 24 hours should have been performed to compute time specific interval changes of the QTc intervals.
3. The QT interval evaluations should have been done by a blinded Cardiologist.
4. Evidence for the adequacy of the heart rate correction algorithm used should have been provided.
5. In the case of ranolazine a rationale for developing the racemate is only given if both enantiomers exert identical PK and PD properties. This study should have determined the effects on QTc following administration of the individual enantiomers.

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STUDY RAN0103 (CL 6596) – A SINGLE DOSE STUDY OF THE PHARMACOKINETICS OF RANOLAZINE IN MALE AND FEMALE HEALTHY YOUNG VOLUNTEERS

STUDY INVESTIGATOR AND SITE: [

]

Report No.: RAN0103 (CL 6596)
Volume No.: 217, ITEM 6

OBJECTIVES:

To compare the pharmacokinetics and tolerability of ranolazine in young male and female volunteers

FORMULATIONS:

400 mg ranolazine dihydrochloride IR capsules (equivalent to 342mg ranolazine base) (Lot No. CT1106SC987D)
Matching placebo (Lot No. CT1106SC2721).

STUDY DESIGN:

This was a double-blind, placebo-controlled, randomized two-way crossover study. In each phase 6 healthy young male and 6 healthy young female volunteers were given a single oral dose of 400 mg ranolazine dihydrochloride (equivalent to 342 mg ranolazine base) or matching placebos. A washout period of at least 72 hours was maintained between the treatments. The number of subjects enrolled was not based on statistical power considerations.

ASSAY:

Plasma levels of ranolazine and RS-88390 (CVT-2514) were measured by HPLC with fluorescence detection ( ] The plasma concentrations were expressed in terms of the dihydrochloride salt. The precision of the method determined from QC samples was ≤ 14.2% and ≤ 16.0% for ranolazine and RS-88390 (CVT-2514), respectively. The recovery for ranolazine ranged between 95.5% and 110% for ranolazine and between 99.0% and 108% for RS-88390 (CVT-2514).

Blood Sample Collection:

Blood samples were collected pre-dose, 20 and 40 minutes and 2, 3, 4, 6, 8 and 12 hours pa.

PK and Satistical Evaluation:

Cmax, tmax, AUC and t1/2 were determined for ranolazine and RS-88390 (CVT-2514). In addition Clpo normalized for body weight was computed from Clpo=Dose/AUC•weight for ranolazine. The ratio of $AUC_{RS\text{-}88390}$ to $AUC_{ranolazine}$ was also computed.
Pharmacokinetic parameters, except for t_{max}, were analyzed using an analysis of variance (ANOVA) model with sex and phase as fixed effects. Untransformed and the log transformed data were used. Following the ANOVA, all comparisons at individual time points used two-sided t-tests. Confidence intervals (95%) for treatment comparisons and for the PK parameters were calculated. No adjustments were made for multiple comparisons.
The tmax data were analyzed using a randomization test and a non-parametric 90% and 95% confidence intervals were calculated for the median difference between the sexes.
For the other PK parameters, a comparison of the mean values between males and females was made.

SAFETY:

A 12 lead ECG was recorded at the following times:
Pre-dose and 2, 4, 6 and 12 hours post-dose.
The standard ECG intervals as measured by the machine were used.
Supine and erect systolic and diastolic blood pressures and heart rate were measured at the following times:
Predose and 1, 2, 3, 4, 6, 8 and 12 hours post-dose.

RESULTS:

Seven males and females were enrolled in the study. All females were premenopausal and on oral contraceptives. One subject vomited about 2 hours following dosing with ranolazine and was deemed non-evaluable for pharmacokinetic analysis. A second subject was withdrawn because of noncompliance with the alcohol restrictions before dosing in Phase 2. The average age of the 6 evaluable female and male subjects was 28.2 years and 26.2 years, respectively.

PK:

The salient pharmacokinetic results of the study are listed in the following table:

MEAN RANOLAZINE AND RS-88390 PHARMACOKINETIC PARAMETERS FOLLOWING SINGLE ORAL ADMINISTRATION OF RANOLAZINE 400 mg IR

Parameter	Ranolazine		RS-88390	
	Females	Males	Females	Males
C_{max} (ng/ml)	1970 ± 819	2260 ± 603	617 ± 281	441 ± 290
t_{max} (h)	1.25 ± 0.697	1.39 ± 0.873	1.81 ± 1.23	1.47 ± 0.909
AUC_{0-} (ng.h/ml)	5670 ± 1700	7800 ± 3400	4050 ± 2500	3530 ± 1320*
$t_{½}$ (h)	1.46 ± 0.236	2.02 ± 0.474**	4.51 ± 1.92	6.58 ± 0.324*
Cl_{po} (ml/min/kg)	20.8 ± 8.11	13.1 ± 6.51**	ND	ND

Values are given as Mean ± SD (n=6) except * n=5

ND = Not Determined.

C_{max} and AUC_{0-} values are given in terms of the dihydrochloride salt.

Statistical significance with respect to female subjects: ** $p<0.05$.

Statistically significant differences between the sexes were noted for t1/2 and Clpo of ranolazine. The respective mean values for t1/2 were 2.02 hour for males and 1.46 hours for females. Clpo in males was smaller (13.1 mL/min/kg) than in females (20.8 mL/min/kg). The mean plasma concentrations of RS-88390 (CVT-2514) were greater and the mean t1/2 longer in females (6.58 hours) than in males (4.51 hours), but these differences did not reach statistical significance. The mean exposure to RS-88390 (CVT 2514) relative to ranolazine was 0.28 and 0.33 in females and males, respectively.

SAFETY:

The effects of ranolazine and placebo on the hemodynamic parameters differed slightly between males and females, but there was no discernible pattern and the extent was not clinically relevant. Also, there were no relevant effects on the QTc-interval as shown in the following table:

MEAN ECG DATA
QT_c Interval (msec) With Single Oral Administration of Ranolazine 400 mg IR or Placebo

Time Post-dose	Group											
	Ranolazine (Males)			Ranolazine (Females)			Placebo (Males)			Placebo (Females)		
	n	mean	se	n	mean	se	n	mean	se	n	mean	se
Pre-dose	7	425.4	15.5	7	399.9	3.1	6	404.7	6.9	7	405.3	5.4
2 h	7	408.4	2.1	7	411.6	5.9	6	408.3	12.0	7	403.6	5.4
4 h	7	423.4	12.7	7	415.7	2.9	6	404.3	6.7	7	412.6	5.5
6 h	7	411.4	6.6	7	397.4	5.3	6	406.2	5.5	7	399.3	6.5
12 h	7	405.1	3.6	7	398.6	3.2	6	400.8	3.2	7	407.0	4.1

Key:

n = number of subjects
mean = raw (unadjusted) mean
se = standard error of the mean

CONCLUSIONS:

The data obtained in this single dose study using sub-therapeutic dose levels appear to indicate that no important sex related differences in the pharmacokinetics and safety of ranolazine exist.

COMMENTS:

1. The results of this single dose study using sub-therapeutic levels cannot be extrapolated to patients receiving ranolazine at postulated therapeutic dose levels. The study should have used therapeutically effective dose levels, the SR formulation and a multiple dose design involving more than 6 females and males.
2. Measuring other major metabolites (RS-94287 (CVT-2738), RS-88640 (CVT-2512)) should have been considered.
3. Phenotyping of the subjects could have rendered the interpretation of the RS-88390 (CVT-2514) data more meaningful
4. No data on the crossvalidation of the HPLC methodwith fluorimetric detection used in the present study and the LC/MS/MS method use in other studies were provided.

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STUDY CVT 301-14: A FIVE PERIOD, CROSS OVER, RANDOMIZED STUDY TO EVALUATE THE PHARMACOKINETICS OF SINGLE DOSES OF A RANOLAZINE ORAL SOLUTION AND FOUR RANOLAZINE SR TABLETS, EACH WITH DIFFERENT DISSOLUTION PROPERTIES IN HEALTHY VOLUNTEERS

STUDY INVESTIGATOR AND SITE: [

]

Report No.: CVT 301-14
Volume: 49,50, ITEM 6

OBJECTIVES:

1) To evaluate the pharmacokinetic profiles of a ranolazine oral solution formulation and 4 ranolazine SR tablet formulations, each with different dissolution properties, to provide information to enable development of an IVIVC model for ranolazine.
2) To develop an IVIVC model.

STUDY DESIGN:

This was a single-center, single-dose, randomized, open-label, 5-period, pharmacokinetic study. During study Period 1, all subjects received a single 500 mg dose of an oral solution. In study Periods 2, 3 and 4, the subjects randomly received a single 500 mg dose of 1 of 3 ranolazine SR tablet formulations. In study Period 5, 8 of the 15 study subjects returned to the clinic and received a single 500 mg dose of a fourth ranolazine SR tablet formulation under fasting conditions. Pharmacokinetic sampling was performed for 48 hours after intake of each dose and the washout time between doses was at least 4 days. Subjects remained confined for 48 hours after each dose of ranolazine. Full pharmacokinetic profiles were evaluated after each dose.

A total of 16 subjects (age: 18-60 years), 12 males and 4 females were enrolled in the study and 1 extra male subject was dropped out of the study.

Blood samples for ranolazine plasma levels were obtained at 0 hour (predose), and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 30, 36, and 48 hours post-dose.

FORMULATIONS:

Treatment A: Ranolazine oral solution 25 mg/mL (20 mL vial)
Lot Number: N01005FPI

Treatment B: Ranolazine, Formula-S, SR, 500 mg tablets
Lot Number: CK1CM01A10

Treatment C: Ranolazine, Formula-F, SR, 500 mg tablets
Lot Number: CK1CM02A06

Treatment D: Ranolazine, SR, 500 mg tablets
Lot Number: 8H2749A

Treatment E: Ranolazine, SR, 500 mg tablets
Lot Number: 1F2701A

ASSAY:

Ranolazine levels in plasma were determined using high performance liquid chromatography with mass-spectrometric detection (HPLC/MS). The calibration range was 50.0 ng/mL to 10'000 ng/mL. Precision was not reported.

Entity	Linearity R^2	LOQ ng/mL	QC Sample ng/mL	Precision %	Accuracy %	Specificity
Ranolazine	0.99	10	100	NA	3.87	No interference
			1000	NA	4.97	
			8000	NA	3.93	

RESULTS:

Based on in vitro dissolution profiles (shown in the Table below), the sponsor selected Formula-S (lot#CK1CM01A10) and Formula-F (lot#CK1CM02A06) formulations to represent slow and fast release in vivo.

Table 1. Dissolution data for the 4 slow release profiles.

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Table 6.6-9 Dissolution Testing for Lots of Ranolazine SR Dosage Forms Used in Clinical Studies (Cont'd)

Clinical Trial	Dosage Form and Strength		Lot Number	Test Date Units (N) Tested	Dissolution Apparatus and Rotation Speed	Media and Temp.	Collection Times	(Range in %LS) Mean % Dissolved in %LS %RSD
CVT 301-14	Tablets	500 mg	6H2749A	11/5/01 N = 12	USP Type 2 rpm	0.1 N HCl	0.5 h 4 h 12 h 24 h	
		500 mg	1P2701A	7/17/01 N = 12			0.5 h 4 h 12 h 24 h	
		500mg Slow	CK1CM01A10	10/30/01 N = 12			0.5 h 4 h 12 h 24 h	
		500 mg Fast	CK1CM02A06	10/23/01 N = 12			0.5 h 4 h 12 h 24 h	

The mean concentration – time profiles of the 5 formulations are shown in Figure 1. Table 2 provides the summary PK parameters. Evaluation of the PK parameters showed that the overall exposure (AUC (0-infinity)) across all the formulations was similar. The Cmaxs for the SR formulations were in general lower than that for the solution, as expected. However, the Cmax for Formula-F (treatment C) was markedly lower than all other formulations. Since the in vitro data were unable to suggest even the order of the release rates in vivo, the sponsor did not attempt to develop an IVIVC, aptly.

Figure 1. Mean ranolazine plasma concentrations following administration of different formulations.

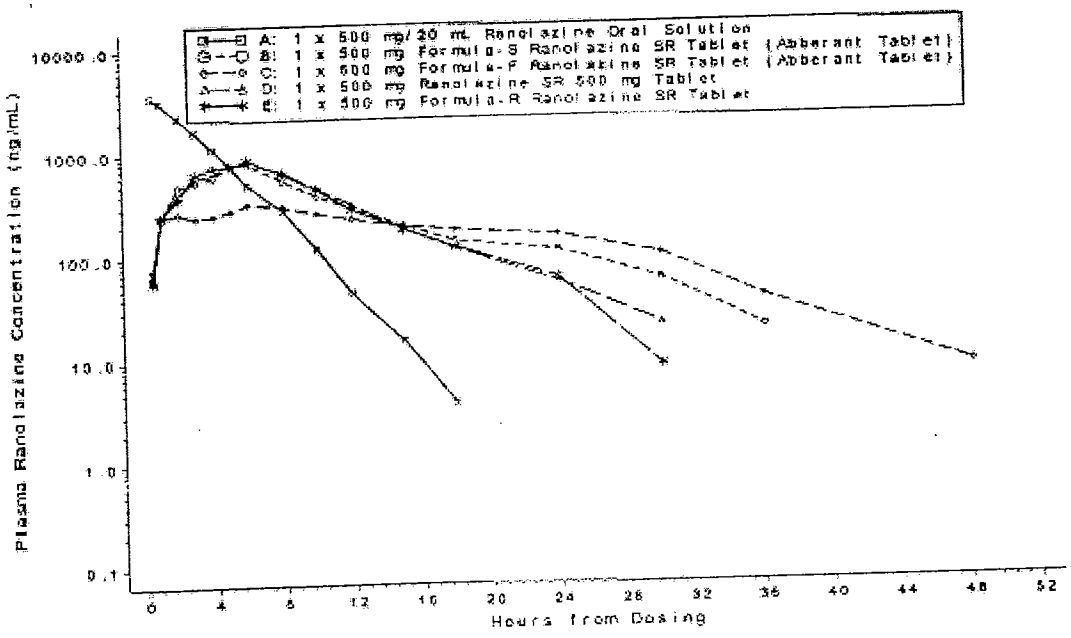

Table 2. Summary of pharmacokinetic parameters for the different formulations of ranolazine.

Summary of the Pharmacokinetic Parameters of Plasma Ranolazine

	Plasma Ranolazine									
	Treatment A		Treatment B		Treatment C		Treatment D		Treatment E	
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	Arithmetic Mean	SD	Arithmetic Mean	SD	Arithmetic Mean	SD
Cmax(ng/mL)	3702.5	821.9	851.1	313.9	451.2	213.7	942.5	291.6	966.0	496.8
Tmax(hr)	0.621	0.224	5.27	1.44	6.60	6.48	5.47	2.26	5.88	2.04
AUC(0-t) (ng*hr/mL)	11460	2802	8397	3527	4377	3570	8025	2377	8054	4027
AUC(0-inf) (ng*hr/mL)	11720	2916	8655	4143	8247	3399	8884	2495	8636	4172
AUCR	0.983	0.00404	0.935	0.0168	0.879	0.135	0.938	0.0321	0.925	0.0372
T1/2(hr)	1.83	0.453	5.07	2.86	7.47	4.53	4.58	2.20	5.10	2.40
Kel(1/hr)	0.398	0.0855	0.186	0.104	0.122	0.0644	0.186	0.0849	0.181	0.126
*Cmax(ng/mL)	3703.4	21.3	803.5	35.5	403.8	53.7	896.1	35	860.1	56.2
*AUC(0-t) (ng*hr/mL)	11147.8	24.6	7578	54.3	5469.8	64.3	7578	40	7350.9	57.5
*AUC(0-inf) (ng*hr/mL)	11384.8	25.3	7846.5	59.8	7562.8	88	8408.5	40.1	7731.1	54.8

* = Geometric Mean value. C.V.% is presented in place of SD. It is calculated as 100*SQRT(EXP(SD^2)-1), based on the SD values for the ln-transformed parameters from Tables 14.2.6-14.2.10

Treatment A = 1 x 500 mg/20 mL Ranolazine Oral Solution
Treatment B = 1 x 500 mg Formula-S Ranolazine SR Tablet (Abberant Tablet)
Treatment C = 1 x 500 mg Formula-F Ranolazine SR Tablet (Abberant Tablet)
Treatment D = 1 x 500 mg Ranolazine SR 500 mg Tablet
Treatment E = 1 x 500 mg Formula-R Ranolazine (Reference) SR Tablet

COMMENTS:

1. The sponsor did not provide any data on the precision of the assay in this study.

RECOMMENDATION:

The composition of the formulations and in vitro dissolution profiles were not submitted. This information was requested from the sponsor. In vitro dissolution cannot be employed to predict in vivo release rates.

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STUDY CVT 3014- A STUDY TO ASSESS THE EFFECT OF FOOD ON THE SINGLE-DOSE PHARMACOKINETICS OF RANOLAZINE AT A DOSE OF 1000 MG IN HEALTHY VOLUNTEERS

STUDY INVESTIGATOR AND SITE: [

]

Report: CVT 3014
Volume: 12, 13, ITEM 6

OBJECTIVES:

1) To compare the pharmacokinetics of a single dose of ranolazine SR given in the fed (high fat breakfast) and fasted states.

DESIGN:

An open-label, randomized, single-dose, two-period, cross-over comparative PK study in which healthy male subjects received 1000 mg ranolazine SR either with or without food.

Subjects were randomly assigned to receive 1000 mg ranolazine SR in the fed or fasted state. Those who were fed in session 1 were fasted in session 2 and vice versa. In the fed session, subjects received the FDA standard high fat breakfast approximately 30 min before dosing. Approximately 25 min was allocated for completion of breakfast and dosing took place 5 min after meal consumption. Dosage was taken with 200 mL water in the sitting position. Subjects in the fasted condition remained so for 4 h after dosing when a light lunch was served.

Blood samples for ranolazine plasma levels were obtained at 0 hour (predose), and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, and 48 hours post-dose.

FORMULATION:

Ranolazine SR, 500 mg tablets
Lot Number: 9G2714A

ASSAY:

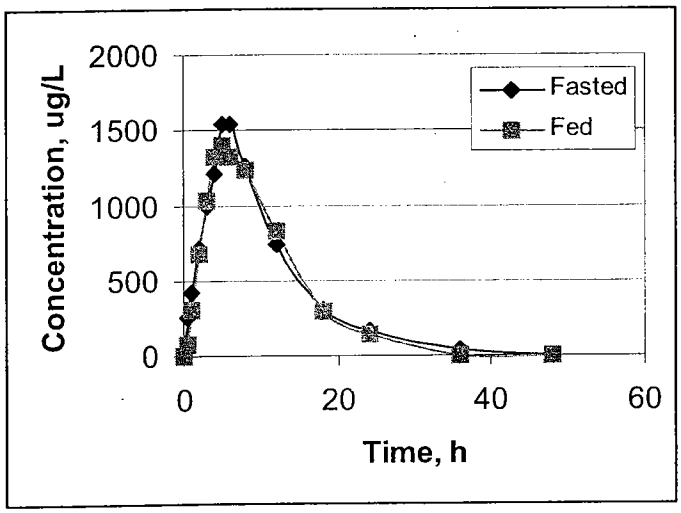
Ranolazine levels in plasma were determined using high performance liquid chromatography with mass-spectrometric detection (HPLC/MS). The calibration range was 50.0 ng/mL to 10'000 ng/mL. Precision was not reported.

Entity	Linearity R^2	LOQ ng/mL	QC Sample ng/mL	Precision %	Accuracy %	Specificity
Ranolazine	0.99	50	100	NA	5.51	No interference
			1000	NA	6.83	
			8000	NA	3.74	

RESULTS:

The mean concentration – time profiles of ranolazine following 1000 mg ranolazine SR tablet with and without food are shown in Figure 1. The PK profiles under fasted and fed conditions appear to be reasonably close.

Figure 1. Ranolazine Plasma Concentrations Following Administration of 1000 mg SR tablet with or without food.



The 90% confidence limits of the ratio of log (AUC) and log(Cmax) fed over fasted are 0.91 – 1.048 and 0.804 – 1.022, respectively. According to the equivalence limits of 0.8 to 1.25, it can be concluded that food does not affect the PK of ranolazine SR tablets.

COMMENT:

The sponsor did not provide any data on the precision of the assay used in this study.

RECOMMENDATION:

Food does not significantly affect the pharmacokinetics of Ranolazine SR tablets.

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STUDY CVT3013: A PHASE I, OPEN LABEL, SINGLE DOSE, PHARMACOKINETIC BIOEQUIVALENCE STUDY COMPARING 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

STUDY INVESTIGATOR AND SITE: [ ]

Report No.: CVT 3013
Volume No.: 10,11

OBJECTIVES:

1) To determine the bioequivalence of ranolazine SR manufactured at a Syntex site (Reference; hereafter referred to as "R") given as two 500-mg tablets compared to the ranolazine SR manufactured at a new site [ ] (Test; hereafter referred to as is "T") given as two 500-mg tablets.

2) To determine the bioequivalence of the ranolazine SR manufactured at a Syntex site (Reference; hereafter referred to as "R") given as one 750-mg tablet compared to the ranolazine SR manufactured at a new site [ ] (Test; hereafter referred to as "T") given as two 375-mg tablets.

STUDY DESIGN:

An open-label, randomized, four-period, cross-over study in which healthy male subjects received each of four treatments (A, B, C, and D) in one of four sequences (i.e., A, B, C, and D, or A, B, D, and C, or B, A, C, and D, or B, A, D, and C), as shown in the table below.

Treatment	Level of Ranolazine SR Dosed on Day 1 of Each Study Period
A	1000 mg as two 500 mg tablets (R)
B	1000 mg as two 500 mg tablets (T)
C	750 mg as one 750 mg tablet (R)
D	750 mg as two 375 mg tablets (T)

On Day 1 of each treatment period at approximately 0800, the single dose was administered to fasting subjects, followed immediately by breakfast. Subjects remained confined from the evening prior to dosing until 48 hours after each dose. A 7-day washout period separated each treatment. The intended population was up to 36 subjects consisting of healthy, male subjects, between the ages of 18 and 45 years. Thirty-four (34) subjects enrolled in and completed the study.

Blood samples for ranolazine plasma levels were obtained at 0 hour (predose), and at 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, and 48 hours post-dose.

FORMULATIONS:

Ranolazine SR, 500 mg tablets (Reference, Treatment A)
Lot Number: 791751

Ranolazine SR, 500 mg tablets (Test, Treatment B)
Lot Number: 8H2749A

Ranolazine SR, 750 mg tablets (Reference, Treatment C)
Lot Number: 791861

Ranolazine SR, 375 mg tablets (Test, Treatment D)
Lot Number: 8H2752A

— kg of each of the formulations was manufactured. — kg batch size represents a nominal [ ] tablets for the 375 mg dosage strength and [ ] tablets for the 500 mg dosage strength. The projected production batch weight is — kg which would equal [ ] tablets. The batch size of — kg is [ ] equals — of the projected production batch size.

ASSAY:

Ranolazine levels in plasma were determined using high performance liquid chromatography with mass-spectrometric detection (HPLC/MS). The method was validated for the analysis of ranolazine over the range of [ ] ng/mL to [ ] ng/mL. Concentrations higher than 800 ng/mL were diluted.

Entity	Linearity R^2	LOQ ng/mL	QC Sample ng/mL	Precision %	Accuracy %	Specificity
Ranolazine	0.99	10	10	2.4	-0.6	No interference
			20	7.2	4.6	
			50	6	-8.1	
			100	4.4	2.6	
			250	3.3	0.4	
			600	7.1	1.2	
			1300	8.2	1.2	

RESULTS:

The mean concentration – time profiles of ranolazine following treatments A and B are shown in Figure 1. Treatment B (test) has higher exposure, at least as reflected by the Cmax, than treatment A (reference).

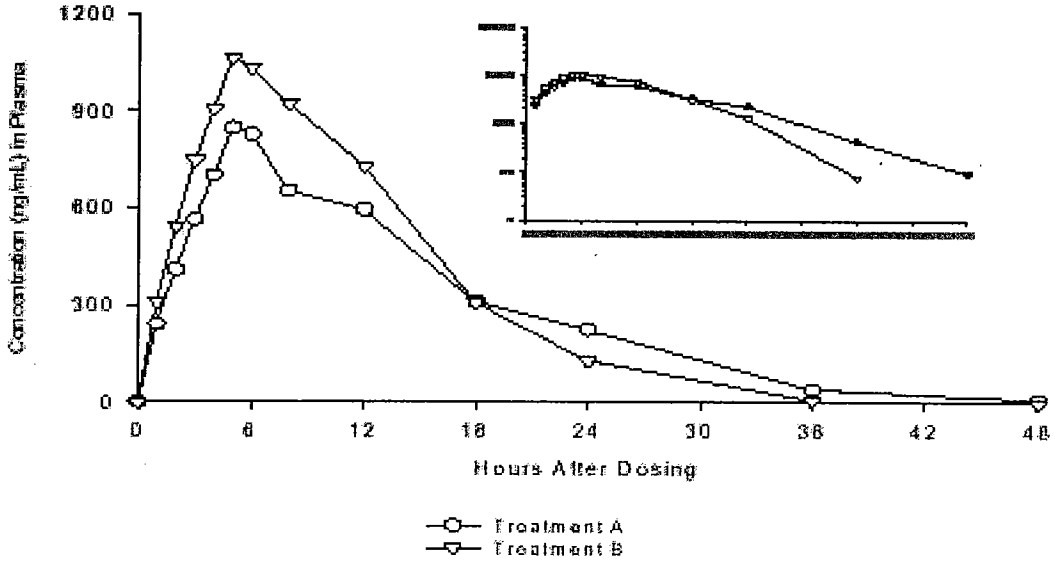

Figure 1. Ranolazine Plasma Concentrations Following Administration of Treatments A and B.

Table 1 presents a summary of the mean pharmacokinetic parameters of ranolazine following single oral dose administration of Treatments A (1000 mg as two 500 mg tablets - Reference) and B (1000 mg as two 500 mg tablets - Test). Treatment B has 33% higher Cmax and 10% higher AUC than Treatment A. The 90% confidence interval for Cmax is not within the equivalence limits of 0.8 and 1.25. While for AUC the equivalence limits are met, systematically the test formulation has higher exposure.

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Table 1. Summary of the mean pharmacokinetic parameters of ranolazine following single oral dose administration of Treatments A (1000 mg as two 500 mg tablets - Reference) and B (1000 mg as two 500 mg tablets - Test).

PK Parameter	Test Mean[a] Treatment B (2 x 500 mg)	Reference Mean[a] Treatment A (2 x 500 mg)	Percent Test/Reference[b]	90% Confidence Interval[c]
C_{max} (ng/mL)	1325	999	133	(118 , 147)
ln(C_{max})	1191	902	132	(118 , 148)
C_{12} (ng/mL)	731	595	123	(110 , 136)
ln(C_{12})	607	477	127	(115 , 141)
t_{max}[d] (hours)	6.00	5.00	NA	NA
AUC_{0-t} (ng·hr/mL)	14332	13128	109	(103 , 115)
ln(AUC_{0-t})	12687	11496	110	(105 , 116)
$AUC_{0-\infty}$ (ng·hr/mL)	14655	13410	109	(103 , 115)
ln($AUC_{0-\infty}$)	12935	11883	109	(104 , 114)
$t_{1/2}$ (hours)	3.92	5.50	71.3	(55.7 , 86.9)

Note: n = 30 for Treatment A and n = 32 for Treatment B $AUC_{0-\infty}$ and $t_{1/2}$.

a Least-squares mean from ANOVA.
Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means).

b Ratio of parameter least squares means for untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed back to linear scale.

c 90% confidence interval for ratio of parameter least squares means of untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.

d Value listed as median.

Similar results were obtained for treatments C and D, as shown in Figure 2 and Table 2.

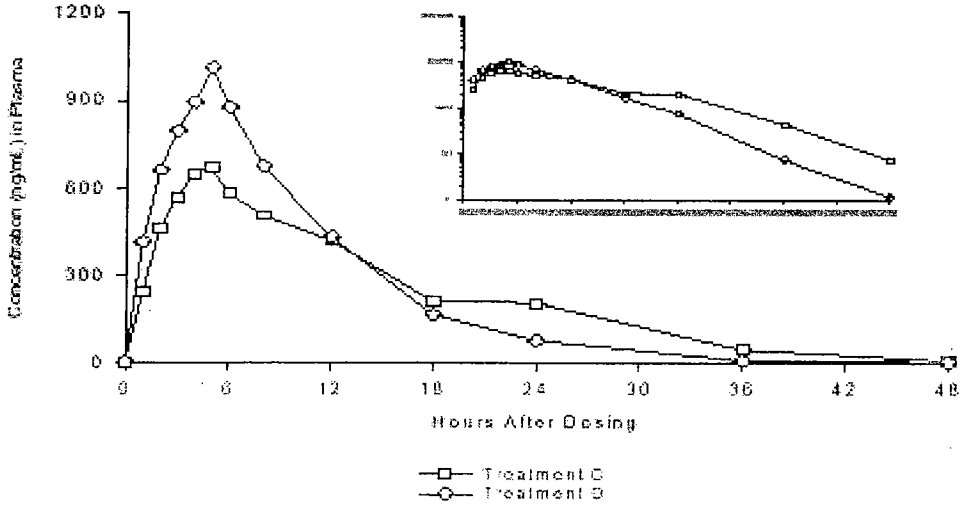

Table 2. Summary of the mean pharmacokinetic parameters of ranolazine following Treatments C (750 mg as one 750 mg tablet - Reference) and D (750 mg as two 375 mg tablets - Test).

PK Parameter	Test Mean[a] Treatment D (2 x 375 mg)	Reference Mean[a] Treatment C (1 x 750 mg)	Percent Test/Reference[b]	90% Confidence Interval[c]
C_{max} (ng/mL)	1183	903	131	(110 , 152)
ln(C_{max})	1060	779	136	(117 , 158)
C_{12} (ng/mL)	427	415	103	(83.9 , 122)
ln(C_{12})	360	332	108	(91.0 , 129)
t_{max}[d] (hours)	5.00	5.00	NA	NA
AUC_{0-t} (ng·hr/mL)	10735	10414	103	(94.4 , 112)
ln(AUC_{0-t})	9768	9185	106	(98.3 , 115)
$AUC_{0-\infty}$ (ng·hr/mL)	11070	10848	102	(89.4 , 115)
ln($AUC_{0-\infty}$)	10129	9549	106	(95.1 , 118)
$t_{1/2}$ (hours)	4.31	5.69	75.8	(57.4 , 94.2)

Note: n = 21 for Treatment C and n = 33 for Treatment D $AUC_{0-\infty}$ and $t_{1/2}$.

a Least-squares mean from ANOVA.
Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means).

b Ratio of parameter least squares means for untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed back to linear scale.

c 90% confidence interval for ratio of parameter least squares means of untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.

d Value listed as median.

RECOMMENDATION:

1. Ranolazine SR manufactured at a Syntex site (Reference) given either as two 500-mg tablets or as two 375 mg tablets compared to the ranolazine SR manufactured at a new site [ ] (Test) given as two 500-mg tablets are not bioequivalent.
2. However, this difference in CMAX between the two formulations is of little consequence to the ability to link the results of the pivotal clinical studies.

3. The following is the list of studies using each of the test formulations:

Strength, Site	Lot#	Clinical Studies Using the formulation
500 mg, [ ]	8H2749A	CVT301-14 (Food effect) CVT3034
375 mg, [ ]	8H2752A	CVT3033 (pivotal)

STUDY CVT 301-15: A SIX PERIOD, REPLICATE DESIGN, CROSS-OVER, RANDOMIZED STUDY TO DETERMINE THE BIOEQUIVALENCE OF THREE RANOLAZINE SR TABLETS IN HEALTHY SUBJECTS AFTER ADMINISTRATION OF SINGLE DOSES

STUDY INVESTIGATOR AND SITE: [redacted]

Report No.: CVT 3013
Volume No.: 14-17, ITEM 6

OBJECTIVES:

1. To evaluate the BE of ranolazine SR tablets from lots # 8E2729A (representative of the CARISA trial), and #1K2754 (intended for commercial use), after a single dose.
2. To evaluate the BE of ranolazine SR tablets from lots # 791771 (representative of the MARISA trial), and #1K2754A (intended for commercial use), after a single dose.
3. To compare AUC after administration of ranolazine SR tablets of lot # 8E2729A (representative of the CARISA trial), with AUC after administration of ranolazine SR tablets of lot # 791991 (representative of the MARISA trial), after a single dose.

STUDY DESIGN:

This was a single-center, single-dose, randomized, repeated single-dose, open-label, pharmacokinetic study. Subjects received an oral dose of 500 mg ranolazine during fasting conditions, as 1 tablet from lot # 8E2729A, #1K2754A, or # 791771, each on two separate occasions in a randomized, six-period, corss-over profile design. Each subject received each formulation on two occasions as shown in Table 1 below.

Table 1. Sequences of drug administration.

	SEQUENCE 1	SEQUENCE 2	SEQUENCE 3
PERIOD 1	A	B	C
PERIOD 2	B	C	A
PERIOD 3	C	A	B
PERIOD 4	A	B	C
PERIOD 5	B	C	A
PERIOD 6	C	A	B

A total of 36 subjects (age: 18-60 years), 12 males and 4 females were enrolled in the study and 1 subject dropped out of the study.

Blood samples for ranolazine plasma levels were obtained at 0 hour (predose), and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 21, 24, 30 and 36 hours post-dose.

FORMULATIONS:

Treatment A: Ranolazine SR tablet, 500 mg (Reference formulation, representative of CARISA trial)
Lot Number: 8E2729A

Treatment B: Ranolazine SR tablet, 500 mg (Test formulation, representative of commercial product)
Lot Number: 1K2754A

Treatment C: Ranolazine SR tablet, 500 mg (Reference formulation, representative of MARISA trial)
Lot Number: 791771

[ ] kg of each of the formulations was manufactured. [ ]kg batch size represents a nominal [ ] tablets for the 375 mg dosage strength and [ ] tablets for the 500 mg dosage strength. The projected production batch weight is [ ] kg which would equal [ ] tablets. The batch size of [ ] kg is [ ] equals [ ] of the projected production batch size.

Composition

Table 2 below shows the composition of the 375 mg and 500 mg strength SR tablets. The column entitled [ ] 'DSM' represents the commercial formulation.

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Table 2. Composition of ranolazine SR tablets.

	Syntex/Syntex		— /DSM		— /DSM[a]	
Potency	**500 mg**	**750 mg[b]**	**375 mg**	**500 mg**	**375 mg**	**500 mg**
Ranolazine (DS)	500.0	750.0	375.0	500.0	375.0	500.0
Methacrylic Acid Copolymer (Type C), NF	[					
Microcrystalline Cellulose, NF						
Hydroxypropyl Methylcellulose USP						
Sodium Hydroxide, NF						
Magnesium Stearate, NF						
Purified Water[c], USP	–	–	–	–	–	–
Core Tablet Weight (mg)						]
Light Blue						
Orange	[					]
Carnauba Wax, NF						
Film-Coated Tablet Weight (mg)	**686.7**	**1000.0**	**515.0**	**686.7**	**515.0**	**686.7**

NA = Not Applicable

[a] Proposed commercial product

[b] [

[c]

[d]

[e]

[f] [ ]

ASSAY:

Ranolazine levels in plasma were determined using high performance liquid chromatography with mass-spectrometric detection (HPLC/MS). The calibration range was 50.0 ng/mL to 10000 ng/mL. Precision was not reported.

Entity	Linearity R^2	LOQ ng/mL	QC Sample Ng/mL	Precision %	Accuracy %	Specificity
Ranolazine	0.99	10	100	NA	2.66	No interference
			1000	NA	2.10	
			8000	NA	2.47	

RESULTS:

The mean concentration – time profiles of the 5 formulations are shown in Figure 1. Evaluation of the PK profiles suggests that all the 3 formulations are similar. Table 3 provides the summary PK parameters. The results indicate that the commercial formulation is bioequivalent to the clinical trial formulations.

Figure 1. Mean ranolazine plasma concentrations following administration of different formulations.

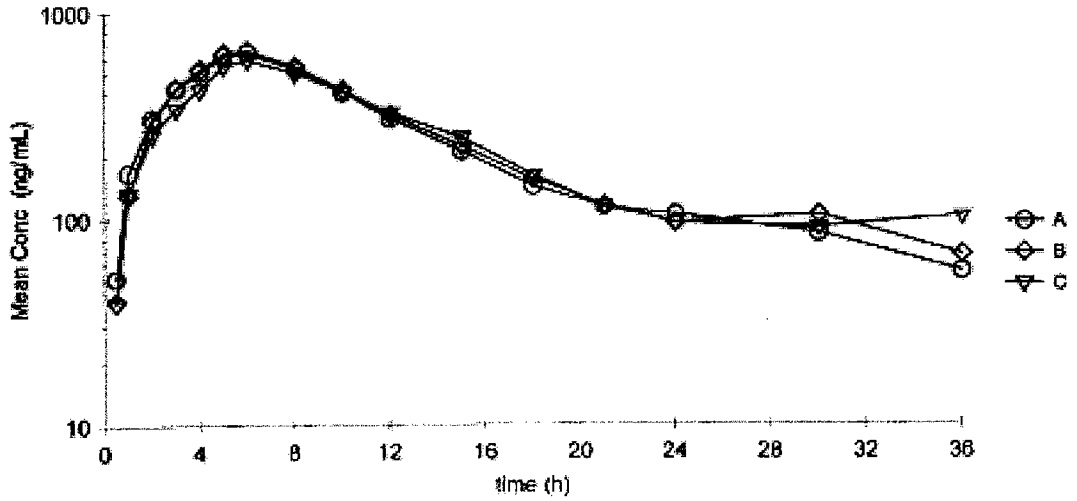

Table 3. Summary of pharmacokinetic parameters for the different formulations of ranolazine.

Parameter and evaluation		LS mean ratio	90% CI lower bound	90% CI upper bound
C_{max} (N=35)[1]	relative bioavailability of B-A	1.03	0.96	1.10
	relative bioavailability of B-C	1.14	1.05	1.24
AUC_{0-t} (N=35)[1]	relative bioavailability of B-A	1.03	0.99	1.09
	relative bioavailability of B-C	1.04	0.98	1.10
$AUC_{0-\infty}$ (N=34)[2]	relative bioavailability of B-A	1.04	0.99	1.10
	relative bioavailability of B-C	1.00	0.94	1.06

RECOMMENDATION:

The formulation developed for commercial use is bioequivalent to the formulations used in the clinical trials, CARISA and MARISA.

STUDY RAN0122 (CL 6979): A MULTIPL-DOSE STUDY TO ASSESS THE COMPARATIVE BIOAIIVAILABILITY OF RANOLAZINE SR ADMINISTERD AS EITHER TWO 375 MG TABLETS OR ONE 750 MG TABLET GIVEN TWICE DAILY IN YOUNG, HEALTHY MALE SUBJECTS

STUDY SITE AND INVESTIGATOR: ⊏

Report No.: RAN0122 (CL 6979)
Volume No.: 233,234, ITEM 6

OBJECTIVES:

To assess the comparative bioavailability of ranolazine SR tablets when administered as either two 375 mg tablets or as one 750 mg.

STUDY DESIGN:

This was a single-center, randomized two-way crossover, multiple-dose, open-label pharmacokinetic study. Subjects received multiple doses of 750 mg ranolazine SR, as either two 375 mg tablets or as one 750 mg tablet, twice daily for 4 days with a single dose on Day 5. Each phase was separated by washout period of at least 6 days. On day 5 of each phase, ranolazine plasma concentrations were measured.

A total of 30 subjects (age: 18-60 years), 12 males and 4 females were enrolled in the study and 1 subject dropped out of the study.

Blood samples for ranolazine plasma levels were obtained at 0 hour (predose), and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 21, 24, 30 and 36 hours post-dose.

FORMULATIONS:

Treatment A: Ranolazine SR tablet, 375 mg
Lot Number: CT1151 6916

Treatment B: Ranolazine SR tablet, 750 mg
Lot Number: CT1151 6763

ASSAY:

Ranolazine levels in plasma were determined using high performance liquid chromatography with fluorometric detection (HPLC/FL). The calibration range was 10.0 ng/mL to 1000 ng/mL. Precision was not reported.

Entity	Linearity R^2	LOQ ng/mL	QC Sample ng/mL	Precision %	Accuracy %	Specificity
Ranolazine	0.99	10	19	NA	12	No interference
			419	NA	7.3	
			947	NA	8.11	

RESULTS:

Table 1 provides the summary PK parameters. The mean concentration – time profiles of the 2 formulations are shown in Figure 1. Evaluation of the PK profiles suggests that the 2 formulations are similar. The results, as shown in Table 2, indicate that the 2X375 mg and one 750 mg tablets are bioequivalent, although the former seems to be slightly higher consistently.

Table 1. Summary of pharmacokinetic parameters for the different formulations of ranolazine.

Parameter	2 x RAN 375		RAN 750	
	Mean	SD	Mean	SD
Cmax (ng/ml)	2539	1004	2359	940
Median Tmax (h)	4.00	-	5.00	-
Cmin (ng/ml)	1015	682	961	608
AUC96-108h (ng.h/ml)	21782	10285	20204	9236
Cave (ng/ml)	1815	857	1684	770
Degree of Fluctuation	0.908	0.251	0.880	0.252

Figure 1. Mean ranolazine plasma concentrations following administration of different formulations.

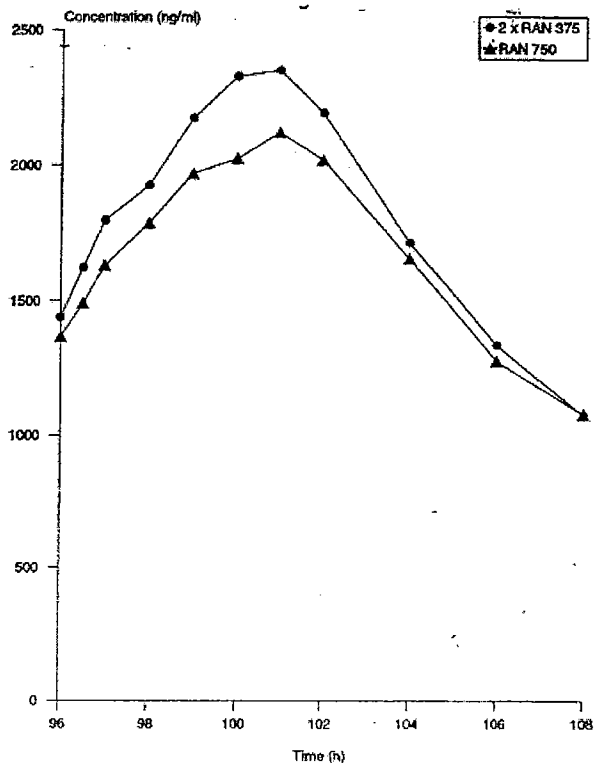

Table 2. Results of the bioequivalence testing to compare 2x375 mg versus 750 mg ranolazine.

Parameter	2 x RAN 375 / RAN 750 90 % CI for ratio of means
Cmax (ng/ml)	(98.8%, 117.8%)
Median Tmax (h)	
Cmin (ng/ml)	(90.1%, 116.9%)
AUC96-108h (ng.h/ml)	(98.8%, 116.7%)
Cave (ng/ml)	(98.8%, 116.7%)
Degree of Fluctuation	(95.0%, 112.1%)

RECOMMENDATION:

The exposures from 2X375 mg and one 750 mg ranolazine SR tablets are bioequivalent. There is dosage form proportionality between the 375 mg and the 750 mg strengths.

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STUDY CVT 3016 – A STUDY TO EVALUATE 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

STUDY INVESTIGATOR AND STUDY SITE: [

]

Report No.: CVT 3016
Volume No.: 18-23, ITEM 6

OBJECTIVES:

To evaluate the pharmacokinetic parameters of ranolazine and metabolites RS-88390 (CVT-2514), RS-88640 (CVT-2512) and RS-94287 (CVT-2738) in subjects with mild moderate or severe renal impairment as compared to matched healthy volunteers

FORMULATIONS:

375 mg SR tablets (Lot No. 9G2715A)
500 mg SR tablets (Lot No. 9G2714A)

STUDY DESIGN:

This was an open-label, multiple dose, pharmacokinetic study. In order to attain steady-state more rapidly the subjects received a loading dose of 875 mg ranolazine in the morning of Day 1, followed by a maintenance dose regimen of 500 mg bid starting in the evening of Day 1 and ending with the morning dose on Day 3. The subjects were enrolled in 4 study groups: Group 1, mild renal impairment (creatinine clearance: 51-80mL/min), Group 2, moderate renal impairment (creatinine clearance: 30-50 mL/min), Group 3: Severe renal impairment (creatinine clearance < 30 mL/min, but not requiring dialysis), Group 4: No renal impairment (creatinine clearance >80 mL/min). Groups 1-3 contained each 7 subjects. Group 4 consisted of 8 healthy volunteers. The healthy subjects were matched for age, body weight and gender. The doses were administered with 250 mL water to the subjects in the sitting position. The subjects were institutionalized from the evening before Day 1 to Day 5.

ASSAY:

All samples were analyzed at CV Therapeutics, Palo Alto, CA.

The plasma and urine concentrations of ranolazine and the metabolites RS-88390 (CVT-2514), RS-88640 (CVT-2512) and RS 94287 (CVT-2738) were measured by a validated HPLC/MS/MS method [redacted] D_3-ranolazine was used as internal standard.
In plasma the lower and upper limits of quantitation for ranolazine were 50 ng/mL and 10'000 ng/mL, respectively. The corresponding values for the metabolites were 10 ng/mL and 2000 ng/mL. The respective standard curves were linear over the defined concentration range ($R^2 \geq$ 0.993). The stability of the analytes in the matrix was demonstrated. The inter-run accuracy (% relative error) and precision (CV, %) for the 4 analytes determined from the QC samples were within the ±15% limits.
In urine the quantification range for the 4 analytes ranged between 200 ng/mL and 50'000ng/mL. The respective standard curves were linear ($R^2 \geq 0.999$). The intra-run and inter-run accuracies and precisions determined from the QC samples were within the ± 15% limits.

Blood Sample Collection:

Blood samples were collected on:
Day 1: Pre-dose and 1, 2, 3, 4, 5, 7, 9 and 12 hours post-dose
Day 2: Immediately before the third (morning) and fourth (evening) doses
Day 3: Pre-dose and 1, 2, 3, 4, 5, 7, 9, 12, 16, 24, 28, 32, 36 and 48 hours post-dose
Urine samples were collected on:
Days 3 -5: 0-12, 12-24, and 24-48 hours post dose 5

PK and Statistical Analysis:

For ranolazine and the metabolites Cmax, AUC0-12, tmax on Days 1 and 3 and t1/2 and fluctuation (Cmax/Cmin) on Day 3 were computed. Renal clearance was obtained from the amounts excreted over 12 hours/AUC0-12 on Day 3. Accumulation was calculated from the respective ratios of Cmax, C12 and AUC0-12 obtained on Days 3 and Day 1. Oral clearance for ranolazine was determined from Dose/AUC0-12.

Attainment of steady state was evaluated for all 4 analytes using the least square means of C12, C24, C36, C48 and C60. The 95% confidence interval of the mean difference between C60 and C48 was computed. Regressions of the respective AUCs of the analytes on creatinine clearance were performed.

SAFETY:

Supine systolic and diastolic blood pressure was measured on:
Day 1: Pre-dose, 2, 5, and 12 hours post-dose.
Day 2: Immediately before the third (morning) and fourth (evening) doses
Day 3: Pre-dose, 2, 5, 12, 24 and 48 hours after administration of dose 5

A 12 Lead ECG was recorded at:
Admission (Day-1) and on Day 1: Pre-dose, 1, 2, 3, 4, 5, 7, 9, and 12 hours following the time"0" ECG (Day-1) or post-dose (Day 1)

Day 3: Pre-dose, 1, 2, 3, 4, 5, 7, 9, 12, 16, 24, 28, 32, 36, and 48 hours after administration of dose 5.

RESULTS:

Twenty nine (29) subjects, 8 females and 21 males, all Caucasians, entered and completed the study. The female contingents in the 4 groups ranged between 25.0% and 28.6%. Age and body weights of the subjects in the different groups were comparable.
The mean age of the subjects was 57.3 years. All subjects were of Caucasian origin.

PK:

The following tables summarize the mean data obtained for ranolazine and the metabolites:

Summary of Pharmacokinetic Parameters: Ranolazine

Impairment		Day 1 (Dose 875 mg)				Day 3 (Dose 500 mg b.i.d)						
		CrCl (mL/min)	AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)	C_{trough}[a] (ng/mL)	$T_{1/2}$ (h)	CL/F (mL/min)	Clrenal (mL/min)
None	N	8	8	8	8	8	8	8	8	7	8	8
	Mean	96.9	6310	5.8	1529	10585	5.9	1287	613	8.9	1021	49.6
	Std Dev	13.7	2848	1.5	731	3679	3.3	620	393	6.0	561	12.3
	%CV	14.1%	45.1%	25.9%	47.8%	53.7%	55.7%	48.2%	64.1%	67.4%	54.9%	24.8%
	Min											
	Median	96.5	5885	6	1365	9652	5	1270	483	6.6	868	49.6
	Max											
Mild	N	7	7	7	7	7	7	7	7	7	7	7
	Mean	63.4	11187	6.1	2546	18568	5.3	2036	1110	5.7	592	27.6
	Std Dev	5.7	5968	1.9	1254	11127	1.3	974	874	1.6	289	12.2
	%CV	9.0%	53.3%	30.4%	49.2%	59.9%	23.7%	47.8%	78.7%	28.0%	48.9%	44.1%
	Min											
	Median	62	11769	7	2690	11331	5	1950	626	5.8	735	28.5
	Max											
Moderate	N											
	Mean	39.4	8679	5.4	1864	18079	5.1	1973	1071	6.9	533	23.7
	Std Dev	7.2	2506	1.1	630	7624	1.9	732	577	3.2	214	14.5
	%CV	18.3%	28.9%	20.9%	33.8%	42.2%	36.3%	37.1%	53.8%	47.1%	40.1%	61.2%
	Min											
	Median	41	7474	5	1610	15361	5	1740	867	4.8	542	22.8
	Max											
Severe	N											
	Mean	20.4	9243	4.7	1994	21059	5.7	2447	1208	4.6	520	17.6
	Std Dev	9.7	3578	2.5	752	11838	2.7	1372	769	1.3	293	6.9
	%CV	47.4%	38.7%	53.0%	37.7%	56.2%	47.1%	56.1%	63.6%	27.7%	56.4%	39.1%
	Min											
	Median	25	8372	4	1690	16736	5	1870	961	4.9	498	20.3
	Max											

a average of predose and 12h concentration

Summary of Pharmacokinetic Parameters: CVT-2512 (RS-88640).

Impairment			Day 1 (Dose 875 mg)				Day 3 (Dose 500 mg b.i.d)					
		CrCl (mL/min)	AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)		AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)	C_{trough}* (ng/mL)	$T_{1/2}$ (h)	Clrenal (mL/min)
None	N	8	7	7	7		8	8	8	8	8	8
	Mean	96.9	423	10.3	103		1432	8.8	132	115	20.4	125.6
	Std Dev	13.7	264	1.6	65		1119	3.7	100	90.1	8.4	22.5
	%CV	14.1%	62.4%	15.6%	63.0%		78.1%	42.7%	75.6%	78.2%	41.0%	17.9%
	Min											
	Median	96.5	412	9	97		1348	8	143	122	17.8	125.0
	Max	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild	N	7	7	7	7		7	7	7	7	7	7
	Mean	63.4	306	10.3	78		1095	7.6	105	92	23.7	79.3
	Std Dev	5.7	244	1.6	65		631	3.9	60	52.0	9.2	35.8
	%CV	9.0%	79.8%	15.6%	83.3%		57.6%	51.6%	56.8%	56.5%	39.0%	45.1%
	Min											
	Median	62	232	9	56		1021	7	103	91	23.3	74.0
	Max	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	N	7	6	6	6		7	7	7	7	7	7
	Mean	39.4	370	11.3	93		1749	7.4	158	140	63.3	42.5
	Std Dev	7.2	202	1.2	30		954	4.4	84	73.8	54.0	15.1
	%CV	18.3%	54.5%	10.6%	33.5%		54.5%	58.6%	53.2%	52.6%	85.3%	35.5%
	Min	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	41	404	12	98		2120	9	194	171	45.4	45.9
	Max											
Severe	N	7	7	7	7		7	7	7	7	9	7
	Mean	20.4	467	11.3	116		3158	16.6	318	267	94.3	25.4
	Std Dev	9.7	298	1.9	74		1646	9.7	174	147.6	97.0	12.6
	%CV	47.4%	63.8%	16.7%	64.1%		52.1%	58.3%	54.7%	55.3%	102.9%	49.8%
	Min											
	Median	25	444	12	94		3021	12	301	241	44.0	27.1
	Max											

average of predose and 12h concentration

Summary of Pharmacokinetic Parameters: CVT-2514 (RS-88390).

Impairment			Day 1 (Dose 875 mg)				Day 3 (Dose 500 mg b.i.d)					
		CrCl (mL/min)	AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)		AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)	C_{trough}* (ng/mL)	$T_{1/2}$ (h)	Clrenal (mL/min)
None	N	8	8	8	8		8	8	8	8	8	8
	Mean	96.9	2198	7.5	487		4285	7.1	455	284	11.6	30.0
	Std Dev	13.7	1236	0.9	268		2500	3.2	265	148.3	6.3	6.3
	%CV	14.1%	56.2%	12.3%	55.0%		58.3%	45.3%	58.3%	52.3%	54.3%	21.0%
	Min	[redacted]										
	Median	96.5	2472	7	548		4875	7	551	289	9.8	28.4
	Max	[redacted]										
Mild	N	7	7	7	7		7	7	7	7	7	7
	Mean	63.4	1588	7.6	358		2944	5.3	321	191	11.2	17.2
	Std Dev	5.7	1180	1.5	279		1527	2.4	205	81.0	4.7	8.6
	%CV	9.0%	74.3%	20.0%	78.1%		51.9%	46.0%	63.9%	42.5%	41.6%	50.1%
	Min	[redacted]										
	Median	62	1359	7	303		2642	5	267	175	10.9	15.5
	Max	[redacted]										
Moderate	N	7	7	7	7		7	7	7	7	7	7
	Mean	39.4	1923	7.3	395		3810	4.9	368	272	13.9	14.2
	Std Dev	7.2	1731	1.8	350		2861	2.2	269	217.3	6.1	7.2
	%CV	18.3%	90.0%	24.7%	88.6%		73.1%	45.2%	73.1%	79.9%	43.9%	50.9%
	Min	[redacted]										
	Median	41	1097	7	210		2992	5	282	224	13.1	16.9
	Max	[redacted]										
Severe	N	7	7	7	7		7	7	7	7	7	7
	Mean	20.4	2272	7.3	468		6531	7.7	716	471	18.9	12.2
	Std Dev	9.7	1631	1.8	332		4922	2.5	549	339.6	9.3	4.3
	%CV	47.4%	71.8%	24.7%	70.9%		75.4%	32.4%	76.6%	72.1%	49.1%	34.8%
	Min	[redacted]										
	Median	25	1891	7	424		3853	7	424	302	16.6	13.7
	Max	[redacted]										

average of predose and 12h concentration

Summary of Pharmacokinetic Parameters: CVT-2738 (RS-94287)

Impairment		Day 1 (Dose 875 mg)				Day 3 (Dose 500 mg b.i.d)					
		CrCl (mL/min)	AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)	C_{trough}[a] (ng/mL)	$T_{1/2}$ (h)	Clrenal (mL/min)
None	N	8	8	8	8	8	8	8	8	8	8
	Mean	96.9	1153	8.8	230	3494	7.1	325	266	11.4	205.9
	Std Dev	13.7	331	0.7	83	811	2.4	71	67.7	2.2	32.1
	%CV	14.1%	28.7%	8.1%	35.2%	23.2%	33.9%	21.9%	25.3%	19.5%	15.6%
	Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	96.5	1065	9	237	3373	7	316	280	11.0	202.1
	Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild	N	7	7	7	7	7	7	7	7	7	7
	Mean	63.4	1726	9.3	416	6335	5.6	605	500	12.5	136.2
	Std Dev	5.7	541	2.1	166	2072	2.8	198	180.4	3.0	57.0
	%CV	9.0%	31.4%	22.2%	39.9%	32.7%	49.5%	32.8%	36.1%	23.8%	41.9%
	Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	62	1577	9	371	6130	5	611	478	12.9	135.1
	Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	N	7	7	7	7	7	7	7	7	7	7
	Mean	39.4	2399	11.1	538	13144	6.4	1235	1046	21.9	69.5
	Std Dev	7.2	1836	1.5	445	10547	1.9	1129	831.1	5.6	26.3
	%CV	18.3%	76.5%	13.1%	79.8%	80.2%	29.6%	90.0%	79.5%	25.4%	37.8%
	Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	41	1501	12	351	9334	5	826	768	20.6	77.1
	Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	N	7	7	7	7	7	7	7	7	7	7
	Mean	20.4	2393	12.0	552	16599	8.4	1326	1342	38.4	47.3
	Std Dev	9.7	1012	0.0	222	9799	3.7	838	811.6	18.2	25.0
	%CV	47.4%	42.3%	0.0%	40.2%	59.0%	44.3%	54.9%	60.5%	47.3%	52.7%
	Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	25	2318	12	570	15815	9	1330	1190	32.8	55.3
	Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] average of predose and 12h concentration

Urinary Excretion of Ranolazine and its Metabolites (Day 3, 0-12 h)

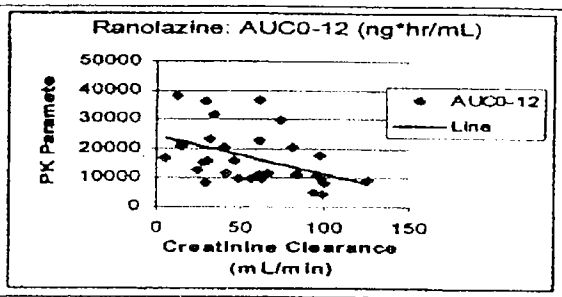
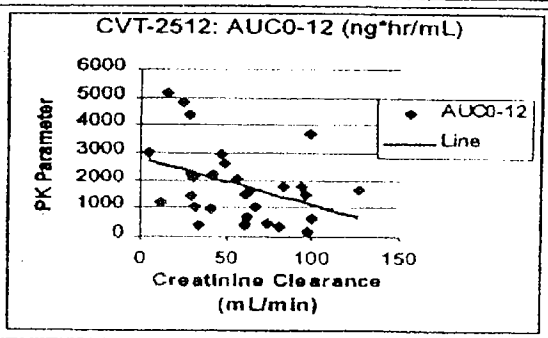
Impairment		CrCl (mL/min)	Amount Excreted in Urine (ug)			
			Ranolazine (CVT-303)	CVT-2512 (RS-88640)	CVT-2514 (RS-88390)	CVT-2738 (RS-94287)
None	N	8	8	8	8	8
	Mean	96.9	31156	9643	7263	42856
	Std Dev	13.7	17932	6294	4038	10642
	%CV	14.1%	57.6%	65.3%	55.6%	24.8%
	Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	96.5	28646	10874	8501	41832
	Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild	N	7	7	7	7	7
	Mean	63.4	30930	4537	2596	55374
	Std Dev	5.68	22417	2464	996	31779
	%CV	9.0%	72.5%	54.3%	38.4%	57.2%
	Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	62.0	23406	3854	2829	66234
	Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	N	7	7	7	7	7
	Mean	39.4	25717	4693	3444	41195
	Std Dev	7.23	19086	3736	2873	14044
	%CV	18.3%	74.2%	79.6%	83.4%	34.1%
	Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	41.0	20060	2710	3819	41202
	Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	N	7	7	7	7	7
	Mean	20.4	20648	4681	4794	36033
	Std Dev	9.69	12423	3322	4013	11627
	%CV	47.4%	60.2%	71.0%	83.7%	32.3%
	Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	25.0	16958	3854	3302	34340
	Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

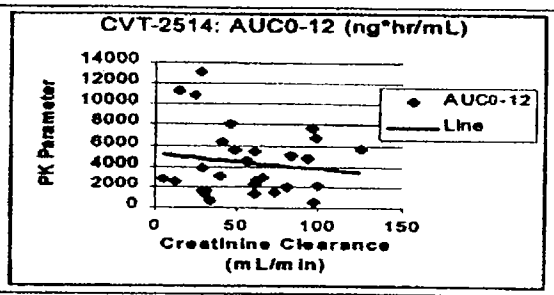
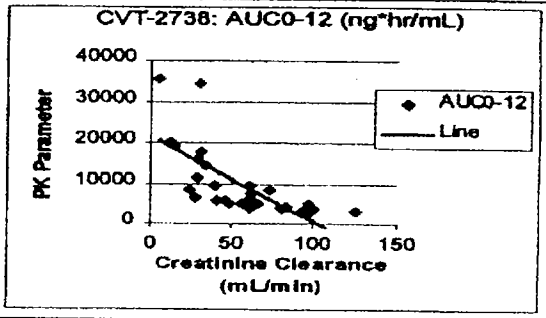
The respective mean renal clearances of ranolazine, RS-88640 (CVT-2512), RS-88390 (CVT-2514) and RS-94287 (CVT-2738) in the healthy volunteers were 49.6 ml/min, 125.6 ml/min, 30.0 mL/min and 205.9 ml/min, indicating that the metabolite RS-94287 (CVT-2738) was eliminated by tubular secretion in addition to glomerular filtration. The respective mean percentages of the dose excreted in urine as ranolazine, RS-88390 (CVT-2514), RS-88640 (CVT-2512) and RS-94287 (CVT-2738) in the healthy volunteers were 6.2%, 1.5%, 2.6% and 14.8% totaling 25.1 %. In the patients with severe renal impairment the respective mean percentages were decreased to 4.1%, 0.99%, 1.3% and 12.5% totaling 18.9%. The observed differences in the extent to which the 4 analytes' urinary recovery was reduced indicated that renal impairment impacted not only the renal elimination of the analytes but also the relative contribution of the different metabolic routes of ranolazine and the metabolites. Patients with severe renal impairment showed an increase in apparent mean half-lives and accumulation ratios of the 3 metabolites relative to healthy volunteers. The median AUC0-12 (Day 3) values of the metabolite in percent of ranolazine in healthy volunteers were 50.5%, 16.0% and 34.9% for RS-88390 (CVT-2514), RS-88640 (CVT-2512) and RS-94287 (CVT-2738), respectively. The corresponding percentages in patients with severe renal impairment were 23.0%, 18.1% and 94.5% for RS-88390 (CVT2514), RS-88640 (CVT-2512), and RS-94287 (CVT-2738), respectively, indicating a reduction for RS-88390 (CVT-2514) and a clear increase for RS-94287 (CVT-2738).

The inter-subject variation (CV, %) about the mean exposure measures for ranolazine (AUC0-12, Cmax) was not importantly different between healthy volunteers and patients with renal impairment.

The following figures show the relationship between AUC0-12 (Day 3) and creatinine clearance:

Equation and graph for AUC_{0-12} for Ranolazine and Metabolites

Equation	Graph
AUC = 24337 – 133×CrCl p = 0.022	
AUC = 2804 – 17×CrCl p = 0.035	

Equation	Graph
AUC = 5157 – 14×CrCl Slope is not statistically significant at the 5% level p = 0.506	
AUC = 39508 – 212×CrCl – 227×Weight p < 0.001	

The AUC0-12 (Day 3) values of ranolazine and the metabolites RS-88390 (CVT-2514) and RS-94287 (CVT-2738) were statistically significantly correlated with the creatinine clearance. For ranolazine the respective increases in median AUC0-12 (Day 3) in mild, moderate and severe renal impairment relative to healthy volunteers were 1.17, 1.59 and 1.73 fold. The corresponding Cmax values for ranolazine increased 1.54, 1.37 and 1.47 fold, respectively. The median exposure (AUC0-12, Day 3) to RS-88390 (CVT-2514) and RS-94287 (CVT-2738) in patients with severe renal impairment relative to healthy volunteers increased 1.96 and 4.69 fold, respectively, whereas the median exposure to RS-88640 (CVT-2512) was not importantly altered. Similar increases in median Cmax were found for RS-88390 (CVT-2514) (2.10 fold) and RS-94287 (CVT-2738) (4.84 fold). Renal impairment did not increase the median Cmax for RS-88640 (CVT-2512).

SAFETY:

The time specific apparent mean maximum changes of the QTc interval relative to the base line were +12.0 (23.1) msec, +5.9 (24.6) msec, +18.6 (19.6) msec and +16.9 (28.6) msec in healthy volunteers, patients with mild, moderate and severe renal impairment. They occurred in the time interval of 3 to 9 hours following administration of the last dose of ranolazine. No important changes in the T-wave morphology were observed. Three (3) subjects in the moderate and 2 subjects in the severe impairment group displayed an increase in creatinine and reported constipation. Both events were judged to be possibly drug related. The subjects with severe renal impairment experienced a mean increase of

The supine diastolic blood pressure ranging between 3.7 mmHg to 17.4 mmHg.

CONCLUSIONS:

In healthy volunteers the mean urinary recovery of unchanged ranolazine is small. The mean t1/2 and accumulation ratios of the 3 metabolites increase with increasing renal impairment. Relative to healthy volunteers AUC0-12 and Cmax increase in the order RS-94287 (CVT-2738) >RS-88390 (CVT-2514) > ranolazine with decreasing renal function. Among the metabolites the median AUC0-12 relative to ranolazine increases for RS-94287 (CVT-2738) and RS-88390 (CVT-2514), but not for RS-88640 (CVT-2512). The exposures to RS-94287 (CVT-2738) and ranolazine are similar in severe renal impairment. The AUC(0-12) of ranolazine, RS-88390 (CVT-2514) and RS-94287 (CVT-2738) are statistically significantly linearly correlated with creatinine clearance.
Renal impairment inhibits not only the renal elimination of ranolazine and the metabolites, but also impacts metabolic enzymes and/or nonrenal transporters.
Mean maximum increases in apparent QTc of 5.9 msec to 18.6 msec were seen after administration of ranolazine to healthy volunteers and patients with renal impairment.
A significant increase of the supine diastolic blood pressure was seen in patients with severe renal impairement.

COMMENTS:

1. A justification for weighting the calibration standards for ranolazine and the metabolites by 1/x was not provided in the validation report
2. In the presence of a circadian rhythm attainment of steady state ought to be tested by comparing concentrations measured at the same time at different days (24 hour intervals instead of 12 hour intervals).
3. The report did not discuss the need for a dose adjustment in renally impaired patients and did not propose a regimen based on the results of the study.
4. The results were obtained at a dose level of 500 mg ranolazine given bid and cannot be extrapolated to dose levels of 750 mg and 1000 mg ranolazine.
5. The relationship between QTc and the plasma oncentrations of ranolazine were not explored.
6. RS-94287 (CVT-2738) is wrongly labeled in Table 6 on p.96, Item 6, Vol 18

Appears This Way
On Original

STUDY CVT 3018 – STUDY TO EVALUATE THE PHARMACOKINETIC PARAMATERS 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

STUDY PINCIPAL INVESTIGATOR AND SITE: [

]

Report No.: CVT 3018
Volume No.: 28-33, ITEM 6

OBJECTIVES:

To evaluate the pharmacokinetic parameters of ranolazine and the metabolites RS-88390 CVT-2514, RS-88640 CVT-2512 and RS-94287 (CVT-2738) in subjects with hepatic impairment and in matched healthy volunteers

FORMULATIONS:

375mg SR tablets (Lot No. 9G2715A)
500mg SR tablets (Lot No. 9G2714A)

STUDY DESIGN:

This was an open-label, multiple dose, pharmacokinetic study. In order to attain steady-state more rapidly the subjects received a loading dose of 875mg ranolazine in the morning of Day 1, followed by a maintenance dose regimen of 500mg bid starting in the evening of Day 1 and ending with the morning dose on Day 3. The subjects were enrolled in 3 study groups: Group1, mild hepatic impairment, Group 2, moderate hepatic impairment, and Group 3, healthy subjects. Groups 1 and 2 contained 8 subjects each. Group 3 consisted of 16 health volunteers. Mild and moderate hepatic impairment were defined by the Child-Pugh classification system. The healthy subjects were matched for age, body weight and gender. The doses were administered with 250mL water to the subjects in the sitting position. The subjects were institutionalized from the evening before Day 1 to Day 5.
At least 3 days prior to study start, the CYP 3A4 activity of the subjects was tested by a 30 second infusion of 0.02mg/kg midazolam.

ASSAY:

All samples for the measurement of ranolazine and the metabolites were analyzed at CV Therapeutics, Palo Alto, CA.

Ranolazine and Metabolites:
The plasma and urine concentrations of ranolazine and the metabolites RS-88390 (CVT-2514), RS-88640 (CVT-2512) and RS-94287 (CVT-2738) were measured by a validated HPLC/MS/MS method [redacted] d_3-ranolazine was used as internal standard. In plasma the lower and upper limits of quantitation for ranolazine were 50 ng/mL and 10'000 ng/mL, respectively. The corresponding values for the metabolites were 10 ng/mL and 2000 ng/mL. The respective standard curves were linear over the defined concentration range ($R^2 \geq 0.996$). The stability of the analytes in the matrix was demonstrated. The inter-run accuracy (% relative error) and precision (CV, %) determined from the QC samples for the 4 analytes were within the ± 15% limits.

Midazolam:

The samples for the measurement of midazolam were analyzed by [redacted] The method used a liquid/liquid extraction followed by GC detection.

Blood Sample Collection:

Blood samples for the measurement of ranolazine and the metabolites were collected on:
Day 1: Pre-dose and 1, 2, 3, 4, 5, 7, 9 and 12 hours post-dose
Day 2: Immediately before the third (morning) and fourth (evening) doses
Day 3: Pre-dose and 1, 2, 3, 4, 5, 7, 9, 12, 16, 24, 28, 32, 36 and 48 hours after last dose

Blood samples (10 mL) were collected no later than 3 days prior to study start for measuring midazolam at the following times after completion of a 30sec infusion:
0, 5, 15, 30, 45 min and 1, 2, 3, 4, and 8 hours.

PK and Statistical Ananalysis:

For ranolazine and the metabolites Cmax, AUC0-12, tmax on Days 1 and 3 and t1/2 and fluctuation (Cmax/Cmin) on Day 3 were computed using standard metodology. Accumulation was calculated from the respective ratios of Cmax, C12 and AUC0-12 obtained on Days 3 and Day 1. Oral clearance for ranolazine was determined from Dose/AUC0-12. AUC, t1/2, Cl and Vss for midazolam were determined using standard methods.
The pre-dose concentrations C (12), C(24), C(36), C(48) and C(60) for ranolazine and the metabolites were fit to a mixed effect model linear model with fixed effect sampling time and random effect patient. The difference in the mean concentrations was calculated using least square means, and 95% confidence intervals were established.
To asses the impact of Child-Pugh hepatic impairment score, weight, sex and age on the PK parameters linear regression models were used. The Child-Pugh group was entered into the

model as a classification variable with levels 1 (healthy), 2 (grade A), and 3 (grade B). Backwards elimination was then used to reduce the model with $p < 0.05$ as criterion.

SAFETY:

A 12 Lead ECG was recorded at the following times:
Admission (Day-1)
Day 1: Pre-dose, 1, 2, 3, 4, 5, 7, 9, and 12 hours following the time"0" ECG (Day-1) or post-dose (Day 1)
Day 3: Pre-dose, 1, 2, 3, 4, 5, 7, 9, 12, 16, 24, 28, 32, 36, and 48 hours after dose 5
Supine systolic and diastolic blood pressures were measured at the following times:
Admission (Day-1)
Day 1: Pre-dose, 2, 5 and 12 hours following dose 1
Day 2: Immediately before the third (morning) and fourth (evening) doses
Day 3: Pre-dose, 2, 5, 12, 24 and 48 hours after dose 5

RESULTS:

32 subjects, 10 females and 22 male subjects, all Caucasian, entered and completed the study. The female contingents in the 3 groups represented between 25.0% and 37.5%. Mean age and body weight of the subjects in the 3 groups were comparable. The mean age was 52.3 years.

PK:

The following tables summarize the mean data obtained for ranolazine and the metabolites:

Summary of Pharmacokinetic Parameters: Ranolazine (CVT-303)

Impairment		Day 1 (Dose 875 mg)				Day 3 (Dose 500 mg b.i.d)					
		AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)		AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)	$T_{1/2}$ (h)	C_{trough}[1] (ng/mL)	CL/F (mL/min)
None	N	16	16	16		16	16	16	16	16	16
	Mean	8509	6.0	1183		9249	4.6	1155	5.34	464	1067
	Std Dev	3506	1.8	524		3756	2.1	558	2.81	197	472
	%CV	41.2%	29.8%	44.3%		40.6%	45.3%	48.3%	52.6%	42.5%	44.2%
	Min										
	Median	8411	7.0	1095		8532	5.0	1024	4.53	426	980
	Max										
Mild	N	8	8	8		8	8	8	8	8	8
	Mean	11792	6.0	1879		9618	4.9	1295	4.09	464	920
	Std Dev	4664	2.3	697		2613	2.1	213	1.07	155	234
	%CV	39.6%	38.8%	37.1%		27.2%	43.1%	16.5%	26.2%	33.4%	25.5%
	Min										
	Median	9625	6.0	2005		9439	4.0	1310	3.72	530	881
	Max										
Moderate	N	8	8	8		8	8	8	8	8	8
	Mean	14041	7.3	1917		16252**	5.0	1747*	5.96	1038**	584
	Std Dev	4768	1.7	805		5271	1.8	512	1.65	442	269
	%CV	34.0%	23.0%	42.0%		32.4%	35.5%	29.3%	27.6%	42.6%	46.1%
	Min										
	Median	14289	7.0	1985		16186	5.0	1790	6.24	1101	516
	Max										

[1] average of predose and 12h concentration
* $p < 0.01$; ** $p < 0.001$ compared to healthy subject

Summary of Pharmacokinetic Parameters: CVT-2512 (RS-88640)

Impairment		Day 1 (Dose 875 mg)				Day 3 (Dose 500 mg b.i.d)				
		AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)		AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)	$T_{1/2}$ (h)	C_{trough}* (ng/mL)
None	N	16	16	16		16	16	16	16	16
	Mean	581	10.9	80.2		1304	7.2	125	16.29	103
	Std Dev	241	1.7	36.2		532	2.8	50	2.45	43
	%CV	41.5%	15.5%	45.1%		40.8%	38.8%	40.2%	15.1%	41.9%
	Min	[redacted]								
	Median	617	12.0	79.8		1281	8.0	117	15.88	100
	Max	[redacted]								
Mild	N	8	8	8		8	8	8	8	8
	Mean	838	8.8	103.0		1219	6.0	118	12.42	90
	Std Dev	462	2.4	52.4		544	2.4	52	3.10	39
	%CV	55.2%	27.8%	50.9%		44.6%	40.8%	44.6%	25.0%	43.1%
	Min	[redacted]								
	Median	741	9.0	103.0		1305	6.0	126	13.02	96
	Max	[redacted]								
Moderate	N	8	8	8		8	8	8	8	8
	Mean	673	10.9	98.2		1344	6.9	125	13.11	106
	Std Dev	402	1.6	48.2		468	2.9	46	1.75	31
	%CV	59.8%	14.3%	49.1%		34.8%	42.9%	36.7%	13.4%	29.6%
	Min	[redacted]								
	Median	523	12.0	85.9		1368	7.0	125	12.61	111
	Max	[redacted]								

*average of predose and 12h concentration

Summary of Pharmacokinetic Parameters: CVT-2514 (RS-88390)

Impairment		Day 1 (Dose 875 mg)				Day 3 (Dose 500 mg b.i.d)				
		AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)		AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)	$T_{1/2}$ (h)	C_{trough}* (ng/mL)
None	N	16	16	16		16	16	16	16	16
	Mean	3457	7.4	435.3		4516	5.2	470	9.60	292
	Std Dev	1542	1.5	205.8		1929	2.3	197	1.89	139
	%CV	44.6%	20.3%	47.3%		42.7%	44.6%	41.9%	19.7%	47.6%
	Min	[redacted]								
	Median	3557	7.0	426.0		4460	5.0	435	9.23	246
	Max	[redacted]								
Mild	N	8	8	8		8	8	8	8	8
	Mean	4551	6.1	644.1		4614	5.5	545	7.13	269
	Std Dev	2048	2.0	353.6		2068	2.0	270	2.00	121
	%CV	45.0%	32.0%	54.9%		44.8%	36.4%	49.5%	28.0%	44.9%
	Min	[redacted]								
	Median	4783	7.0	656.0		4989	5.0	559	6.44	299
	Max	[redacted]								
Moderate	N	8	8	8		8	8	8	8	8
	Mean	2683	9.0	359.8		4051	6.5	391	8.58	298
	Std Dev	1742	2.1	203.8		1361	2.1	151	1.69	78
	%CV	64.9%	23.0%	56.6%		33.6%	31.8%	38.5%	19.7%	26.2%
	Min	[redacted]								
	Median	2349	9.0	352.0		3943	7.0	371	7.70	312
	Max	[redacted]								

*average of predose and 12h concentration

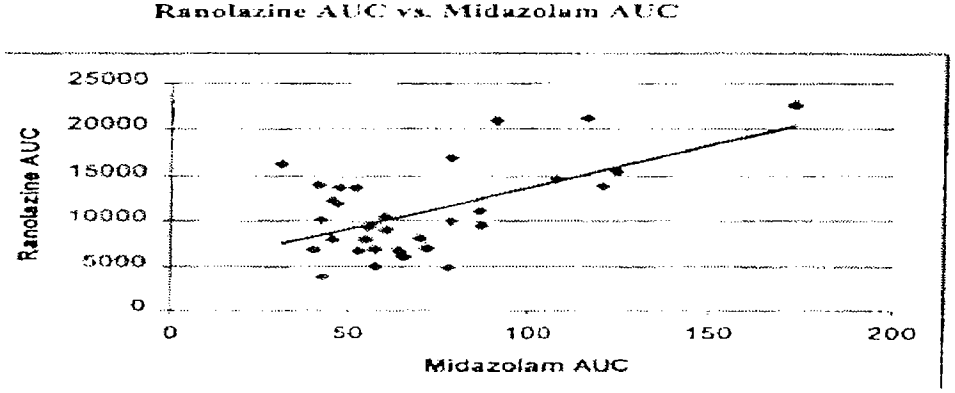
Summary of Pharmacokinetic Parameters: CVT-2738 (RS-94287)

Impairment		Day 1 (Dose 875 mg)				Day 3 (Dose 500 mg b.i.d)				
		AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)		AUC_{0-12} (ng*h/mL)	T_{max} (h)	C_{max} (ng/mL)	$T_{1/2}$ (h)	C_{trough} (ng/mL)
None	N	16	16	16		16	16	16	16	16
	Mean	1866	7.8	235.4		3500	5.3	343	9.50	247
	Std Dev	1080	2.7	152.1		2018	2.2	218	1.78	134
	%CV	57.9%	34.8%	64.6%		57.7%	41.4%	63.6%	18.8%	54.2%
	Min									
	Median	1559	8.0	199.0		3197	5.0	301	9.44	239
	Max									
Mild	N	8	8	8		8	8	8	8	8
	Mean	1777	7.0	219.5		2511	5.5	250	8.21	172
	Std Dev	583	2.4	77.8		718	2.0	66	1.10	55
	%CV	32.8%	34.1%	35.4%		28.6%	36.4%	26.4%	13.4%	32.0%
	Min									
	Median	1533	8.0	193.0		2187	5.0	222	8.51	149
	Max									
Moderate	N	8	8	8		8	8	8	8	8
	Mean	1420	10.3	185.5		3010	4.6	271	10.50	233
	Std Dev	978	2.0	107.1		1211	2.0	104	1.55	94
	%CV	68.9%	19.3%	57.7%		40.2%	43.1%	38.2%	14.7%	40.4%
	Min									
	Median	1117	10.5	150.5		2896	5.0	263	10.48	229
	Max									

[a] average of predose and 12h concentration

Compared to healthy volunteers, the median AUC0-12 (Day 3) values for ranolazine increased 1.11 and 1.90 fold, respectively, in patients with mild and moderate impairment. Similar increases were observed for Cmax (1.28 and 1.75 fold). These changes were not associated with an important prolongation of the apparent half-life of ranolazine. The exposure to the 3 metabolites in the patients with liver impairment and in healthy volunteers was similar. The AUC0-12 (Day 3) of the three metabolites relative to ranolazine was about 50% smaller in patients with moderate hepatic impairment relative to healthy volunteers. The intersubject variation (CV, %) about the mean exposure measures for ranolazine (AUC0-12, Cmax) tended to be smaller in the patients with hepatic impairment than in the healthy subjects.

The following figure shows a statistically significant correlation between AUC0-12 (Day 3) and midazolam AUC ($p<0.0006$):



SAFETY:

The respective time specific apparent mean (SD) maximum changes from baseline in QTc on Day 3 were +12.5 (20.3) msec, +18.1 (19.4) msec and +20.8 (22.1) msec in healthy volunteers and patients with mild and moderate liver impairment. They occurred between 5 and 7 hours after administartion of the last dose of ranolazine.
A mean increase of 17.5 mmHg from baseline (pre-dose Day-1) in supine systolic blood pressure was observed pre-dose PM on Day 2 in subjects with mild hepatic impairment. Four (4) of 8 subjects displayed an increase of more than 20 mmHg. The increase in supine diastolic blood pressure at the same time point was 9.5 mmHg, but only 1 of 8 subjects in the mild hepatic impairment group displayed an increase exceeding 20 mmHg. At the Day 2 pre-dose PM time point also the mean pulse rate was elevated in all 3 groups and 2 of the 16 healthy volunteers and 5 of the 8 patients with mild hepatic impairment showed abnormal increases (>90 bpm). The potassium levels of the subjects were in the normal range throughout the study.

CONCLUSIONS:

Moderate hepatic impairment results in a 1.90 fold mean increase in exposure to ranolazine. The exposure to ranolazine in patients with mild hepatic impairment and healthy volunteers is comparable. The exposure to the measured metabolites in patients with liver impairment and in healthy volunteers is similar. The AUC0-12 on Day 3 of ranolazine is correlated with the AUC of intravenously administered midazolam, suggesting that liver impairment is associated with a decrease in CYP 3A4 activity. The mean maximum increase of QTc from baseline is greater in the patients with liver impairment than in healthy volunteers. Mean systolic and diastolic blood pressures are significantly increased after administration of ranolazine in the patients with mild hepatic impairment.

COMMENTS:

1. A justification for the weighting of the calibration standards for ranolazine and the metabolites by 1/x was not provided in the validation report
Analytical and validation reports for the midazolam assay were not submitted.
2. In the presence of a diurnal rhythm attainment of steady state ought to be tested by comparing concentrations measured at the same time of the day on different days
3. The report ought to specify the subjects studied in site 1 and 2.
4. Given that the exposure to the measured metabolites in the patients with moderate hepatic impairment and healthy volunteers was not different an increased exposure to unidentified metabolites in patients with moderate impairment cannot be excluded.
5. The report did not discuss the need for a dose adjustment in hepatically impaired patients and did not propose a regimen based on the results of the study
6. No attempt was made to explore the relationship between QTc and the plasma concentrations of ranolazine.
7. No information on the validation of the assay for midazolam was provided.
8. Magnesium levels were not measured in the subjects.

STUDY CVT 3031- A DOUBLE BLIND, PLACEBO-CONTROLLED, 4-PERIOD 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

STUDY INVESTIGATOR AND COUNTRIES:

United States: Jerome Anderson, MD; W. Tyson Bennett, MD; Richard Carson, MD; Steven Chrysant, MD; Bart Denys, MD; Vincent DeQuattro, MD; Harold Fleming, MD; Joe Gaddy, MD; Stephen Glasser, MD; Jeffrey Gorwit, MD; William Grossman, MD; Peter Hanley, MD; General K. Hilliard, MD; Michael J. Koren, MD; Rafael Levites, MD; Mark Litt, MD; Frank D. McBarron, MD; Sukh Mehta, MD; James B. Miller, MD; Douglas P. Mooney, MD; Asim Nisar, MD; Carl Pepine, MD; Steven D. Promisloff, MD; Robert Rosenstein, MD; William Smith, MD; Melvin Tonkon, MD; Douglas Waldo, MD; Laurence Yellen, MD.

Canada: Peter Klinke, MD; Murray F. Matangi, MD; John O. Parker, MD; Richard St. Hillaire, M.D.

Czech Republic: MUDr. Petr Fridl; MUDr. P. Jansky; MUDr. Gabriel Marcinek; MUDr. Jaroslav Meluzin; MUDr. Jaroslav Skopal; MUDr. Roman Stipal; MUDr. Frantisek Tousek.

Poland: Prof. L. Ceremuzynski; Prof. Jan Goch; Prof. Bogumil Halawa; Dr. Kazimierz Janicki; Prof. K. Kawecka-Jaszcz; Prof. Krzeminska-Pakula; Prof. J. Kuch; Dr. Janusz Maciejewicz; Prof. Halina Nowosad; Dr. Wieslaw Piotrowski; Prof. Andrzej Rynkiewicz.

Report No.: CVT 3031
Volume No.: 64-77, IITEM 6

OBJECTIVES:

Primary: Determine the effect of ranolazine SR monotherapy compared to placebo in patients with chronic stable angina on exercise treadmill test (ETT) duration at the time of trough plasma levels (12 hours postdose) when given at the following doses: 500 mg bid, 1000 mg bid and 1500 mg bid

Secondary: Determine the following in patients with chronic stable angina during ETT:

1. The effect at trough on time of onset of angina and time to 1mm ST-segment depression of the 3 doses of ranolazine SR monotherapy compared to placebo
2. The effect at the approximate time of peak ranolazine plasma concentrations (4 hours postdose) on exercise duration, time of onset of angina, and time to 1mm ST-segment depression of the 3 doses of ranolazine SR monotherapy compared to placebo

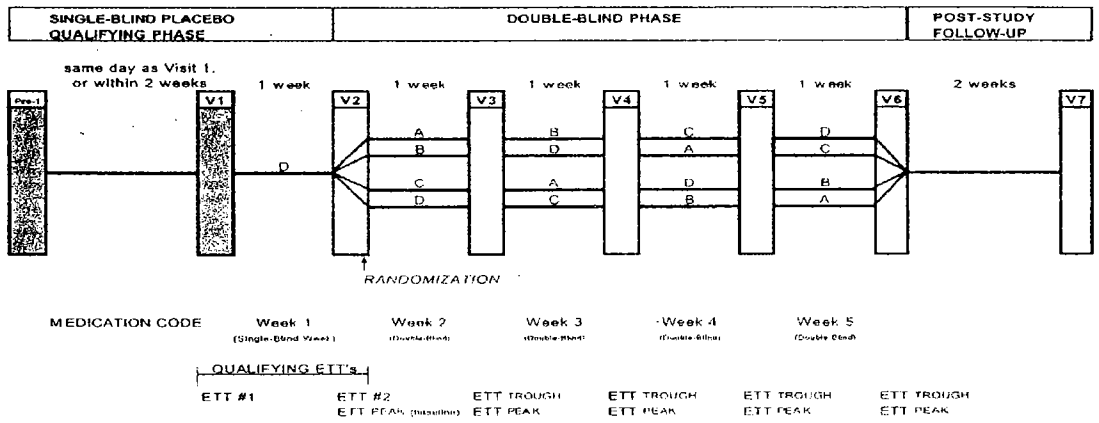
FORMULATIONS:

500mg SR tablets (Lot No.791771 and 791751)
Matching placebo tablets (Lot No.6995, 8007, 7314, 7492)

STUDY DESIGN:

This was an international, multicenter, double-blind, randomized, placebo-controlled, multiple-dose, dose definition study of ranolazine SR. Ranolazine was used as monotherapy in patients with chronic stable angina in this 4-period Latin Square crossover study. The study was composed of 2 phases: A single blind placebo qualifying phase of approximately 1 week's duration (which included 2 qualifying ETTs (3min ≥ exercise duration ≤ 9min) and a placebo-controlled, double-blind, crossover treatment phase lasting 4 weeks. There were no washout periods. A follow-up visit was performed 2 weeks after completion of the double-blind phase. Patients meeting the inclusion criteria at the end of the placebo qualifying phase were randomized to receive ranolazine SR 500 mg bid, 1000 mg bid, 1500 mg bid, and placebo. Patients received a 1 week's treatment with each of the 4 treatment regimens in randomized order and performed ETTs at the end of each treatment week (Visits 3, 4, 5, and 6). At each weekly visit, ETTs were performed using a modified Bruce protocol on motor-driven treadmills at time points coinciding with anticipated trough and peak ranolazine concentrations. Safety parameters (vital signs, ECGs, clinical laboratory measurements, and adrenocorticotropic hormone (ACTH) stimulation testing) were assessed at baseline and at scheduled visits throughout the study. AEs were assessed throughout the study.
The following 2 schemes show the study design and event schedule:

Study Design



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

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Schedule of Events

Visit	1	2	3	4	5	6	7
Procedure	Screening (may be same day as Pre-1)	Screen/ Qualifying	Double-Blind (1st DB Visit)	Double-Blind (2nd DB Visit)	Double-Blind (3rd DB Visit)	Termination Double-Blind (4th & last DB Visit)	Post-Study Follow-up
Time		1 week	1 week	1 week	1 week	1 week	2 weeks later
History (Medical & Cardiovascular)	x*					x	x
Medication History	x						
Physical Exam	x*					x	x**
Weight	x*						
Inclusion/Exclusion Criteria Met	x*	x					
Vital Signs & Hemodynamic Measurements (BP & HR)	x	x	x	x	x	x	
Lab Tests: Hematology, Serum Chemistry, UA	x*					x	
Lab Tests: Cholesterol, HDL, LDL, VLDL, Triglycerides	x*					x	
Lab Tests: TSH & T4	x*						
Lab Tests: Coagulation (PT & PTT)	x*					x	
Lab Tests: Stool Guaiac Test	x*					x	
Serum HCG Test (Females Only)	x*		x			x	
D/C Anti-Anginals At Least 48 Hours Prior to Visit 1	x						
Plasma for Trough Ranolazine Levels			x	x	x	x	
Plasma for Peak Ranolazine Levels			x	x	x	x	
ECG Trough	x	x	x	x	x	x	
ECG Peak		x	x	x	x	x	
ETT Trough	x	x	x	x	x	x	
ETT Peak		x	x	x	x	x	
ACTH testing (where available)		x				x	
Adverse Events		x	x	x	x	x	x
Concomitant Medications Use	x	x	x	x	x	x	x
Dispense Single-Blind Placebo	x						
Collect Single-Blind Placebo from Previous Visit		x					
Dispense Double-Blind Study Drug		x	x	x	x		
Collect Double-Blind Placebo from Previous Visit			x	x	x	x	
Drug to be Dispensed	Week 1	Week 2	Week 3	Week 4	Week 5		

* Items marked with an asterisk could have been completed at an optional Pre-1 Visit. If this option was used, then the asterisked items should not have been repeated at Screening Visit 1.
** A modified PE was performed at Visit 7.
Note: UA = Urinalysis; D/C = Discontinued

The primary efficacy variable was ETT duration (time to reach severity of symptoms causing the patient to stop exercising) at the morning trough concentration, measured after 1 week on each of the 4 treatments.
Secondary endpoints included the following parameters that were obtained during ETT at the time of morning trough concentration and at the 4 hour post-dose peak concentration: Onset of angina, time to 1mm ST-segment depression, maximum
ST-segment depression, primary reason for stopping the ETT and exercise duration during ETT at the approximate peak concentration

ASSAY:

All plasma concentrations of ranolazine were measured by C
J

The plasma concentrations of ranolazine were measured by a HPLC/MS/MS method C
J The internal standard employed was d3-

ranolazine. The upper and lower limits of quantitation for ranolazine in plasma were 10 ng/mL and 1300 ng/mL. The standard curves over the defined concentration range were linear with R^2>0.995 when the concentrations were weighted by $1/x^2$. The stability of ranolazine in plasma was established. Inter-run accuracy (nominal concentration, %) and precision (CV, %) using the QC samples were within the ±15% limits.

Blood Sample Collection:

Blood samples were collected at the time of the approximate peak (4 hours after morning dose) and trough (12 hours after evening dose) ranolazine plasma concentrations after one week treatment with each of the 4 regimens.

SAFETY:

Supine and erect blood pressures and heart rate were recorded at rest and as part of the ETT safety monitoring. Standard supine 12-lead ECGs were obtained prior to each ETT at screening, Visit 1), at peak and trough at Visit 2 and throughout the double-blind treatment phase. If at any time during the double-blind treatment phase the QTc (Bazett) lengthened to >130% of its duration at Visit 2 and was then longer than 500msec, the patient was to be withdrawn. The standard ECG intervals were measured and QT corrections for heart rate performed in accordance with Bazett, Fridericia, Framingham and modified Framingham. An evaluation of changes in the morphology of the QRS-ST-T-Wave morphology was also done. In addition ACTH testing was performed at Visits 2 and 6.

RESULTS:

PK:

191 patients were randomized, 23 discontinued prematurely. The ITT population consisted of 185 subjects.

Efficacy:

The following table lists the salient findings of the study:

	Placebo		500 mg bid		1000 mg bid		1500 mg bid	
	trough	peak	trough	peak	trough	peak	trough	peak
Exercise Duration (sec)	506	502	529	531	539	552	552	557
p-value vs. placebo	-	-	0.003	<0.001	<0.001	<0.001	<0.001	<0.001
Time to Angina (sec)	407	416	434	452	453	473	467	485
p-value vs. placebo	-	-	0.005	<0.001	<0.001	<0.001	<0.001	<0.001
Time to 1 mm ST Depression (sec)	443	436	471	475	488	492	508	505
p-value vs. placebo	0	0	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

The data presented by the sponsor indicated statistically significant differences in primary and secondary efficacy variables between placebo and active treatment at peak and trough concentrations of ranolazine at the 3 dose levels. Based on the results of the statistical analysis performed by he sponsor a carry-over effect could be ruled out. The mean ETT duration on drug was dose and concentration dependently prolonged. The respective mean increase in ETT durations at the 500 mg, 1000 mg and 1500 mg dose levels were 4.5%, 6.5% and 9.1% at trough and 5.8%, 10.0% and 11.0% at the peak concentrations of ranolazine. There was a borderline statistically significantly greater increase in the ETT duration at peak in males compared to females.

The following table shows the mean peak and trough concentrations of ranolazine at the 3 tested dose levels:

Ranolazine SR Concentration Measurements - Safety Population

Parameter	Statistic	Placebo (N=179)	Ran SR 500 mg (N=181)	Ran SR 1000 mg (N=180)	Ran SR 1500 mg (N=187)
Total Number of Patients in SP	N=191				
Plasma Concentration at Trough (ng/mL)	Mean	16.0	848.9	1959.2	3241.0
	S.E.	11.3	55.0	107.5	150.9
Plasma Concentration at Peak (ng/mL)	Mean	35.2	1122.6	2476.0	3930.5
	S.E.	19.5	55.9	115.1	161.3
Data Source: Table 1.14.0					

The mean trough and peak plasma concentrations increased more than dose proportional and the fluctuation decreased at the higher dose levels. There was considerable inter-subject variation. Maximum trough and peak concentrations of 10'000 ng/mL and 14'300 ng/mL, respectively, were observed in 2 of the individuals at the 1500 mg dose level. These values exceeded the mean values by 208.9% and 263.8%, respectively. One patient had through and peak ranolazine concentrations of 7580 ng/mL and 8650 ng/ml, respectively, at the 1000 mg dose level. The corresponding plasma concentrations at the 1500 mg dose level were not available in this patient.

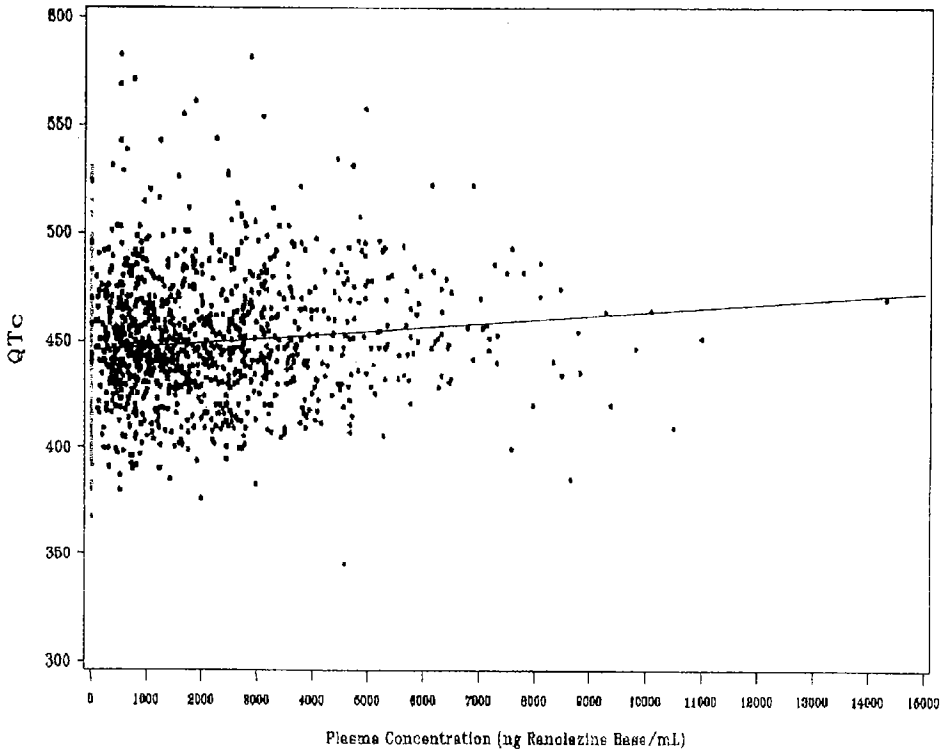
There were six subjects with positive samples while on placebo. In two of these subjects the peak and trough concentrations were in the population range of concentrations observed with the active treatments. The samples obtained from these individuals during one of the active treatments were negative. This suggested that they either received the wrong treatment or their samples were mixed up. The ranolazine concentrations in the remaining four individuals were in the range of 10.3 ng/mL to 29.0 ng/mL. In three of these individuals the samples received while they were on active treatments contained concentrations of ranolazine in the population range. A protracted elimination of ranolazine cannot be excluded in these patients. In the fourth subject an incomplete set of samples was obtained and the cause for the positive sample obtained while on placebo is uncertain.

There was no overt evidence that gender, congestive heart failure or the co-administration of statins had an impact on the ranolazine plasma concentrations.

Safety:

The following figure shows a statistically significant linear correlation between QTc interval duration and plasma concentrations of ranolazine:

QTc Interval (BAZETT Correction) versus Ranolazine Plasma Concentration at Peak and Trough Based on MAX QT



Regression Equation: QTc Interval (BAZETT Correction) = 445.9831 + (0.001754 * Plasma Concentration)
P value: <.0001 R: 0.11337 R Square: 0.01285

The QTc data show significant scatter. The QTc interval increased dose dependently with a slope of 0.1754 msec/1000 ng/mL and the increase at all 3 dose levels was statistically significantly different from placebo. The values for QTc computed by the Bazett, Fridericia, Framingham or modified Framingham formula showed equivalent treatment effects. The T-wave amplitude decreased statistically significantly at all three dose levels compared to placebo.

The number (percentage) of patients with QTc intervals > 500 msec and increases of QTc over baseline ≥ 60msec in the patients when they received active treatment compared to when they receive placebo is shown in the next table:

Frequency of QTc (Bazett) Change from Baseline to ≥60 msec and to >500 msec, n (%) of Patients

	Placebo	RAN SR 500 mg	RAN SR 1000 mg	RAN SR 1500 mg
Trough	1/176 (0.6)	2/177 (1.1)	2/178 (1.1)	2/171 (1.2)
Peak	0/177 (0)	4/177 (2.3)	0/177 (0)	4/169 (2.4)

Standing systolic and diastolic blood pressures, heart rate and rate pressure product showed small decreases that were largest at the 1500 mg dose level and at the time of the peak plasma concentration of ranolazine. The cardiovascular effects were more pronounced in females than in men. The ACTH function testing did not show changes in adrenal function.
One sudden death occurred in a patient with extensive medical and surgical history of CAD receiving the 500 mg bid treatment. It is unclear whether the death was treatment or CAD related.

CONCLUSIONS:

The sponsor's evaluation of the data suggests anti-anginal efficacy of ranolazine at all three dose levels and at both peak and trough concentrations. The drug effect is dose and concentration dependent. The mean plasma concentrations at peak and trough increase more than dose proportional. Gender, congestive heart failure or the co-administration of statins has no overt impact on the plasma concentrations of ranolazine in the target population. The QTc interval duration is linearly correlated with the plasma concentrations of ranolazine. The QTc interval increases dose dependently and the increase is statistically significant compared to placebo. The frequency of QTc interval durations >500 msec and changes from base line ≥ 60 msec is greater during active treatments than on placebo.

COMMENTS:

1. The study evaluated the efficacy parameters at the morning trough levels. However, it should be noted that in this study, but also in a number of other studies (RAN0114 (CL 6876), RAN0114 (CL 6876), RAN0117 (CL6922) the morning trough concentrations of ranolazine were found to be from 18.3% to 68.9% greater than the evening trough concentrations. If efficacy can be demonstrated at trough in the morning efficacy at the evening trough cannot necessarily be assumed.
2. The sponsor did not evaluate a possible diurnal rhythm of QTc caused by either changes in the PK and/or PD of ranolazine.
3. A justification was not provided for weighting the calibration standards by 1/x2.

4. A definition of what a clinically significant antianginal constiutes is missing and thus, the appropriateness of the 12 hour dose interval used is uncertain

STUDY CVT 3033 –A DOUBLE-BLIND, RANDOMIZED, STRATIFIED, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY OF RANOLAZINE SR AT DOSES OF 750 MG BID TWICE A DAY AND 1000 MG TWICE A DAY IN COMBINATION WITH OTHER ANTI-ANGINAL MEDICATIONS IN PATIENTS WITH CHRONIC STABLE ANGINA PECTORIS

STUDY INVESTIGATOR AND SITE: Multi-center study with investigators and sites in the US, Canada, Czech Republic, Poland, New Zealand, Israel, UK, Spain, Australia, Italy, Ireland, Russia, Georgia, Greece, and Romania

Report No.: CVT 3033
Volume No: 78-162, ITEM 6

OBJECTIVES:

Primary objective: To determine the effect of ranolazine SR at doses of 750 mg bid and 1000 mg bid compared to placebo on symptom limited treadmill exercise duration at trough plasma concentrations of ranolazine (12 hours post-dose) after 12 weeks of dosing in patients with chronic stable angina receiving a stable dose of a single concomitant anti-anginal medication (diltiazem 180 mg qd, atenolol 50 mg qd or amlodipine 5 mg qd)

Secondary objectives: To determine
-The effect during exercise treadmill testing on time of onset of angina, time to 1mm ST-segment depression, maximum ST-segment depression, and reason for stopping the exercise treadmill test at trough and peak ranolazine plasma concentrations (12 hours and 4 hours post-dose, respectively)
-The effect during exercise treadmill testing on total duration at peak ranolazine plasma concentrations (4 hours post-dose)
-The effect of ranolazine SR on angina frequency, severity and duration, and on nitroglycerin consumption
-If there were any rebound increases in angina, as measured by exercise treadmill test duration, following discontinuation of ranolazine SR at doses of 750 mg or 1000 mg bid compared to patients who were maintained on placebo during a 12 week treatment period
- Safety and tolerability of ranolazine by evaluation of their effects relative to placebo on the incidence of adverse events, on blood pressure and heart rate (both at rest and during exercise), and on routine laboratory measurements including standard blood tests, ECGs, and (in Italian centers only) 2-D echocardiograms.

FORMULATIONS:

375 mg ranolazine SR tablets (Lot No. 8E2728A, 8H2752A, 9L2753A, 9G2715A)
500 mg ranolazine SR tablets (Lot No. 8E2729A, 8H2748A, 8E2729A, 9L2755A, 9G2714A)

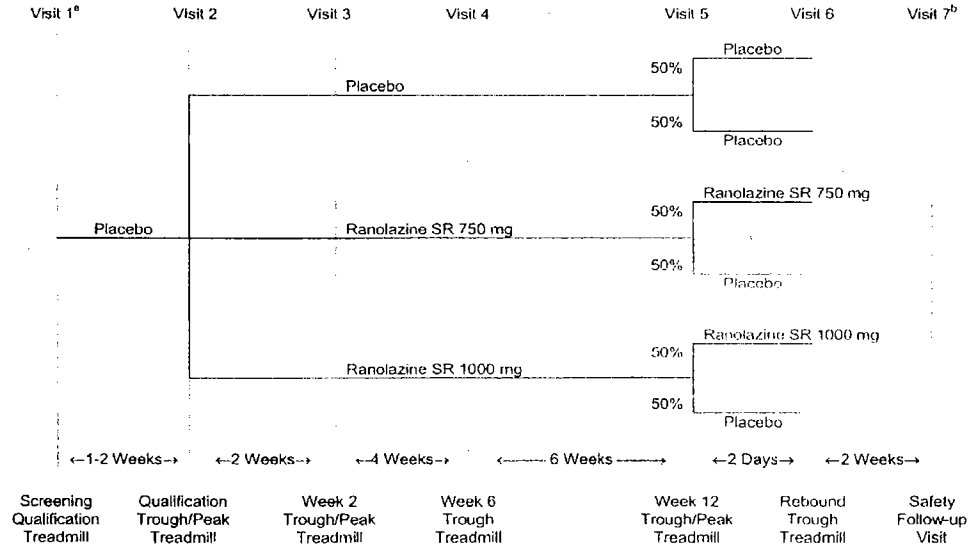
Matching placebo tablets (respective Lot Nos. 8E2730A, 8E2727A, 8J2773A, 8J2774A, 9L2753A, 9L2755A)

STUDY DESIGN:

This was a randomized, multiple-dose, parallel group design study consisting of 3 phases (1) a single blind placebo qualifying phase of 1-2 weeks, (2) a double-blind treatment phase of 12 weeks and (3) a rebound assessment phase of 2 days. At the end of Phase 1 patients meeting the double-blind entry criteria were stratified to their background concomitant anti-anginal therapy and randomized to either receive placebo or ranolazine 750 mg bid or 1000 mg bid. At Weeks 2 and 12 of the double-blind treatment Phase 2 the patients performed an exercise treadmill test at trough and peak. At Week 6 the patients performed an exercise treadmill test at trough only. In Italian centers only, at Weeks 0, 2 and 12 the patients underwent an echocardiographic evaluation in the interval between trough and peak. At the end of 12 week double-blind treatment phase the patients entered Phase 3 with the rebound assessment during which they received in a double-blind manner, either the same treatment or placebo. After completion of Phase 3 the patients returned to the clinic for a final exercise treadmill test. After an additional 14 days the patients returned to the clinic for a safety follow-up.

The following schemes depict the study sequence and event schedule:

Study Sequence (Schematic)



[a] An optional pre-screening visit could be performed at which all the screening procedures could be performed except vital signs, ECG and exercise treadmill test measurements.

[b] Visit 7 was not necessary for patients who enrolled in the long-term, open-label safety study, CVT 3034.

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Schedule of Study Events

Procedure	Visit/Time						
	1	2	3	4	5	6	7
	Screening (may be same day as Pre –1)	Screen/ Qualifying	Double-blind Treatment	Double-blind Treatment	Double-blind Treatment/Early Withdrawal	Rebound Assessment	Safety Follow-up[a]
	-	1-2 weeks (5-17 days after Visit 1)	2 weeks (11-17 days after Visit 2)	4 weeks (25-31 days after Visit 3)	6 weeks (39-45 days after Visit 4)	2 days (48 h after Visit 5)	2 weeks (11-17 days after Visit 6)
Consent	X*						
History (Medical and Cardiovascular)	X*						
Medication History	X						
Physical Examination	X*				X		X
Body Weight	X*				X		
Inclusion/Exclusion Criteria Met	X*	X					
Vital Signs and Hemodynamic Measurement (BP & HR)	X	X	X	X	X	X	
Angina and Nitroglycerin Use Diary Review		X	X	X	X	X	
Laboratory Tests: Hematology, Serum Chemistry, Urinalysis	X*				X		
Lab Tests: Cholesterol, HDL, LDL, VLDL, Triglycerides	X*				X		
Lab Tests: TSH and T_4	X*						
Lab Tests: Coagulation (PT & PTT)	X*				X		
Serum HCG Test (Females Only)	X*		X	X	X		
Stool Guaiac	X*				X		
Plasma for Trough Ranolazine Levels			X	X	X	X	
Plasma for Peak Ranolazine Levels			X		X		
ECG Trough	X	X	X	X	X	X	
ECG Peak		X	X		X		
ETT Trough	X	X	X	X	X	X	
ETT Peak		X	X		X		

* May be completed at an optional Pre –1 Visit. If this option is used, then asterisked items should not be repeated at Screening (Visit 1).

[a] Visit 7 was not necessary for patients who enrolled in the long-term, open-label safety study CVT 3034.

[b] Echocardiographs at Visits 3 and 5 need only be obtained in patients with adequate echocardiographic images at Visit 2, as determined by the Core Echocardiography Laboratory.

Schedule of Study Events (continued)

Procedure	Visit/Procedure/Time						
	1	2	3	4	5	6	7
	Screening (may be same day as Pre –1)	Screen/ Qualifying	Double-blind Treatment	Double-blind Treatment	Double-blind Treatment/Early Withdrawal	Rebound Assessment	Safety Follow-up[a]
	-	1-2 weeks (5-17 days after Visit 1)	2 weeks (11-17 days after Visit 2)	6 weeks (25-31 days after Visit 3)	12 weeks (39-45 days after Visit 4)	2 days (48 h after Visit 5)	2 weeks (11-17 days after Visit 6)
Two-dimensional Echocardiogram (In Italy Only)		X	X[b]		X[b]		
Adverse Events		X	X	X	X	X	X
Concomitant Medications Use	X	X	X	X	X	X	X
Dispense Single-blind Placebo	X						
Collect Single-blind Placebo from Previous Visit		X					
Dispense Double-blind Study Drug		X	X	X			
Collect Double-blind Study Drug from Previous Visit			X	X	X		
Dispense Rebound Assessment Study Drug					X		
Collect Rebound Assessment Study Drug						X	

* May be completed at an optional Pre –1 Visit. If this option is used, then asterisked items should not be repeated at Screening (Visit 1).

[a] Visit 7 was not necessary for patients who enrolled in the long-term, open-label safety study CVT 3034

[b] Echocardiographs at Visits 3 and 5 need only be obtained in patients with adequate echocardiographic images at Visits 2, as determined by the Core Echocardiography Laboratory.

A modified Bruce exercise protocol was used for each ETT.

ASSAY:

All plasma concentrations of ranolazine and its metabolites were assayed by [redacted] Plasma concentrations of ranolazine, RS-88390 (CVT-2514), RS-88640 (CVT-2512) and RS-94287 (CVT-2738) were measured by LC/MS/MS [redacted] d3-ranolazine as internal standard. The upper and lower limits of quantitation were 50 ng/ml and 10'000 ng/ml for ranolazine and 10.0 ng/ml and 2000ng/mL for RS-88640 (CVT-2512), RS-88390 (CVT-2514) and RS-94287 (CVT-2738). The standard curves over the defined concentration ranges were linear with $R^2 \geq 0.991$ when the respective calibrant concentrations were weighted by $1/X^2$. The stability of ranolazine and the metabolites in plasma was established. Accuracy (bias, %) and precision (CV, %) for ranolazine, RS-88640 (CVT-2512) and RS-94287 (CVT-2738) were within ±15%.
Accuracy for RS-88390 (CVT-2514) was also within the limits whereas the precision (15.2%) for this metabolite exceeded the upper limit slightly.

Blood Sample Collection:

Blood samples were collected at Visits 3, 4, 5 and 6 at the time of the anticipated morning trough concentrations of ranolazine, 12 hours post-dose. Blood samples were also collected at Visits 3 and 5 at the anticipated time of the peak concentration of ranolazine, 4 hours post-dose.

SAFETY:

Vital signs were recorded at the following times:
At supine rest (after 5 min in a supine position) and at standing rest (after 2 min standing) and during the last minute of each exercise test and at the end of exercise.
Standard supine and standing 12-lead ECGs were recorded at rest immediately before exercise, at supine rest and at standing rest. ECGs were also taken during exercise (every 30 sec, at the end of each stage of exercise, at the end of exercise, and periodically during recovery until values returned to baseline.

RESULTS:

PK:

A total of 823 patients were randomized from 118 sites in 15 countries and 269 received placebo, 279 received ranolazine SR 750mg bid and 275 ranolazine SR 1000 mg bid. The distribution of the three types of co-medicated background therapy among the three groups was similar. A total of 731 patients completed the study: 243 patients receiving placebo (90.3%), 250 patients on ranolazine 750 mg bid (89.6%) and 238 (86.5%) patients on ranolazine 1000 mg bid. The

majority of the patients in the three groups were male (75.1% to 79.6%). The mean age and weight of the participants was 64.0 years and 80.6 kg, respectively with no statistically significant difference among the treatment groups. The large majority of the patients (97.5%) was Caucasian.

Efficacy:

The salient results of the analysis of the efficacy data by the sponsor are listed in the following two tables:

Change from Baseline in ETT Duration (s) at Trough Levels of Ranolazine at Week 12 (LOCF), Comparison of Treatment Differences from ANCOVA: ITT Population

	Treatment		
	Ranolazine SR 750 mg vs Placebo	Ranolazine SR 1000 mg vs Placebo	Average of the ranolazine SR dose groups vs placebo
Mean Difference	23.7	24.0	23.9
SE	10.9	11.0	9.5
95% CI	(2.3, 45.1)	(2.4, 45.7)	(5.2, 42.6)
P-value	0.030	0.029	0.012

Note: Data summarized above are located in Table 2.0.0.
Mean difference (and SE) is the least square mean difference from the ANCOVA model

Change from Baseline in ETT Duration (s) at Peak Levels of Ranolazine at Weeks 2 and 12, Comparison of Treatment Differences from ANCOVA: ITT Population

	Treatment			
	Ranolazine SR 750 mg vs Placebo		Ranolazine SR 1000 mg vs Placebo	
	Week 2	Week 12	Week 2	Week 12
Mean Difference	51.2	34.2	41.7	24.3
SE	8.8	11.1	8.9	11.2
95% CI	(34.0,68.5)	(12.5,55.9)	(24.2,59.2)	(2.2,46.3)
P-value	<0.001	0.002	<0.001	0.031

Note: Data summarized above are located in Table 2.1.5.
Mean difference (and SE) is the least square mean difference from the ANCOVA model

The 12 week data suggest that ranolazine administered in addition to background anti-anginal therapy statistically significantly increased symptom limited ETT duration at trough at the 750 mg and 1000 mg dose levels by 23.7 sec and 24.0 sec, respectively, compared to placebo. Similarly, statistically significant increases in ETT duration at peak (24.3 sec with 1000 mg ranolazine bid and 34.2 sec with 750 mg ranolazine bid) were observed. The time to onset of angina and ST-segment depression were also increased at both dose levels. A statistically signiifcant effect of ranolazine on ETT was also observed at peak at the end of a 2 week treatment.There was no evidence for a rebound effect for patients withdrawn from ranolazine during the rebound phase of the study. There were no statistically significant differences in response between patients taking different background therapies (diltiazem, atenolol or amlodipine). The mean trough concentrations of ranolazine at weeks 2, 6 and 12 are shown in the following table:

Safety Analysis: Ranolazine Plasma Concentrations (ng/mL) at Trough at Week 2, 6 and 12
Adjusted Descriptive Statistics from ANCOVA Model 7
Descriptive Statistics: Safety Population

Assessment	Statistic	Ran SR 750 mg	Ran SR 1000 mg
Week 2	N	271	261
	Mean	1683.0	2350.4
	SE	70.5	107.0
	Median	1490	1930
	Min	[	)
	Max		
	LS Mean	1737.8	2399.9
	SE (LS Mean)	92.6	94.7
Week 6	N	261	246
	Mean	1578.3	2285.2
	SE	63.8	105.1
	Median	1390	1920
	Min	[	)
	Max		
	LS Mean	1660.0	2367.6
	SE (LS Mean)	89.5	93.3
Week 12	N	256	237
	Mean	1577.6	2164.7
	SE	71.0	89.2
	Median	1380	1940
	Min	[	)
	Max		
	LS Mean	1595.1	2187.0
	SE (LS Mean)	81.9	86.5

Note: LS Mean and corresponding standard error are Least Square Mean estimates from ANOVA model with effects for treatment, pooled site and background therapy.
Note: 9, 4 and 2 placebo patients at Weeks 2, 6 and 12 respectively had non zero ranolazine plasma concentrations.
Note: Data summarised in the above table are listed in data listing 13.2

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The following table lists the trough ranolazine plasma concentrations at weeks 2, 6 and 12 according to background therapy:

Safety Analysis: Ranolazine Plasma Concentrations (ng/mL) at Trough at Week 2, 6 and 12
Investigating Interaction With Background Therapy
Adjusted Descriptive Statistics from ANOVA Model 8
Descriptive Statistics: Safety Population

Assessment	Statistic	Ran SR 750 mg			Ran SR 1000 mg		
		Diltiazem	Atenolol	Amlodipine	Diltiazem	Atenolol	Amlodipine
Week 2	N	71	114	86	64	112	85
	Mean	2264.1	1452.0	1509.5	2859.4	2176.9	2195.6
	SE	170.6	90.2	105.7	250.8	163.3	154.3
	Median	1920	1245	1445	2710	1755	1860
	Min	[					]
	Max						
	LS Mean	2289.2	1423.2	1521.2	2852.7	2154.2	2169.5
	SE (LS Mean)	174.6	139.4	159.1	183.6	141.1	160.3
Week 6	N	68	110	83	60	107	79
	Mean	1888.5	1465.8	1473.2	2834.7	2097.6	2122.0
	SE	157.8	92.8	85.9	260.6	150.1	153.9
	Median	1785	1315	1370	2270	1800	1880
	Min	[					]
	Max						
	LS Mean	1959.3	1476.7	1517.0	2870.5	2132.6	2133.5
	SE (LS Mean)	169.1	133.6	153.5	179.7	137.7	157.6
Week 12	N	65	108	83	54	102	81
	Mean	1998.1	1430.0	1440.4	2793.5	2051.2	1888.3
	SE	175.1	93.1	112.3	218.4	120.3	142.2
	Median	1680	1355	1270	2715	1940	1520
	Min	[					]
	Max						
	LS Mean	2012.4	1355.2	1403.6	2798.5	1973.4	1822.7
	SE (LS Mean)	157.1	122.2	139.4	172.5	127.9	141.1

Note: LS Mean and corresponding standard error are Least Square Mean estimates from ANOVA model with effects for treatment, pooled site, background therapy and treatment by background therapy interaction.
Note: Data summarised in the above table are listed in data listing 13.2

The peak concentrations of ranolazine at weeks 2 and 12 are listed in the following table:

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Safety Analysis: Ranolazine Plasma Concentrations (ng/mL) at Peak at Week 2 and 12
Adjusted Descriptive Statistics from ANOVA Model 7
Descriptive Statistics: Safety Population

Assessment	Statistic	Ran SR 750 mg	Ran SR 1000 mg
Week 2	N	268	252
	Mean	2219.0	2908.4
	SE	76.6	105.9
	Median	1960	2505
	Min	[	
	Max		]
	LS Mean	2274.8	2960.0
	SE (LS Mean)	94.1	97.4
Week 12	N	249	236
	Mean	2031.1	2607.1
	SE	78.8	90.0
	Median	1790	2375
	Min	[	
	Max		]
	LS Mean	2065.6	2632.5
	SE (LS Mean)	89.1	92.6

Note: LS Mean and corresponding standard error are Least Square Mean estimates from ANOVA model with effects for treatment, pooled site and background therapy.
Note: 6 and 4 placebo patients at Weeks 2 and 12 respectively had non zero ranolazine plasma concentrations.
Note: Data summarised in the above table are listed in data listing 13.2

The trough concentrations of ranolazine at the 1000 mg dose levels tended to be more than dose proportional. The mean trough plasma concentrations of ranolazine in patients with diltiazem background therapy exceeded those in patients on atenolol or amlodipine background therapy at the 3 time points by 28.2% to 55.9% indicating that diltiazem increases the exposure to ranolazine. The mean peak concentrations of ranolazine exceeded the trough concentrations after 2 and 6 weeks of treatment at the 750 mg dose level by 31.8% and 28.7 %, respectively. The corresponding values at the 1000 mg dose level were 23.7% and 20.4%, respectively. The individual maximum peak concentrations observed at the 1000 mg and 750 mg dose levels were [ ] ng/mL, respectively

Safety:

Treatment with ranolazine was associated with statistically significant decreases of systolic blood pressure (range 2.3-8.7 mmHg) and heart rate (range 2.7-7.2 bpm).
The following table lists the values for heart rate, the PR, QRS, QT and QTc intervals and T-amplitude after 12 weeks of treatment with ranolazine compared to placebo:

Statistical Analysis of ECG Variables at Peak at Week 12 by Treatment: Safety Population

Variable		Treatment	
		Ranolazine SR 750 mg vs Placebo	Ranolazine SR 1000 mg vs placebo
Heart Rate	Mean difference (b.p.m)	-1.5	-0.8
	SE of mean difference	0.8	0.8
	Confidence interval	-3.0, 0.1	-2.4, 0.8
	p-value	0.066	0.33
PR Interval	Mean difference (ms)	2.3	2.4
	SE of mean difference	1.5	1.5
	Confidence interval	-0.6, 5.3	-0.6, 5.4
	p-value	0.12	0.12
QRS Interval	Mean difference (ms)	2.2	2.0
	SE of mean difference	0.9	0.9
	Confidence interval	0.4, 3.9	0.2, 3.7
	p-value	0.014	0.030
T amplitude	Mean difference (ms)	-0.6	-0.8
	SE of mean difference	0.1	0.1
	Confidence interval	-0.8, -0.3	-1.0, -0.5
	p-value	<0.001	<0.001
QT Interval	Mean difference (ms)	11.2	11.7
	SE of mean difference	2.3	2.3
	Confidence interval	6.7, 15.7	7.1, 16.2
	p-value	<0.001	<0.001
QTc Interval (Bazett)	Mean difference (ms)	6.1	9.2
	SE of mean difference	1.3	1.4
	Confidence interval	3.5, 8.8	6.5, 11.9
	p-value	<0.001	<0.001
QT Dispersion	Mean difference (ms)	2.2	0.0
	SE of mean difference	1.3	1.3
	Confidence interval	-0.3, 4.7	-2.5, 2.6
	p-value	0.079	0.97

Note: Data summarized above are located in Tables 3.8.5.0, 3.8.6.0, 3.8.7.0, 3.8.8.0, 3.8.9.0, 3.8.13.0 and 3.8.14.0.

There were statistically significant changes in the QT and QTc intervals and T-wave amplitude at the peak and trough concentrations of ranolazine. The respective mean (se) increases in apparent QTc Bazett at peak at the 750 mg and 1000 mg dose levels were 6.1 (1.3) msec and 9.2 (1.4) msec and the corresponding values at trough were 4.5 (1.1) msec and 7.7 (1.2) msec. Patients on concomitant diltiazem showed the greatest increase in apparent QTc (9.8 msec -11.8 msec at peak). No patient met the withdrawal criteria of a > 130% increase in QTc over baseline and QTc

Patients with QTc Values Above 500 ms

Patient Number	Age	Gender	Ranolazine Dose (mg)	Plasma Concentration (ng/ml)	Week and Timepoint	Max QTc	CHF	Comments
1829368	71	Male	1000	2590	12 peak	511	No	-
5199210	62	Male	750	1770 (510 ms) 1250 (502 ms) BQL (504 ms)	2 peak 6 trough RB trough	510	Yes	Last ECG, with QTc 504 ms, was on placebo (during rebound)

Note: Data presented above are derived from Data Listings 9.2.3.1 and 13.2.
BQL = below quantifiable level.
RB = rebound assessment.

>500 msec. Two patients exhibited QTc > 500 msec as shown in the following table:

The plasma concentrations for ranolazine in these patients in comparison to the mean concentrations of the entire patient populations were unremarkable. QT corrections for heart rate according to Bazett, Fridericia, Framingham and modified Framingham yielded comparable results. The T-wave amplitude was decreased and T-wave notching was also observed in a significant number of subjects on ranolazine. At peak the QRS interval was also statistically significantly increased.

Six (6) deaths occurred, 3 in the placebo group and 3 in the ranolazine groups. None were judged drug related. Constipation, dizziness and nausea were more frequent in the ranolazine groups than in the patients receiving placebo. Of the 63 SAEs reported 5 were judged to be probably drug related and included syncope, sinus bradycardia, headache, vertigo and myocardial infarction.

CONCLUSION:

The 12 week data analysis provided by the sponsor suggests that ranolazine administered in addition to background antianginal therapy increases symptom limited ETT duration at trough and peak. The mean plasma concentrations tend to increase more than dose proportionately at the higher compared to the lower dose level. The mean peak concentrations exceed the mean trough concentrations of ranolazine by between 20.4% to 31.8 %. Co-administration of diltiazem increases the exposure to ranolazine by between 28.2% and 55.9%.
The QTc Bazett apparently increases by 9.2 msec at peak concentrations at the 1000 mg dose level. Two (2) patients with unremarkable plasma concentrations of ranolazine exhibit QTc >500 msec. Patients on background therapy with diltiazem show the greatest apparent increase in mean QTc ranging between 9.8 msec to 11.8 msec. The T-wave amplitude is decreased and notching is observed. Three (3) deaths unrelated to ranolazine and 5 probably drug related SAEs including syncope, sinus bradycardia, headache, vertigo and myocardial infarction are reported.

COMMENTS:

1. A justification for weighting the calibration standards by $1/X^2$ should be provided

2. Subjects on background therapy with diltiazem displayed on average 40% greater trough concentrations compared to the subjects on atenolol or amlodipine background therapy. In a study with young healthy male volunteers receiving comparable multiple co-administered doses of diltiazem (180 mg qd) and ranolazine (1000 mg bid) the increase in the trough concentrations of ranolazine relative to placebo was 50% in agreement with the findings in the patients.

3. Ranolazine is subject to circadian rhythm. Trough concentrations in the morning are from 18.3 % to 68.9% greater than the trough concentrations in the evening. The ETT measurements were performed at morning through and peak. Efficacy of ranolazine at trough in the evening cannot be concluded from the results obtained at trough in the morning .

4. The target population for ranolazine includes subjects who cannot tolerate marketed anti-anginal drugs or in whom marketed anti-anginal drugs are inadequate.The patient population tested in the present study does not correspond to the target population.

5. Eighteen (18) subjects on placebo had 23 samples with measurable ranolazine concentrations and 20 subjects on drug had 24 samples with ranolazine concentrations < LLOQ.

6. The plasma concentrations of the metabolites RS-88390 (CVT-2514), RS-88640 (CVT-2514) and RS-94287 (CVT-2738) are missing.
7. The difference between the doses is 25% which seems to be too small given the high inter-subject variation of the PK of the drug.

8. A definition of what constitutes a clinically significant anti-anginal effect is missing. Thus, the appropriateness of the 12 hour dosage interval is uncertain

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STUDY 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

STUDY INVESTIGATOR AND SITE: Multiple Investigators and sites

Report No: CVT 3021
Volume No: 53-63, ITEM 6

OBJECTIVES:

Primary: To determine the pharmacokinetics of ranolazine SR at a dose of 750 mg twice daily (bid) in patients with congestive heart failure (CHF).
Secondary: To determine if there was a pharmacokinetic interaction between digoxin 0.125 mg every day (qd) and ranolazine 750 mg twice a day (bid) in CHF patients when the ranolazine morning dose was administered 2 hours after the digoxin daily dose.
To determine the safety and tolerability of ranolazine SR at a dose of 750 mg bid in patients with stable CHF.

FORMULATIONS:

Ranolazine 375mg SR tablets (Lot No. 9G2715A)
Matching placebo tablets (Lot No. 8E2730A)
Digoxin 0.125mg capsules (Lot No. 0ZP0909, Lanoxin®, Glaxo-Wellcome)
Matching placebo capsules (Lot No. GUS00930.002)

STUDY DESIGN:

This was a multi-center, double-blind, randomized placebo controlled, parallel group PK and safety study of ranolazine SR 750 mg administered with digoxin 0.125 mg or digoxin placebo in male and female patients in the age between 18 and 75 years with NYHA Class III and IV CHF with right ventricular ejection fraction (RVEF) <35%. The study comprised a 2 week screening period (Days -14 to Day-1), a double-blind digoxin/digoxin placebo run-in phase (Days 1-8), a double-blind ranolazine/ranolazine placebo treatment phase (Days 9-14) with study termination on Day 16. Based on the results of study CVT 3011 a sample size of 13 per treatment was determined to be sufficient to demonstrate the absence of an interaction with 80% power for digoxin AUC0-24 and Cmax.

The dosing schedule is outlined in the following table:

Dosing Regimen

Treatment Group	Double-Blind Digoxin Run-In Phase Days 1-8	Double-Blind Inpatient Treatment Phase Days 9-14			
	Time of Dose (hours)				
	0	0	2	12	14*
	Dose 1 (eg, 8 AM)	Dose 1 (eg, 8 AM)	Dose 2 (eg, 10 AM)	Dose 3 (eg, 8 PM)	Dose 4 (eg, 10 PM)
A	DP	RP, DP	RP	RP	RP
B	DP	RA, DP	RP	RA	RP
C	DA	RP, DA	RP	RP	RP
D	DA	RA, DA	RP	RA	RP
E	DA	RP, DA	RA	RP	RA

Where:

RA = Ranolazine Active
RP = Ranolazine Placebo
DA = Digoxin Active
DP = Digoxin Placebo

* On Day 14 only the morning ranolazine dose was administered.

ASSAY:

Ranolazine: The plasma concentrations were analyzed at [redacted] validated LC/MS/MS method [redacted] d_3-ranolazine was used as internal standard. The calibration curve was linear with LOQs of 25 ng/mL and 12'500 ng/mL ($R^2 \leq 0.995$). Accuracy (bias, %) and precision (CV, %) determined from QC samples were within the ± 15% limits.

Digoxin: The plasma and urine samples were analyzed at [redacted] Validated RIA assays were used with both matrices. In plasma the method was validated over the concentration range of 0.150 ng/mL to 8 ng/mL. Accuracy (bias, %) and precision (CV, %) of the assay were within the ± 15 % limits. In urine the method was validated over the concentration range 1 ng/mL and 40 ng/mL. Accuracy (bias, %) and precision (CV, %) determined from QC samples were within the ± 15% limits.

Blood and Urine Sample Collection:

Digoxin:
Blood:
Double-blind digoxin run-in phase:

Days 5-7: Pre-dose 1
Day 8: Pre-dose, 20, 40 minutes and 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18 and 24 hours after administration of dose 1
Double-blind ranolazine treatment phase:
Days 10-13: Pre-dose 1
Day 14: Pre-dose, 20, 40 minutes and 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours after administration of dose 1

Urine:
Double-blind digoxin run-in phase:
Day 8:0-24 hours after administration of dose 1
Double-blind ranolazine treatment phase:
Day 14: 0-24 hours after administration of dose1

Ranolazine:
Double-blind ranolazine treatment phase:
Day 9: Pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14 hours after dose 1
Day 10-13: Pre- dose 1 and 2
Day 14: Pre-dose, 20 and 40 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18, 20, 2, 26, 36, and 38 hours after dose 1

PK and Statistical Analysis

Standard compartment model independent methods were used to compute from the plasma data Cmax, Tmax, AUC0-12 or AUC0-24, Cave, Cmin, λz and t1/2 for digoxin and ranolazine. From the urine data Ae0-24 and Clr from Ae0-24/AUC0-24 were determined for digoxin.

Ranolazine:
The data of Groups B, D and E were evaluated. A one-way analysis of variance (ANOVA) model was run to test for differences in ranolazine PK parameters between test (ranolazine with concomitant digoxin; ranolazine administered 2 hours post digoxin dose) and reference (ranolazine administered with digoxin placebo) treatments.
Ninety (90) % confidence intervals for the pairwise differences between test and reference treatments were computed and expressed as percentage of reference. Untransformed and logarithmically transformed AUCtau and Cmax were used.

Digoxin: for Groups C, D, and E, an ANOVA model was run to test for differences in digoxin PK parameters between test (ranolazine with concomitant digoxin, ranolazine administered 2 hours post digoxin dose) and reference (digoxin and ranolazine placebo) treatments. Ninety (90) % confidence intervals for the pairwise differences between test and reference treatments were computed and expressed as percentage of reference. Untransformed and logarithmically transformed Cmax and AUC0-24 were used. In addition, within-patient comparisons of Cmax and AUC0-24 on Days 8 and 14 were explored for Groups D and E using ANOVA with terms for patient and day. Point estimates and 90 % confidence intervals for the difference between Day 8 and 14 were constructed. Again the untransformed and logarithmically transformed parameters were used.

Safety:

Supine 12 Lead ECG recordings were performed at the following times:
Day 8 of the double-blind digoxin run-in phase and on Day 14 of the double-blind ranolazine treatment phase:

Pre-dose, and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18 20, 24, 26, 36, and 38 hours after dose 1
Days 10-13: Pre-dose 1
An ECG Core lab was used for the analysis of the PR interval, QRS duration and QT interval. The QTc interval was computed by using the Fridericia correction formula.

Supine and erect blood pressure and heart rate were measured on Days 1 and 5-8 of double-blind run in phase and during the the double-blind ranolazine treatment phase on Days 9-14: Predose and 2 and 4 hours after dose 1.

RESULTS:

A total of 85 patients, 59 males and 26 females were enrolled in the study. The average age of the population was 56 (28-80) years. There were 49 Caucasians, 27 Blacks and 9 Hispanics. Eighty three (83) completed the double-blind digoxin run-in phase and 81 completed the study (Group A: 17, Group B: 16, Group C: 17, Group D: 15 and Group E: 16). Sixty seven (67) patients were included in the PK analysis. Seventeen (17) patients of Group A received erroneously placebo/placebo instead of digoxin/placebo. In addition 1 patient was excluded because of site intermixing and/or mislabeling of the plasma samples. There was evidence from the plasma concentration data that 3 patients may have been dosed incorrectly during the double-blind ranolazine treatment phase. Two patients of Group C receiving digoxin/ranolazine placebo had measurable ranolazine plasma concentrations and were included in the PK analyses of the digoxin data. A third patient of Group B receiving digoxin placebo /ranolazine had plasma concentrations of ranolazine below LLOQ and was excluded from the ranolazine PK analyses. A total of 50 patients (Groups C, D and E) were included in the digoxin PK analysis and a total of 49 patients were included in the ranolazine PK analysis (Groups B, D and E).

PK:

The mean Cmax and AUC0-24 values for digoxin in Groups C, D and E on Day 8 of the double-blind digoxin run-in phase are shown in the following table:

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Table J. Digoxin Pharmacokinetic Parameters at Steady State (Day 14)

Parameter	Treatment: Digoxin 0.125 mg QD + Ranolazine placebo BID — Group C (n=18)	Treatment: Digoxin 0.125 mg QD + Ranolazine 750 mg BID — Group D (n=16)	Treatment: Digoxin 0.125 mg QD + Ranolazine 750 mg BID 2 hours post digoxin dose — Group E (n=16)
AUC_{0-24} (hr.ng/mL) Mean (SD)	11.5485 (4.37782)	21.7601 (12.26450)	16.2178 (7.04606)
Range	[		]
C_{max} (ng/mL) Mean (SD)	0.9502 (0.25787)	1.5975 (0.76309)	1.2401 (0.57682)
Range	[		]
T_{max} (hr) Mean (SD)	1.192 (0.7499)	1.516 (0.9358)	1.668 (1.0018)
Range	[		]
C_{ave} (ng/mL) Mean (SD)	0.4812 (0.18241)	0.9067 (0.51102)	0.6757 (0.29359)
Range	[		]
C_{min} (ng/mL) Mean (SD)	0.2886 (0.11501)	0.5432 (0.34469)	0.3619 (0.18129)
Range	[		]
λ_z (1/hr) Mean (SD)	0.0309 (0.03341)	0.0224 (0.01311)	0.0304 (0.02026)
Range	[		]
$t_{1/2}$ (hr) Mean (SD)	31.994 (13.0023)	43.147 (27.3118)	27.859 (10.0255)
Range	[		]

The results of the statistical analysis of the data are presented in the following 2 tables:

Bioequivalence Analysis of Log-Transformed PK Parameters for Digoxin and Ranolazine

Digoxin Day 14					
	Treatment: Digoxin 0.125 mg QD + Ranolazine Placebo BID	Treatment: Digoxin 0.125 mg QD + Ranolazine 750 mg BID	Treatment: Digoxin 0.125 mg QD + Ranolazine 750 mg BID 2 hours post digoxin dose		
Parameter	Group C (n=18)	Group D (n=16)	Group E (n=16)	Comparison	p-value
AUC_{0-24} (hr.ng/mL) Mean (SD)	11.545 (4.37782)	21.7601 (12.26450)	16.2178 (7.04606)	D/C	0.0016
				E/C	0.0587
Range	[		]		
C_{max} (ng/mL) Mean (SD)	0.9502 (0.25787)	1.5975 (0.76309)	1.2401 (0.57682)	D/C	0.0024
				E/C	0.1514
Range	[		]		
Ranolazine Day 14					
	Treatment: Digoxin Placebo QD + Ranolazine 750 mg BID	Treatment: Digoxin 0.125 mg QD + Ranolazine 750 mg BID	Treatment: Digoxin 0.125 mg QD + Ranolazine 750 mg BID 2 hours post digoxin dose		
Parameter	Group B (n=17)	Group D (n=16)	Group E (n=16)	Comparison	p-value
AUC_{0-12} (hr.ng/mL) Mean (SD)	25070.40 (12363.858)	30647.18 (23996.880)	24928.11 (14099.801)	D/B	0.7427
				E/B	0.8882
Range	[		]		
C_{max} (ng/mL) Mean (SD)	2890.47 (1311.114)	3414.07 (2455.993)	2984.13 (1565.550)	D/B	0.8177
				E/B	0.9821
Range	[		]		

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Interaction Analysis of Log-Transformed PK Parameters for Digoxin

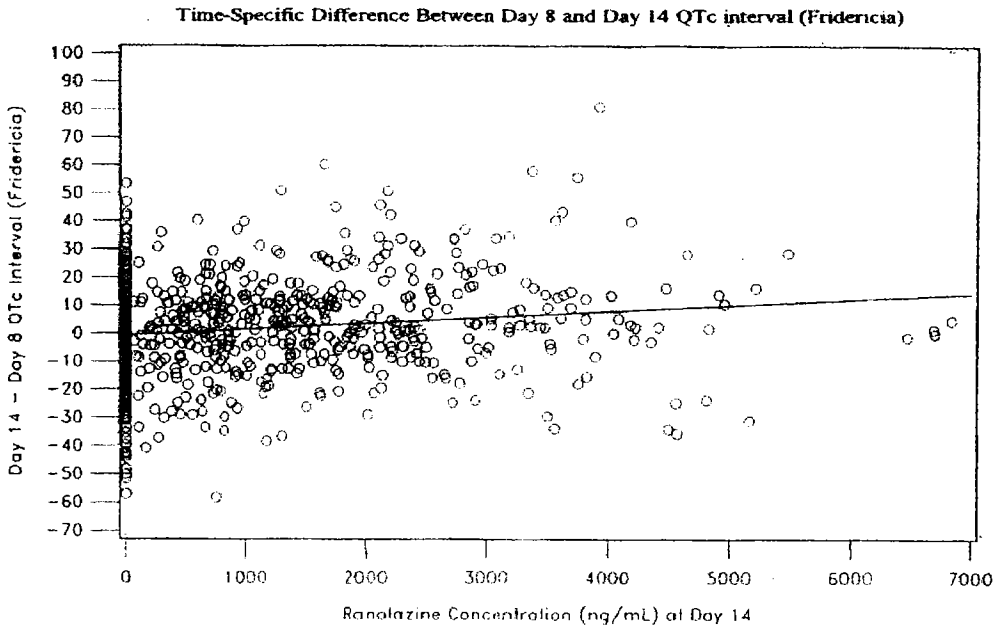
Parameter	Day 8 Digoxin Only	Day 14 Digoxin+Ranolazine*	Ratio Day 14/Day 8	p-value**
		Group D		
AUC_{0-24} (hr.ng/mL) Mean (SD) Range	13.3100 (6.29663) [redacted]	21.7601 (12.26450) [redacted]	152.32	<0.0001
C_{max} (ng/mL) Mean (SD) Range	0.9506 (0.35520) [redacted]	1.5975 (0.76309) [redacted]	160.31	0.0002
		Group E		
AUC_{0-24} (hr.ng/mL) Mean (SD) Range	11.7325 (5.89405) [redacted]	16.2178 (7.04606) [redacted]	145.02	<0.0001
C_{max} (ng/mL) Mean (SD) Range	0.8696 (0.37437) [redacted]	1.2401 (0.57682) [redacted]	141.81	0.0002

Digoxin: The mean plasma concentrations of digoxin in Groups C, D and E on Day 8 of the double-blind digoxin run-in phase were comparable. Patients randomized to Group D (digoxin/concurrent ranolazine) displayed on Day 14 greater mean AUC0-24, Cmax, Cave, Cmin and t1/2 values for digoxin than patients in Group C (digoxin/concurrent placebo) or Group E (digoxin/ranolazine 2 hours post digoxin) and the respective differences for AUC0-24 and Cmax. were statistically significant. Compared to Group C, the mean values for AUC0-24 and Cmax were increased 1.88 and 1.68 fold, respectively, in Group D. The corresponding values in Group E relative to Group C were also increased 1.31 and 1.40 fold, respectively. Group D (digoxin/concurrent ranolazine) showed a decrease in geometric mean CLr of digoxin from 3387 ml/hour (56.5 mL/min) on Day 8 to 1897 mL/hour (31.6 mL/min) on Day 14. Gender and RVEF were statistically significant independent predictors of Cave of digoxin. The Cave increased with decreasing RVEF and was 68 % greater in females than in males.

Ranolazine: The mean values for AUC0-12, Cave and Cmin of ranolazine in Groups D (digoxin/concurrent ranolazine), B (digoxin placebo/concurrent ranolazine) and E (digoxin/ranolazine 2 hours post digoxin) on Day 14 were statistically not significantly different. The mean Cave and Clpo for ranolazine computed from the combined data of Groups B, D and E was 2237 ng/mL and 27.9 L/h (465 mL/min), respectively. The Cmax and AUC values of ranolazine in Group D relative to Group B increased 1.18 and 1.22 fold, respectively, for ranolazine.

Safety:

The relationship between the time specific difference in the QTc interval on Day 8 of the digoxin alone treatment and Day 14 of the digoxin and concomitant ranolazine treatment plotted against the ranolazine concentrations is depicted in the following figure:



Note: Regression model: Change in Fridericia QTc = -0.57 + 0.00212*concentration

There existed an apparent linear relationship between the ranolazine induced increase in QTc and the ranolazine plasma concentrations resulting in a mean increase of 2.12 msec/1000 ng/mL. At no time during the study did any patient meet the withdrawal criteria of 130% increase in QTc resulting in a value >500 msec from baseline or displayed an increase in QTc>60 msec.

Seven (7) patients experienced 8 SAEs. None were judged to be possibly or probably drug related. No deaths were reported. One patient experienced a syncope and another patient a tachycardia during treatment with ranolazine. The most frequently reported AE was headache. Diziness was repoerted by 12 patients receiving ranolazine. 2 patients receiving digoxin during the digoxin run-in phase and 4 patients receiving ranolazine placebo. Nausea was reoported by 10 patients receiving ranolazine and 1 patient receiving ranolazine placebo. Hypotension and postural hypotension were reported by 6 patients receiving ranolazine. Constipation was reported by 5 patients on ranolazine.

CONCLUSIONS:

Treatment with 750 mg ranolazine bid increases steady state AUC0-24 and Cmax of co-administered digoxin in CHF patients of NYHA Class III or IV with a RVEF of <35% by 88.4% and 68.1%, respectively. Co-administration of ranolazine decreases the Clr of digoxin. Staggering the dosing of ranolazine by 2 hours does not prevent ranolazine from interacting with

digoxin. RVEF and gender are independent predictors of Cave of digoxin. Co-administration of ranolazine increases the QTc interval by 2.12 msec/1000 ng/ml.
Co-administration of digoxin has no impact on the PK of ranolazine.
In vitro data suggest that ranolazine is an inhibitor of P-glycoprotein and this could be the mechanism responsible for the increased exposure of digoxin in the presence of ranolazine (CVT 303.010-N).

COMMENTS:

1. A justification for the applied formula for correcting the QT interval for heart rate was not provided.
2. The results obtained with a combination treatment of 0.125mg digoxin and 750 mg ranolazine may not be extrapolated to higher maintenance doses of digoxin (0.250 mg qd) and ranolazine 1000 mg bid.

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STUDY CVT 3011 – A STUDY TO INVESTIGATE THE POTENTIAL PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTION BETWEEN RANOLAZINE SR 1000MG BID AND DIGOXIN 0.125 MG QD IN HEALTHY YOUNG MEN

STUDY INVESTIGATOR AND SITE: [ ]

Report No.: CVT 3011
Volume No.: 3-6, ITEM 6

OBJECTIVES:

To determine the effect of ranolazine SR on digoxin pharmacokinetics and to investigate possible pharmacodynamic interactions between digoxin and ranolazine SR

FORMULATIONS:

Ranolazine 500 mg SR tablets (Lot No. 791771)
Matching placebo tablets (Lot No. 7492)
Lanoxin® 0.125mg digoxin tablets (Lot No.7ZP1093, Wellcome)

STUDY DESIGN:

This was a double-blind, placebo controlled, parallel group study of ranolazine SR 1000 mg bid or placebo administered with digoxin 0.125mg qd in healthy male subjects. Sixteen subjects received oral 0.125mg doses of digoxin qd on Days 1-14. Eight of the subjects received placebo tablets bid and the other 8 subjects received ranolazine 1000 mg bid on Days 7 to 14. Drug intake was about 1 hour after food intake. The subjects were institutionalized throughout the 15 days duration of the study. Based on the results from Study CVT 3021 a sample size of 8 subjects per group was considered to be sufficient.

ASSAY:

Digoxin: All the samples were analyzed by [ ] The plasma and urine concentrations were measured by a direct immunoassay. In plasma the method was validated over the concentration range 0.150 ng/ml to 8 ng/mL. In urine the method was validated over the concentration range 1ng/mL to 40 ng/mL. Inter-assay and intra-assay accuracy (bias, %) and precision (CV, %) determined from QC samples were within the ± 15% limits.

Ranolazine: was not measured

Blood Sample Collection:

Blood samples for digoxin were collected at the following times:
Days 5 and 6: Pre-digoxin dose
Days 8, 10, 12 and 13: Pre-dose and 4 hours after the digoxin dose.
Days 7 and 14: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose.
Total urine volumes were collected:
Days 7 and 14: 0-24 hour

PK and Statistical Analysis:

The following PK parameters using standard compartment model independent methods were calculated from the samples obtained on Days 7 and 14: Cmax, tmax, Cmin, AUC0-24 and Clr. AUC0-24 was computed on application of the linear trapezoidal rule. If the digoxin concentration 24 hours after dosing was <LLOQ AUC0-24 was obtained from AUC0-∞ - C24/Ke, where C24 is the plasma concentration 24 hours after dosing determined by extrapolation from the log linear regression during the terminal elimination phase. Clr was obtained from Ae0-24/AUC0-24, where Ae0-24 represents the amounts of digoxin excreted in urine over a period of 24 hours.
An ANOVA model was used to test for differences in Cmax, Cmin, AUC0-24, Clr between test (digoxin in combination with ranolazine) and reference (digoxin alone) treatments. 90% confidence intervals were computed from the ratio of the untransformed and ln transformed parameters. For testing differences in tmax Wilcoxon's two-sample test was applied.

Safety:

Standard supine 12 Lead ECG recordings were performed at the following times:
Days 5 and 6: Pre-dose.
Days 8, 10, 12, and 13: Pre-dose and 4 hour post-dose
Days 7 and 14: Pre-dose and at 4, 8, 12, and 24 hours post-dose.
The analysis of the ECG data was by a centralized ECG Core Laboratory at St. Louis University, St. Louis, MO.
Supine and erect blood pressure and heart rate was monitored at the following times:
Days 5 ,6: Pre-dose
Days 8, 10, 12, and 13: Pre-dose and 4 hours post-dose.
Days 7 and 14: Pre-dose and 4, 8, 12 and 24 hours post-dose

RESULTS:

Sixteen (16) male subjects entered and completed the study. Their mean age was 29.1 years. Thirteen (13) were of Caucasian, 1 of Hispanic, 1 of Black and 1 of other origin. Five (5) subjects had 0-24hour urine volumes reported in error and Clr was not calculated. Several subjects had C24 values of 0 and a value of 1 was added prior to ln transformation.

PK:

The mean PK parameters and results of the statistical analysis for digoxin when administered together with placebo or ranolazine on Days 7 and 14 are listed in the following table:

Means and 90% Confidence Intervals for Ranolazine SR with Digoxin Compared to Digoxin Alone

Parameter	Study Day	Test Mean[a]	Reference Mean[a]	Test/Reference Mean[b]	90% Confidence Interval[c]	P-value[d]
C_{max}	7	0.659	0.585	112.7	(95.8 , 129.7)	0.2075
$\ln(C_{max})$	7	0.651	0.576	113.0	(97.2 , 131.3)	0.1750
C_{min}	7	0.129	0.079	164.5	(57.7 , 271.4)	0.3055
$\ln(C_{min})^e$	7	0.125	0.075	166.6	(58.6 , 283.1)	0.3026
AUC_{0-24}	7	6.58	4.75	138.4	(106.3 , 170.4)	0.0535
$\ln(AUC_{0-24})$	7	6.44	4.41	146.2	(109.0 , 196.2)	0.0391
CL_r	7	107	138	77.4	(47.9 , 106.9)	0.1978
T_{max}	7	2.00[f]	2.00[f]	Not Applicable	Not Applicable	0.5048[g]
C_{max}	14	0.712	0.489	145.5	(129.2 , 161.9)	0.0002
$\ln(C_{max})$	14	0.707	0.480	147.2	(126.4 , 171.4)	0.0005
C_{min}	14	0.298	0.121	246.0	(186.0 , 306.0)	0.0008
$\ln(C_{min})^e$	14	0.296	0.118	251.1	(186.4 , 319.9)	0.0007
AUC_{0-24}	14	9.73	6.10	159.5	(139.9 , 179.1)	0.0001
$\ln(AUC_{0-24})$	14	9.65	6.01	160.4	(137.9 , 186.7)	0.0001
CL_r	14	93.9	109	86.2	(54.6 , 117.9)	0.4451
T_{max}	14	2.00[f]	2.00[f]	Not Applicable	Not Applicable	0.5288[g]

[a]Least-squares mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means).
[b]Ratio of natural log parameter means calculated by transforming the difference in natural log means back to the linear scale. The ratio is expressed as a percentage.
[c]90% confidence interval for natural log parameter means calculated by transforming the 90% confidence interval of the difference in natural log means back to the linear scale. The confidence interval endpoints are expressed as a percentage.
[d]P-value for difference between test and reference means from ANOVA.
[e]A value of 1 was added to all C_{min} values prior to natural log transformation.
[f]Median values.
[g]P-value for difference between test and reference means from 2-sample Wilcoxon's test.

Mean Cmax, AUC0-24, Cmin and Clr of digoxin on Days 7 and 14 in the presence and absence of ranolazine were not equivalent. The least square means of AUC0-24 and Cmax of digoxin on Day 14 during ranolazine co-administration were 1.60 and 1.46 fold, respectively, greater and Clr was 13.8% smaller than in the absence of ranolazine.
Tmax of digoxin was not affected by the co-administration of digoxin.

Safety:

The mean QTc intervals are listed in the following table:

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REST ECG: SUMMARY STATISTICS FOR QTc INTERVAL, BY TREATMENT GROUP AND STUDY DAY

		QTc Interval (msec)		
VISIT	N	Placebo	N	1000 mg BID Ranolazine SR
Screening	8	370.1 ± 6.93 (350,403)	8	390.1 ± 7.44 (358,423)
Day 5, 0 hour	8	386.4 ± 10.13 (359,449)	8	400.4 ± 6.81 (368,424)
Day 6, 0 hour	8	374.0 ± 6.47 (338,398)	8	384.2 ± 6.31 (360,415)
Day 7, 0 hour	8	373.1 ± 5.96 (348,391)	8	399.3 ± 4.22 (376,418)
Day 7, 4 hour	8	361.5 ± 3.29 (352,378)	8	382.1 ± 4.82 (360,407)
Day 7, 8 hour	8	365.6 ± 6.38 (335,388)	8	390.8 ± 5.56 (371,413)
Day 7, 12 hour	8	370.3 ± 2.42 (364,386)	8	390.0 ± 4.00 (376,405)
Day 7, 24 hour	8	365.2 ± 7.45 (327,388)	8	398.6 ± 7.71 (369,427)
Day 8, 4 hour	8	361.4 ± 5.11 (338,380)	8	380.1 ± 6.17 (354,404)
Day 10, 0 hour	8	373.1 ± 7.25 (328,394)	8	397.0 ± 6.01 (370,420)
Day 10, 4 hour	8	363.8 ± 10.39 (320,423)	8	385.0 ± 3.89 (370,400)
Day 12, 0 hour	8	376.4 ± 8.53 (331,418)	8	403.2 ± 8.58 (356,433)
Day 12, 4 hour	8	354.8 ± 6.69 (320,381)	8	381.3 ± 5.32 (361,399)
Day 13, 0 hour	8	384.1 ± 8.29 (338,421)	8	397.2 ± 6.87 (376,425)
Day 13, 4 hour	8	363.8 ± 8.66 (315,400)	8	389.5 ± 6.41 (368,420)
Day 14, 0 hour	8	377.6 ± 7.43 (343,402)	8	402.8 ± 7.43 (371,433)
Day 14, 4 hour	8	367.6 ± 6.98 (343,396)	8	379.3 ± 6.61 (340,399)
Day 14, 8 hour	8	376.0 ± 16.64 (341,487)	8	392.1 ± 6.73 (360,416)
Day 14, 12 hour	8	375.3 ± 6.18 (352,402)	8	395.1 ± 6.68 (365,429)
Day 14, 24 hour	8	364.4 ± 6.69 (329,394)	8	388.0 ± 9.25 (364,439)

Note:
Values are mean ± standard error (minimum,maximum).
N = sample size.

The subjects on ranolazine placebo displayed smaller mean QTc values at screening and on Day 5 pre-dose in comparison to the group receiving ranolazine. The subsequently recorded mean QTc values in the ranolazine placebo receiving group were all smaller than the values determined at screening or on Day 5 pre-dose. In contrast, the mean QTc values of the patients on ranolazine displayed 2 values that were greater than either reference QTc values and 7 values that were greater than one of the reference values. Thes results suggested that ranolazine incerased the QTc interval.
No clinically important changes in the T-wave were observed.

CONCLUSIONS:

Co-administration of 1000 mg ranolazine bid to healthy male subjects volunteers receiving digoxin doses of 0.125 mg qd results in a 1.60 and 1.46 fold increase of AUC0-24 and Cmax of digoxin, respectively, whereas mean Clr decreases by 13.8%.

In vitro data suggest that ranolazine is an inhibitor of P-glycoprotein and this could be the mechanism responsible for the increased exposure of digoxin in the presence of ranolazine.

COMMENTS:

1. In view of the insufficient sensitivity of the assay an increase of the digoxin dose to 0.250 mg should have been considered.
2. No female subjects were included in the study. Study CVT 3021 reported an impact of sex on the PK of ranolazine.
3. The study was conducted in healthy subjects and the results may not be extrapolated to patients with the target disease.
4. The observed increase in the arithmetic mean Cmax and AUC values of digoxin in the presence of ranolazine in the present study in healthy volunteers is smaller than in the patients with congestive heart failure in study CVT 3021 even though the ranolazine dose used in the present study (1000 mg) was greater than in Study CVT 3021 (750 mg).

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STUDY CVT 3012 – A STUDY TO INVESTIGATE THE POTENTIAL PHARMACOKINETIC AND PHARMACODYNAMYC INTERACTION BETWEEN RANOLAZINE SR 1000 MG BID AND ONCE DAILY MODIFIED RELEASE DILTIAZEM AT DOSES OF 180 MG, 240 MG, AND 360 MG OR PLACEBO IN HEALTHY YOUNG MEN

STUDY INVESTIGATOR AND SITE: [

]

Report No.: CVT 3012
Volume No.: 6-9, ITEM 6

OBJECTIVES:

To determine the effect of diltiazem MR on ranolazine SR pharmacokinetics and to evaluate the pharmacodynamic interactions between diltiazem MR and ranolazine SR when they are co-administered

FORMULATIONS:

SR tablets containing 500 mg ranolazine (Lot No. 791771)
Over-encapsulated Cardizem® CD 180 mg tablets containing 180 mg diltiazem (Lot No. P31021)
Over-encapsulated Cardizem® CD 240 mg tablets containing 240 mg diltiazem (Lot No. P41093)
Matching placebos capsules

Dissolution studies were performed on the over-encapsulated Cardizem® CD tablets and the dissolution specifications were met.

STUDY DESIGN:

This was a double-blind, randomized, placebo-controlled, parallel group study in which healthy male subjects received diltiazem MR (180 mg, 240 mg, or 360 mg) or placebo once daily for 8 days with the co-administration of ranolazine SR 1000 mg bid beginning Day 4 and continuing through the morning of Day 8. The subjects were institutionalized for the 9 days length of study participation. Thirty-two (32) subjects were to be randomized to receive diltiazem or placebo on Days 1-8, 1000 mg ranolazine bid on Days 4 through 7 and one dose of ranolazine in the morning of Day 8. Dosing occurred in the morning about 1 hour following breakfast and drug intake was together with 240 mL water.

ASSAY:

Plasma concentrations of ranolazine and its metabolite RS-88390 (CVT-2514) were measured by [ ] using a validated HPLC assay with fluorescence detection. RS-87986-193 was used as internal standard. The respective LLOQ for ranolazine and RS-88390 (CVT-2514) were 10 ng/mL and 8.5 ng/mL. The calibration curves were linear with $R^2 \geq 0.991$ Mean accuracy (bias, %) and precision (CV, %) determined from QC samples were for both ranolazine and RS-88390 (CVT-2514) within the ±15% limits.
The plasma concentrations of the metabolite RS-94287 were measured at CV Therapeutics, Inc., Palo Alto, CA, using a LC/MS/MS. The LLOQ was 5 ng/mL and the linear range of the calibration curve was between 5 ng/ml and 2500 ng/mL (R2 ≥ 0.993) . Mean accuracy (bias, %) and precision (CV, %) determined from QC samples were within the ± 15% limits.

Blood Sample Collection:

Blood samples for the determination of ranolazine were collected at the following times: Days 4 and 8: Pre-, 1, 3, 4, 6, 8, and 12 hours post-dose
Days 5, 6 and 7: Pre-dose and 4 hours post-dose.
Day 9: prior to discharge

PK and Satistical Analysis:

The following pharmakinetic parameters were determined for ranolazine and the metabolites: Cmax, C12, tmax AUC0-12, AUC0-24, AUC0-∞. Estimates for AUC0-∞ were obtained from AUC0-∞ = AUC0-24 +C/β, where C is the plasma concentration at 24 hours and β is the terminal phase elimination rate constant estimated using log-linear regression. The number of points used was determined by visual inspection of the data describing the terminal phase. At least the last three points were used in computing β.
The t1/2 of the terminal elimination phase was obtained form t1/2=0.693/β.

An analysis of variance (ANOVA) model was run to test for differences between test (each diltiazem dose with ranolazine) and reference (ranolazine with placebo) treatments following single dose administration on Day 4 and multiple dose administration on Day 8. The 90% confidence interval for the difference between test and reference treatments was calculated using the ESTIMATE statement of the SAS® PROCMIX procedure. To test for drug interaction this result was used to compute the 90% confidence interval for the ratio of the test/reference treatments for primarily Cmax and AUC0-12 . The same calculations were also performed for C12, T1/2, AUC0-24, and AUC0-∞. The un-transformed and the ln transformed parameter values were used in the calculations. For the analysis of Tmax Wilcoxon's two sample test was used.

Safety:

Supine 12 Lead ECG recordings, supine and standing blood pressure and heart rate were performed at the following times:
Screening
Days 2 and 3: Pre-dose (24 hours after the previous diltiazem or placebo dose)
Days 5,6 and 7: Pre-dose (12 hours after the previous ranolazine dose) and 4 hours post-dose
Days 4 and 8: Pre-dose, 4, 8, and 12 hours post-dose and 24 hours post-dose (morning of Day 9)
The ECGs were inspected by the Investigator. Subjects in whom the QTc increased to ≥130% of the baseline value at screening and exceeded 500 msec were to be withdrawn from the study.
The final analysis of the ECG parameters PR, QRS, QT, QTc and T-wave was performed by St. Louis University/Core ECG Laboratory Health Science Center, School of Medicine in St. Louis, MO.

RESULTS:

Thirty-four (34) healthy male subjects (24 Caucasians, 5 African-American, 4 Hispanics, and 1 Native American) with a mean age of 28.1 years were enrolled and 31 completed the study. Three (3) subjects were discontinued because of AEs.

PK:

The following 3 tables list the salient findings the impact of co-administration of diltiazem (180 mg, 240 mg and 360 mg) has on the pharmacokinetics of ranolazine:

Table 16.2-26 Statistical Analysis of Pharmacokinetic Results for Drug Interaction Between 180 mg Diltiazem MR and Ranolazine SR (Confidence Intervals Based on Ranolazine Concentrations)

Parameter	Units	Day	Test Mean[a]	Reference Mean[a]	Percent[b] Test/Reference	90% Confidence Interval[c]	P-value[d]
C_{max}	ng/mL	4	1479	778	190	(131 , 269)	0.0634
		8	3198	2138	150	(108 , 192)	0.0547
ln(C_{max})	ng/mL	4	1428	772	185	(134 , 256)	0.0032
		8	3088	2104	147	(116 , 186)	0.0102
C_{12}	ng/mL	4	986	470	210	(82.7 , 337)	0.1529
		8	1561	1003	156	(47.6 , 264)	0.3887
ln(C_{12})	ng/mL	4	917	456	201	(124 , 327)	0.0208
		8	1315	862	153	(85.0 , 274)	0.2292
AUC_{0-12}	ng·hr/mL	4	12414	5757	216	(143 , 289)	0.0116
		8	28631	18847	152	(99.3 , 205)	0.1044
ln(AUC_{0-12})	ng·hr/mL	4	11938	5699	209	(153 , 287)	0.0004
		8	26739	18137	147	(109 , 199)	0.0374
AUC_{0-24}	ng·hr/mL	8	41459	26591	156	(89.0 , 223)	0.1660
ln(AUC_{0-24})	ng·hr/mL	8	38317	25297	151	(106 , 216)	0.0558
$AUC_{0-\infty}$	ng·hr/mL	8	50873	30582	166	(116 , 217)	0.0336
ln($AUC_{0-\infty}$)	ng·hr/mL	8	48115	29415	164	(119 , 226)	0.0158
$T_{1/2}$	hour	8	6.11	6.27	97.5	(73.3 , 122)	0.8618
ln($T_{1/2}$)	hour	8	6.02	6.14	98.0	(76.1 , 126)	0.8923
T_{max}	hour	4	6.50	4.00	NA	NA	0.0588
		8	3.60	4.00	NA	NA	0.7900

NA Not Applicable.
Notes: Test refers to ranolazine SR administered in combination with different doses of diltiazem MR. Reference refers to ranolazine SR administered with placebo.
a Least-squares mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means). For T_{max}, these are the median values.
b Ratio of parameter least squares means for untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed back to linear scale.
c 90% confidence interval for ratio of parameter least squares means of untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.
d P-value for difference between test and reference means from ANOVA. For T_{max}, the p-value is from Wilcoxon's 2-sample test.

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Table 16.2-27 Statistical Analysis of Pharmacokinetic Results for Drug Interaction Between 240 mg Diltiazem MR and Ranolazine SR (Confidence Intervals Based on Ranolazine Concentrations)

Parameter	Units	Day	Test Mean[a]	Reference Mean[a]	Percent[b] Test/Reference	90% Confidence Interval[c]	P-value[d]
C_{max}	ng/mL	4	1866	778	240	(161 , 319)	0.0055
		8	4033	2138	189	(147 , 231)	0.0013
$ln(C_{max})$	ng/mL	4	1673	772	217	(157 , 300)	0.0004
		8	3809	2104	181	(143 , 229)	0.0002
C_{12}	ng/mL	4	1409	470	300	(173 , 427)	0.0123
		8	2562	1003	255	(147 , 363)	0.0210
$ln(C_{12})$	ng/mL	4	1002	456	220	(135 , 358)	0.0101
		8	2050	862	238	(133 , 427)	0.0178
AUC_{0-12}	ng·hr/mL	4	13696	5757	238	(165 , 311)	0.0032
		8	36366	18847	193	(140 , 246)	0.0056
$ln(AUC_{0-12})$	ng·hr/mL	4	12151	5699	213	(155 , 293)	0.0003
		8	33705	18137	186	(137 , 251)	0.0017
AUC_{0-24}	ng·hr/mL	8	55487	26591	209	(142 , 276)	0.0101
$ln(AUC_{0-24})$	ng·hr/mL	8	49618	25297	196	(138 , 279)	0.0031
$AUC_{0-\infty}$	ng·hr/mL	8	50801	30582	166	(118 , 214)	0.0282
$ln(AUC_{0-\infty})$	ng·hr/mL	8	47420	29415	161	(118 , 220)	0.0149
$T_{1/2}$	hour	8	5.80	6.27	92.4	(69.2 , 116)	0.5821
$ln(T_{1/2})$	hour	8	5.55	6.14	90.5	(70.9 , 115)	0.4864
T_{max}	hour	4	4.50	4.00	NA	NA	0.7358
		8	4.50	4.00	NA	NA	0.3226

NA Not Applicable.
Notes: Test refers to ranolazine SR administered in combination with different doses of diltiazem MR. Reference refers to ranolazine SR administered with placebo.
a Least-squares mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means). For T_{max}, these are the median values.
b Ratio of parameter least squares means for untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed back to linear scale.
c 90% confidence interval for ratio of parameter least squares means of untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.
d P-value for difference between test and reference means from ANOVA. For T_{max}, the p-value is from Wilcoxon's 2-sample test.

Table 16.2-28 Statistical Analysis of Pharmacokinetic Results for Drug Interaction Between 360 mg Diltiazem MR and Ranolazine SR (Confidence Intervals Based on Ranolazine Concentrations)

Parameter	Units	Day	Test Mean[a]	Reference Mean[a]	Percent[b] Test/Reference	90% Confidence Interval[c]	P-value[d]
C_{max}	ng/mL	4	2186	778	281	(204 , 358)	0.0004
		8	4919	2138	230	(187 , 274)	0.0001
$ln(C_{max})$	ng/mL	4	1989	772	258	(188 , 354)	0.0001
		8	4797	2104	228	(178 , 291)	0.0001
C_{12}	ng/mL	4	1351	470	288	(161 , 415)	0.0181
		8	2849	1003	284	(172 , 396)	0.0092
$ln(C_{12})$	ng/mL	4	1236	456	271	(167 , 441)	0.0016
		8	2436	862	283	(154 , 518)	0.0069
AUC_{0-12}	ng·hr/mL	4	15849	5757	275	(203 , 348)	0.0003
		8	44986	18847	239	(184 , 293)	0.0002
$ln(AUC_{0-12})$	ng·hr/mL	4	14887	5699	261	(191 , 358)	0.0001
		8	43580	18137	240	(176 , 328)	0.0001
AUC_{0-24}	ng·hr/mL	8	68907	26591	259	(190 , 328)	0.0006
$ln(AUC_{0-24})$	ng·hr/mL	8	65450	25297	259	(179 , 373)	0.0001
$AUC_{0-\infty}$	ng·hr/mL	8	80673	30582	264	(211 , 317)	0.0001
$ln(AUC_{0-\infty})$	ng·hr/mL	8	79579	29415	271	(193 , 380)	0.0001
$T_{1/2}$	hour	8	7.52	6.27	120	(94.5 , 146)	0.1909
$ln(T_{1/2})$	hour	8	7.29	6.14	119	(91.0 , 155)	0.2792
T_{max}	hour	4	6.00	4.00	NA	NA	0.0402
		8	4.00	4.00	NA	NA	0.5378

NA Not Applicable.
Notes: Test refers to ranolazine SR administered in combination with different doses of diltiazem MR. Reference refers to ranolazine SR administered with placebo.
a Least-squares mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means). For T_{max}, these are the median values.
b Ratio of parameter least squares means for untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed back to linear scale.
c 90% confidence interval for ratio of parameter least squares means of untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.
d P-value for difference between test and reference means from ANOVA. For T_{max}, the p-value is from Wilcoxon's 2-sample test.

The following 3 tables list the parameter values of RS-88390 (CVT-2514) in the presence and absence of diltiazem (180 mg, 240 mg and 360 mg):

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Table 16.2-30 Statistical Analysis of Pharmacokinetic Results for Drug Interaction Between 240 mg Diltiazem MR and Ranolazine SR (Confidence Intervals Based on RS-88390 Concentrations)

Parameter	Units	Day	Test Mean[a]	Reference Mean[a]	Percent[b] Test/Reference	90% Confidence Interval[c]	P-value[d]
C_{max}	ng/mL	4	540	591	91.5	(42.2 , 141)	0.7716
		8	1074	1116	96.2	(58.1 , 134)	0.8669
$ln(C_{max})$	ng/mL	4	508	541	94.0	(49.6 , 178)	0.8698
		8	986	1050	94.0	(60.6 , 146)	0.8109
C_{12}	ng/mL	4	428	527	81.2	(35.3 , 127)	0.4929
		8	777	757	103	(63.9 , 141)	0.9091
$ln(C_{12})$	ng/mL	4	404	462	87.5	(51.0 , 150)	0.6758
		8	743	654	114	(74.2 , 174)	0.6126
AUC_{0-12}	ng·hr/mL	4	4082	4592	88.9	(43.2 , 135)	0.6823
		8	10377	11012	94.2	(58.1 , 130)	0.7883
$ln(AUC_{0-12})$	ng·hr/mL	4	3794	4270	88.9	(50.9 , 155)	0.7210
		8	9773	10061	97.1	(63.1 , 150)	0.9099
AUC_{0-24}	ng·hr/mL	8	17411	17996	96.7	(60.8 , 133)	0.8786
$ln(AUC_{0-24})$	ng·hr/mL	8	16586	16344	101	(66.8 , 154)	0.9526
$AUC_{0-\infty}$	ng·hr/mL	8	23893	25163	95.0	(56.4 , 134)	0.8233
$ln(AUC_{0-\infty})$	ng·hr/mL	8	23397	22984	102	(63.6 , 163)	0.9484
$T_{1/2}$	hour	8	12.8	13.4	95.4	(66.4 , 124)	0.7873
$ln(T_{1/2})$	hour	8	12.1	13.0	93.4	(69.4 , 126)	0.6934
T_{max}	hour	4	12.0	6.00	NA	NA	0.1761
		8	7.00	4.00	NA	NA	0.0704

NA Not Applicable.

Notes: Test refers to ranolazine SR administered in combination with different doses of diltiazem MR. Reference refers to ranolazine SR administered with placebo.

a Least-squares mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means). For T_{max}, these are the median values.

b Ratio of parameter least squares means for untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed back to linear scale.

c 90% confidence interval for ratio of parameter least squares means of untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.

d P-value for difference between test and reference means from ANOVA. For T_{max}, the p-value is from Wilcoxon's 2-sample test.

Table 16.2-29 Statistical Analysis of Pharmacokinetic Results for Drug Interaction Between 180 mg Diltiazem MR and Ranolazine SR (Confidence Intervals Based on RS-88390 Concentrations)

Parameter	Units	Day	Test Mean[a]	Reference Mean[a]	Percent[b] Test/Reference	90% Confidence Interval[c]	P-value[d]
C_{max}	ng/mL	4	468	591	79.2	(29.9 , 129)	0.4802
		8	823	1116	73.7	(35.6 , 112)	0.2506
$ln(C_{max})$	ng/mL	4	428	541	79.2	(41.8 , 150)	0.5397
		8	736	1050	70.1	(45.2 , 109)	0.1790
C_{12}	ng/mL	4	385	527	73.0	(27.0 , 119)	0.3259
		8	501	757	66.2	(27.5 , 105)	0.1478
$ln(C_{12})$	ng/mL	4	345	462	74.8	(43.6 , 128)	0.3676
		8	459	654	70.2	(45.9 , 108)	0.1699
AUC_{0-12}	ng·hr/mL	4	3930	4592	85.6	(39.9 , 131)	0.5956
		8	7694	11012	69.9	(33.7 , 106)	0.1675
$ln(AUC_{0-12})$	ng·hr/mL	4	3575	4270	83.7	(47.9 , 146)	0.5917
		8	6902	10061	68.6	(44.5 , 106)	0.1490
AUC_{0-24}	ng·hr/mL	8	12753	17996	70.9	(34.9 , 107)	0.1786
$ln(AUC_{0-24})$	ng·hr/mL	8	11491	16344	70.3	(46.3 , 107)	0.1627
$AUC_{0-\infty}$	ng·hr/mL	8	18497	25163	73.5	(35.0 , 112)	0.2492
$ln(AUC_{0-\infty})$	ng·hr/mL	8	15766	22984	68.6	(42.9 , 110)	0.1817
$T_{1/2}$	hour	8	13.7	13.4	102	(73.0 , 131)	0.9064
$ln(T_{1/2})$	hour	8	13.2	13.0	102	(75.7 , 137)	0.9147
T_{max}	hour	4	8.00	6.00	NA	NA	0.2301
		8	5.00	4.00	NA	NA	0.3927

NA Not Applicable.

Notes: Test refers to ranolazine SR administered in combination with different doses of diltiazem MR. Reference refers to ranolazine SR administered with placebo.

a Least-squares mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means). For T_{max}, these are the median values.

b Ratio of parameter least squares means for untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed back to linear scale.

c 90% confidence interval for ratio of parameter least squares means of untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.

d P-value for difference between test and reference means from ANOVA. For T_{max}, the p-value is from Wilcoxon's 2-sample test.

Table 16.2-31 Statistical Analysis of Pharmacokinetic Results for Drug Interaction Between 360 mg Diltiazem MR and Ranolazine SR (Confidence Intervals Based on RS-88390 Concentrations)

Parameter	Units	Day	Test Mean[a]	Reference Mean[a]	Percent[b] Test/Reference	90% Confidence Interval[c]	P-value[d]
C_{max}	ng/mL	4	704	591	119	(71.2 , 167)	0.5020
		8	1227	1116	110	(70.5 , 149)	0.6714
$ln(C_{max})$	ng/mL	4	436	541	80.7	(43.3 , 150)	0.5615
		8	1026	1050	97.7	(62.1 , 154)	0.9323
C_{12}	ng/mL	4	618	527	117	(71.2 , 163)	0.5304
		8	862	757	114	(73.8 , 154)	0.5612
$ln(C_{12})$	ng/mL	4	457	462	99.1	(57.8 , 170)	0.9768
		8	752	654	115	(73.9 , 179)	0.5949
AUC_{0-12}	ng·hr/mL	4	5825	4592	127	(81.1 , 173)	0.3264
		8	11492	11012	104	(66.9 , 142)	0.8443
$ln(AUC_{0-12})$	ng·hr/mL	4	4130	4270	96.7	(55.4 , 169)	0.9198
		8	9735	10061	96.8	(61.9 , 151)	0.9011
AUC_{0-24}	ng·hr/mL	8	19753	17996	110	(72.6 , 147)	0.6584
$ln(AUC_{0-24})$	ng·hr/mL	8	17063	16344	104	(67.7 , 161)	0.8667
$AUC_{0-\infty}$	ng·hr/mL	8	29424	25163	117	(73.5 , 160)	0.5081
$ln(AUC_{0-\infty})$	ng·hr/mL	8	26702	22984	116	(68.4 , 197)	0.6301
$T_{1/2}$	hour	8	14.3	13.4	107	(74.4 , 140)	0.7121
$ln(T_{1/2})$	hour	8	13.7	13.0	106	(75.6 , 147)	0.7840
T_{max}	hour	4	8.00	6.00	NA	NA	0.3705
		8	4.00	4.00	NA	NA	0.6803

NA Not Applicable.
Notes: Test refers to ranolazine SR administered in combination with different doses of diltiazem MR. Reference refers to ranolazine SR administered with placebo.
a Least-squares mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means). For T_{max}, these are the median values.
b Ratio of parameter least squares means for untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed back to linear scale.
c 90% confidence interval for ratio of parameter least squares means of untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.
d P-value for difference between test and reference means from ANOVA. For T_{max}, the p-value is from Wilcoxon's 2-sample test.

The following 3 tables show the impact of co-administration of diltiazem (180 mg, 240 mg and 360 mg) on the pharmacokinetics of RS-94287 (CVT-2738):

Table 16.2-32 Statistical Analysis of Pharmacokinetic Results for Drug Interaction Between 180 mg Diltiazem MR and Ranolazine SR (Confidence Intervals Based on RS-94287 Concentrations)

Parameter	Units	Day	Test Mean[a]	Reference Mean[a]	Percent[b] Test/Reference	90% Confidence Interval[c]	P-value[d]
C_{max}	ng/mL	4	197	213	92.2	(65.7 , 119)	0.6216
		8	649	657	98.8	(68.7 , 129)	0.9449
$ln(C_{max})$	ng/mL	4	191	210	90.9	(68.5 , 121)	0.5726
		8	602	645	93.4	(69.9 , 125)	0.6903
C_{12}	ng/mL	4	189	202	93.6	(70.7 , 116)	0.6347
		8	505	543	93.0	(63.2 , 123)	0.6927
$ln(C_{12})$	ng/mL	4	185	198	93.0	(69.5 , 125)	0.6766
		8	462	529	87.3	(63.2 , 120)	0.4779
AUC_{0-12}	ng·hr/mL	4	1523	1771	86.0	(69.6 , 102)	0.1565
		8	6837	6903	99.0	(69.7 , 128)	0.9562
$ln(AUC_{0-12})$	ng·hr/mL	4	1489	1747	85.2	(68.8 , 106)	0.2149
		8	6343	6792	93.4	(69.8 , 125)	0.6910
AUC_{0-24}	ng·hr/mL	8	11465	11524	99.5	(69.1 , 130)	0.9776
$ln(AUC_{0-24})$	ng·hr/mL	8	10545	11305	93.3	(68.8 , 127)	0.7005
$AUC_{0-\infty}$	ng·hr/mL	8	16830	15083	112	(70.1 , 153)	0.6384
$ln(AUC_{0-\infty})$	ng·hr/mL	8	15141	14733	103	(71.8 , 147)	0.8977
$T_{1/2}$	hour	8	13.3	10.7	125	(88.2 , 161)	0.2603
$ln(T_{1/2})$	hour	8	13.0	10.6	123	(95.7 , 157)	0.1731
T_{max}	hour	4	12.0	10.0	NA	NA	0.4432
		8	5.50	6.50	NA	NA	0.3273

NA Not Applicable.
Notes: Test refers to ranolazine SR administered in combination with different doses of diltiazem MR. Reference refers to ranolazine SR administered with placebo.
a Least-squares mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means). For T_{max}, these are the median values.
b Ratio of parameter least squares means for untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed back to linear scale.
c 90% confidence interval for ratio of parameter least squares means of untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.
d P-value for difference between test and reference means from ANOVA. For T_{max}, the p-value is from Wilcoxon's 2-sample test.

Table 16.2-33 Statistical Analysis of Pharmacokinetic Results for Drug Interaction Between 240 mg Diltiazem MR and Ranolazine SR (Confidence Intervals Based on RS-94287 Concentrations)

Parameter	Units	Day	Test Mean[a]	Reference Mean[a]	Percent[b] Test/Reference	90% Confidence Interval[c]	P-value[d]
C_{max}	ng/mL	4	207	213	97.1	(70.5 , 124)	0.8522
		8	608	657	92.5	(62.5 , 123)	0.6761
$ln(C_{max})$	ng/mL	4	189	210	89.6	(67.5 , 119)	0.5151
		8	583	645	90.4	(67.7 , 121)	0.5585
C_{12}	ng/mL	4	159	202	78.5	(55.6 , 101)	0.1199
		8	496	543	91.3	(61.5 , 121)	0.6237
$ln(C_{12})$	ng/mL	4	146	198	73.5	(54.9 , 98.4)	0.0836
		8	469	529	88.6	(64.2 , 122)	0.5283
AUC_{0-12}	ng·hr/mL	4	1309	1771	73.9	(57.5 , 90.3)	0.0114
		8	6419	6903	93.0	(63.6 , 122)	0.6867
$ln(AUC_{0-12})$	ng·hr/mL	4	1283	1747	73.4	(59.3 , 91.0)	0.0207
		8	6153	6792	90.6	(67.8 , 121)	0.5667
AUC_{0-24}	ng·hr/mL	8	10940	11524	94.9	(64.5 , 125)	0.7789
$ln(AUC_{0-24})$	ng·hr/mL	8	10393	11305	91.9	(67.8 , 125)	0.6420
$AUC_{0-\infty}$	ng·hr/mL	8	17136	15083	114	(72.1 , 155)	0.5810
$ln(AUC_{0-\infty})$	ng·hr/mL	8	15501	14733	105	(73.5 , 151)	0.8111
$T_{1/2}$	hour	8	14.8	10.7	139	(103 , 176)	0.0772
$ln(T_{1/2})$	hour	8	13.9	10.6	131	(102 , 168)	0.0725
T_{max}	hour	4	12.0	10.0	NA	NA	0.8612
		8	4.00	6.50	NA	NA	0.0539

NA Not Applicable.

Notes: Test refers to ranolazine SR administered in combination with different doses of diltiazem MR. Reference refers to ranolazine SR administered with placebo.

a Least-squares mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means). For T_{max}, these are the median values.

b Ratio of parameter least squares means for untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed back to linear scale.

c 90% confidence interval for ratio of parameter least squares means of untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.

d P-value for difference between test and reference means from ANOVA. For T_{max}, the p-value is from Wilcoxon's 2-sample test.

Table 16.2-34 Statistical Analysis of Pharmacokinetic Results for Drug Interaction Between 360 mg Diltiazem MR and Ranolazine SR (Confidence Intervals Based on RS-94287 Concentrations)

Parameter	Units	Day	Test Mean[a]	Reference Mean[a]	Percent[b] Test/Reference	90% Confidence Interval[c]	P-value[d]
C_{max}	ng/mL	4	170	213	79.7	(53.9 , 106)	0.1908
		8	763	657	116	(85.1 , 147)	0.3826
$ln(C_{max})$	ng/mL	4	160	210	76.0	(57.7 , 100)	0.1018
		8	712	645	110	(81.7 , 149)	0.5813
C_{12}	ng/mL	4	165	202	81.4	(58.6 , 104)	0.1768
		8	617	543	114	(82.8 , 145)	0.4568
$ln(C_{12})$	ng/mL	4	154	198	77.5	(57.9 , 104)	0.1497
		8	578	529	109	(78.3 , 153)	0.6539
AUC_{0-12}	ng·hr/mL	4	1196	1771	67.5	(51.1 , 83.9)	0.0022
		8	8090	6903	117	(86.8 , 148)	0.3435
$ln(AUC_{0-12})$	ng·hr/mL	4	1133	1747	64.9	(52.4 , 80.4)	0.0019
		8	7573	6792	111	(82.6 , 151)	0.5426
AUC_{0-24}	ng·hr/mL	8	13901	11524	121	(89.1 , 152)	0.2745
$ln(AUC_{0-24})$	ng·hr/mL	8	13073	11305	116	(84.4 , 159)	0.4394
$AUC_{0-\infty}$	ng·hr/mL	8	23399	15083	155	(112 , 198)	0.0377
$ln(AUC_{0-\infty})$	ng·hr/mL	8	21987	14733	149	(103 , 216)	0.0771
$T_{1/2}$	hour	8	18.3	10.7	172	(134 , 209)	0.0033
$ln(T_{1/2})$	hour	8	17.3	10.6	164	(127 , 212)	0.0029
T_{max}	hour	4	12.0	10.0	NA	NA	0.3519
		8	5.00	6.50	NA	NA	0.0799

NA Not Applicable.

Notes: Test refers to ranolazine SR administered in combination with different doses of diltiazem MR. Reference refers to ranolazine SR administered with placebo.

a Least-squares mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means). For T_{max}, these are the median values.

b Ratio of parameter least squares means for untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed back to linear scale.

c 90% confidence interval for ratio of parameter least squares means of untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.

d P-value for difference between test and reference means from ANOVA. For T_{max}, the p-value is from Wilcoxon's 2-sample test.

Following the first dose of ranolazine on Day 4 the least square mean AUC0-12 of ranolazine was 2.16., 2.38 and 2.75 fold increased when diltiazem in doses of 180 mg, 240 mg and 360 mg, respectively, was co-administered than when placebo was co-administered with ranolazine. The corresponding values for Cmax were increased 1.90, 2.40 and 2.81 fold. The 90% confidence intervals for the untransformed and transformed data were not contained within the 80% to 125% range indicating a drug interaction between diltiazem and ranolazine occurring at all 3 dose levels of diltiazem.

On Day 8 following 9 doses of ranolazine AUC0-12 was 1..52 , 1.93 and 2.39 times greater when diltiazem in doses of 180 mg, 240 mg, and 360 mg,, respectively, was co-administered than when placebo was co-administered to ranolazine. The corresponding values for Cmax were 1.50, 1.89 and 2.30 times greater in the presence of diltiazem than in the absence of diltiazem. The 90% confidence intervals for the ln transformed data were not contained in the 80% to 125% range indicating that after multiple dosing a drug interaction between diltiazem and ranolazine at all three dose levels of diltiazem took place. The extent of the interaction after multiple doses of ranolazine was smaller than after single dose administration of ranolazine at all 3 dose levels of diltiazem. The increase in AUC0-12 of ranolazine on Day 8 relative to Day 4 in the presence of 180 mg, 240 mg and 360 mg diltiazem, respectively, was reduced by 55%, 33% and 21%. Tmax for ranolazine on Day 4 was consistently greater than on Day 8 for all treatments. The mean t1/2 value for ranolazine on co-administration of placebo was 6.27 hours and did not change importantly after co-administration of the different diltiazem doses.
Co-administration of diltiazem and ranolazine appeared to impact the mean Cmax and AUC0-12 values of the metabolites RS-88390 (CVT-2514) and RS-94287 (CVT-2738) not relevantly. The 90% confidence intervals for the ln transformed data were for all test treatments not contained in the 80% to 125% range. The respective mean Tmax values for the RS-88390 (CVT-2514) were on Day 4 and Day 8 7.75 hours and 3.75 hours, respectively, in the absence of diltiazem. In the presence of diltiazem the Tmax values tended to slightly increase, but Tmax on Day 8 was clearly smaller compared to Day 4. The mean t1/2 of RS-88390 (CVT-2514) after administration of the last dose of ranolazine and placebo on Day 8 was 13.4 hours and did not change importantly when diltiazem was co-administered.

The mean Tmax value of RS 94287 after co-administration of ranolazine and placebo was on Day 4 7.75 hours and on Day 8 3.75 hours. Co-administration of diltiazem at all dose levels tended to increase the Tmax values, but the difference between the values on Days 4 and 8 remained. The mean t1/2 of RS 94287 (CVT-2738) after administration of the last dose of ranolazine and placebo on Day 8 was 10.7 hours and the corresponding value after co-administration of ranolazine and diltiazem tended to increase.

Safety:

The mean QTc intervals and plasma concentrations of ranolazine of the different treatment groups are shown in the following table:

Mean QT_c Intervals and Ranolazine C_{max} Levels after Single and Multiple Ranolazine SR Doses

	Ran/Placebo	Ran/Dilt 180 mg	Ran/Dilt 240 mg	Ran/Dilt 360 mg
	Ranolazine C_{max} (ng/mL) mean ± SD			
Day 4	778 ± 112.2	1479 ± 451.8	1866 ± 959.9	2186 ± 955.5
Day 8	2138 ± 406.9	3198 ± 958.9	4033 ± 1471.5	4919 ± 1104.0
	QT_c (msec) mean ± SE			
Screening	427.0 ± 4.36	416.0 ± 7.82	419.4 ± 8.89	418.4 ± 10.70
Day 4, Hour 0	425.6 ± 8.50	429.7 ± 8.04	422.6 ± 7.77	423.8 ± 16.39
Day 4, Hour 4	428.6 ± 6.94	421.0 ± 11.08	411.0 ± 6.10	401.3 ± 10.70
Day 4, Hour 12	419.2 ± 5.62	421.6 ± 9.78	417.7 ± 7.13	413.3 ± 8.98
Day 8, Hour 0	439.6 ± 9.79	435.4 ± 7.00	443.3 ± 6.11	433.1 ± 7.66
Day 8, Hour 4	433.5 ± 5.97	429.4 ± 7.49	420.8 ± 5.28	413.4 ± 9.03
Day 8, Hour 12	438.9 ± 7.53	432.2 ± 8.49	430.5 ± 11.23	418.1 ± 10.01

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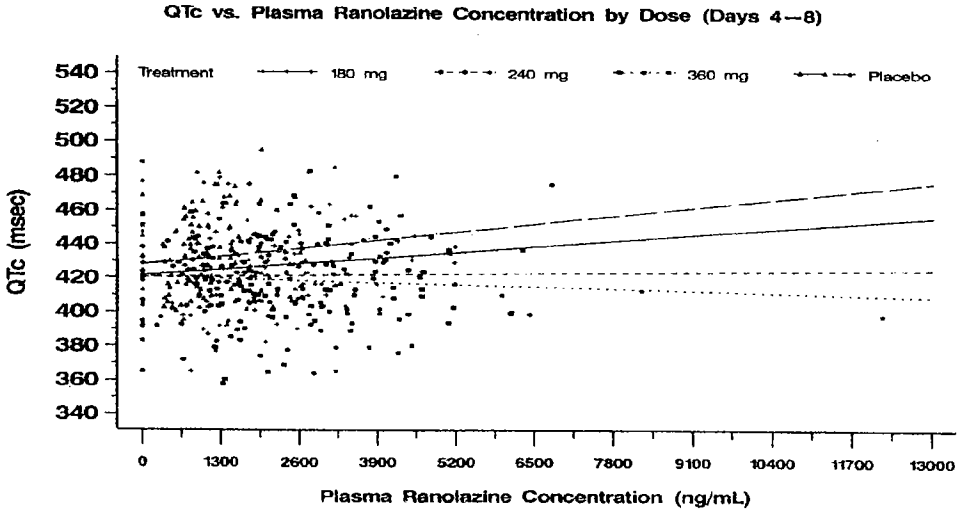
The following table lists the mean QTc intervals determined in the study:

ECG SUMMARY STATISTICS FOR QTc, BY TREATMENT GROUP AND STUDY DAY

		QTc (msec)						
VISIT	N	Placebo	N	180 mg Diltiazem MR	N	240 mg Diltiazem MR	N	360 mg Diltiazem MR
Screening	8	427.0 ± 4.36 (411,444)	8	416.0 ± 7.82 (386,445)	8	419.4 ± 8.89 (393,455)	7	418.4 ± 10.70 (386,461)
Day 2, 0 hour	8	424.9 ± 10.60 (376,463)	8	426.1 ± 11.10 (397,487)	8	412.8 ± 7.33 (369,432)	7	398.0 ± 10.62 (362,444)
Day 3, 0 hour	8	429.0 ± 5.61 (405,451)	8	417.2 ± 9.89 (380,468)	8	429.0 ± 7.34 (393,453)	7	412.5 ± 9.59 (365,447)
Day 4, 0 hour	8	425.6 ± 8.50 (395,469)	8	429.7 ± 8.04 (403,477)	8	422.6 ± 7.77 (383,458)	7	423.8 ± 16.39 (365,488)
Day 4, 4 hour	8	428.6 ± 6.94 (395,454)	8	421.0 ± 11.08 (377,465)	8	411.0 ± 6.10 (378,435)	7	401.3 ± 10.70 (358,444)
Day 4, 8 hour	8	422.3 ± 7.40 (402,461)	8	408.6 ± 10.01 (365,449)	8	415.0 ± 7.02 (372,435)	7	402.8 ± 9.60 (360,443)
Day 4, 12 hour	8	419.2 ± 5.62 (401,440)	8	421.6 ± 9.78 (387,476)	8	417.7 ± 7.13 (383,442)	7	413.3 ± 8.98 (379,459)
Day 5, 0 hour	8	429.5 ± 7.01 (406,460)	8	437.7 ± 10.31 (406,482)	8	424.5 ± 7.13 (389,444)	7	433.5 ± 5.80 (406,451)
Day 5, 4 hour	8	435.5 ± 10.62 (402,482)	7	419.9 ± 8.03 (390,445)	8	415.9 ± 8.69 (364,440)	5	393.4 ± 6.75 (369,410)
Day 6, 0 hour	8	438.3 ± 5.85 (417,459)	8	427.2 ± 9.55 (392,475)	8	418.3 ± 8.12 (385,443)	7	426.5 ± 12.93 (365,462)
Day 6, 4 hour	8	428.1 ± 3.98 (409,444)	8	425.0 ± 9.76 (403,485)	8	412.1 ± 6.91 (390,444)	7	414.7 ± 12.11 (365,469)
Day 7, 0 hour	8	444.0 ± 6.75 (415,468)	8	438.2 ± 8.30 (406,482)	8	422.1 ± 5.81 (400,442)	7	436.6 ± 11.08 (395,483)
Day 7, 4 hour	8	428.4 ± 8.85 (392,474)	8	423.1 ± 9.04 (382,457)	8	421.7 ± 8.05 (394,453)	7	414.0 ± 7.82 (376,437)
Day 8, 0 hour	8	439.6 ± 9.79 (408,495)	8	435.4 ± 7.00 (416,464)	8	443.3 ± 6.11 (426,475)	7	433.1 ± 7.66 (405,464)
Day 8, 4 hour	8	433.5 ± 5.97 (413,466)	8	429.4 ± 7.49 (401,462)	8	420.8 ± 5.28 (398,444)	7	413.4 ± 9.03 (393,457)
Day 8, 8 hour	8	435.8 ± 8.26 (403,464)	8	418.7 ± 5.76 (394,446)	8	419.5 ± 7.07 (379,443)	7	425.1 ± 14.48 (380,480)
Day 8, 12 hour	8	438.9 ± 7.53 (414,475)	8	432.2 ± 8.49 (397,468)	8	430.5 ± 11.23 (383,475)	7	418.1 ± 10.01 (379,464)
Day 9, 24 hour	8	428.1 ± 7.66 (396,466)	8	426.1 ± 7.50 (388,455)	8	405.0 ± 6.82 (383,434)	7	407.4 ± 9.94 (376,456)

Note:
Values are mean ± standard error (minimum,maximum).
N = sample size.
Subject Nos. 2018, 2027, and 2040 were prematurely terminated from the 360 mg treatment group due to adverse events and were not included in these statistics.

A plot of the QTc intervals against the plasma ranolazine concentrations is shown in the next figure:



The QTc data showed significant scatter. There was no overt evidence for an important increase in the apparent QTc intervals in the presence of diltiazem. This is also reflected by the plots of the QTc intervals against the plasma concentrations that show positive slopes only for 2 of the 4 treatment groups. None of the subjects had QTc values exceeding 130% of the baseline values and exceeding 500 msec.
The T-wave amplitude appeared to decrease modestly after administration of the higher doses of diltiazem and the addition of ranolazine did not appear to have an additional effect.
Relevant adverse events during the diltiazem/placebo treatment phase included chest pain (2 subjects), palpitation (1 subject), AV block 2° (1 subject), dizziness (1 subject) and paresthesia (1 subject). Except for palpitation and paresthesia all the other AEs occurred in subjects receiving 360mg diltiazem. Relevant Adverse events during the diltiazem/placebo and ranolazine treatment phase included chest pain (2 subjects), palpitations (2 subjects), dizziness (5 subjects) and AV block 2° (2 subjects). Except for dizziness that was also experienced by 2 subjects receiving placebo, all the other AEs occurred in subjects receiving diltiazem.

CONCLUSIONS:

The results indicate that diltiazem interacts with ranolazine clinically relevantly. The extent of the interaction between diltiazem and ranolazine depends on the dose of diltiazem. The impact of diltiazem on the plasma concentration of ranolazine apears to be greater after a single dose than after multiple doses of ranolazine. Relative to ranolazine the impact of co-administration of diltiazem on the pharmacokinetics of the metabolites RS-88390 (CVT-2514) and 94287 (CVT-2738) is much smaller.

The extent of the interaction between diltiazem and ranolazine is apparently dose and time dependent. Diltiazem and ranolazine are both substrates and inhibitors of CYP 3A4 and P-glycoprotein.

COMMENTS:

1. The plasma concentrations of diltiazem, a substrate and inhibitor of CYP 3A4 should have been measured to better understand the dose and apparent time dependency of the interaction between diltiazem and ranolazine.
2. A statistical analysis of whether steady-state concentrations of ranolazine in the presence and absence of diltiazem were reached was not performed.
3. A justification for the used heart rate correction algorithm was not provided.
4. The study was conducted in healthy male subjects with baseline QTc < 430msec and the results may not be extrapolated to female and male patients with the target disease and longer QTc intervals.
5. The QT interval at baseline should have been recorded over a 24 hour period to determine time specific change in the QTc interval.
6. The % increase of Cmax and AUC (0-12) in Tables 11.1 and 11.2 and in the text on pp.51, 52 of Item 6, Vol 6 are erroneous (overstimation by 100%)

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STUDY CVT 3017 - AN OPEN LABEL, MULTIDOSE STUDY TO ASSESS THE POTENTIAL PHARMACOKINETIC INTERACTION OF RANOLAZINE SR WITH SIMVASTATIN IN HEALTHY VOLUNTEERS

STUDY INVESTIGATOR AND SITE: [

]

Report No.: CVT 3017
Volume No.: 24-27, ITEM 6

OBJECTIVES:

To evaluate the effect of ranolazine SR at steady state on the pharmacokinetics of simvastatin after a single dose of simvastatin and with simvastatin at steady state and to evaluate the effect of simvastatin at steady state on the pharmacokinetuics of ranolazine SR at steady state.

FORMULATIONS:

Ranolazine tablets containing 375 mg (Lot No. 9G2715A)
Ranolazine tablets containing 500 mg (Lot No. 9G2714A)
Simvastatin tablets containing 40 mg simvastatin (Lot No. HL67080 and HL67100)

STUDY DESIGN:

This was an open-label, multiple dose comparison of the pharmacokinetics of simvastatin given with and without ranolazine and of ranolazine given with and without simvastatin. Eighteen (18) subjects were to receive the following dosing schedule:

	Dosing Regimen								
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Simvastatin (a.m.)	80 mg	X	X	X	X	80 mg	80 mg	80 mg	80 mg
Ranolazine SR (a.m.)	X	X	1750 mg	1000 mg	1000 mg	1000 mg	1000 mg	1000 mg	1000 mg
Ranolazine SR (p.m.)	X	X	1000 mg	1000 mg	1000 mg	1000 mg	1000 mg	1000 mg	X

X = no medication given at this timepoint

The primary endpoints were Cmax, AUC and oral clearance of simvastatin and ranolazine. Secondary endpoints were safety parameters and the impact of concomitant therapy. In addition selected simvastatin metabolites and HMG-CoA reductase inhibition activity was assessed.

ASSAY:

Ranolazine:
The determinations of ranolazine in plasma were performed by [redacted]. The determinations of simvastatin lactone, simvastatin acid, 6'-exomethylenesimvastatin and 3'-hydroxysimvastatin were performed at [redacted]. The HMG-CoA reductase inhibition analysis was done at CV Therapeutics in Palo Alto, CA.
Ranolazine was determined in plasma by a [redacted] method using [redacted] d3-ranolazine was used as internal standard. The linear range of the validated assay was between 50.0ng/mL and 12'500ng/mL. The calibration standard concentrations were weighted by $1/X^2$ (R2 ≥0.997). Accuracy (bias, %) and precision (CV, %) determined from QC samples were contained within the ± 15% limits.

Simvastatin lactone and metabolites:
Simvastatin and its metabolites were measured using an assay [redacted] analysis. Simvastatin lactone, 3'-hydroxy simvastatin lactone and 6'-exomethylenesimvastatin lactone were analyzed by a positive signal method. Simvastatin acid was run using a different method for negative signals.
The linear range of the respective calibration curves for simvastatin lactone and the metabolites was between 0.5µg/mL and 75µg/mL, corresponding to the LLOQ and ULOQ (R= 0.999). Inter-day precision (CV, %) and accuracy (bias, %) determined from the QC samples were for simvastatin and the metabolites simvastatin acid, 3'-hydroxy simvastatin lactone, and 6'-exomethylenesimvastatin lactone within the ±15% limits.

HMG-CoA reductase inhibition:
The assay measures the combined inhibitory activities of all active simvastatin metabolites. The assay involved extraction from simvastatin and metabolites from human plasma, followed by incubation of ^{14}C-β-hydroxy-β-methylglutaryl (HMG) CoA, NADPH, buffer and HMG CoA reductase prepared from human liver microsomes. The reaction product, ^{14}C-mevalonate was assayed [redacted]. The LLOQ of the method was 0.5 ng/mL. The assay accuracy (bias, %) and precision (CV, %) based on QC samples were within the ±15% limits.

Blood Sample Collection:

Blood samples were collected on the following times:

Ranolazine:

Days 3 and 4: Pre-dose for both doses (a.m. and p.m. doses)
Day 5: Pre-a.m. dose, 1, 2, 3, 4, 5, 7, 9, and 12 hours post a.m. dose
Days 6, 7 and 8: Pre-dose both doses (a.m. and p.m. doses)
Day 9: Pre a.m. dose, 1, 2, 3, 4, 5, 7, 9, 12, 16, 24, 28, 32, 36 and 48 hours post a.m. dose

Simvastatin:

Day 1: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 8, 12, and 24 hours post-dose
Day 6: 0.5, 1, 1.5, 2, 3, 4, 8, 12 hours post-dose
Days 7 and 8: Pre-dose
Day 9: Predose, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 18, 24, 30, 36, 42, 48 hours post-dose

HMG-CoA reductase inhibition:

Day 1: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 8, 12, and 24 hours post-dose
Day 6: 0.5, 1, 1.5, 2, 3, 4, 8, 12, and 24 hours post-dose
Day 9: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 18, 24, 30, 36, 42, 48 hours post-dose

PK and Statistical Analysis:

The following pharmacokinetic parameters were determined using standard methodology: Cmax, Tmax, Ctrough, Kel, t1/2 AUC12h, AUC24h, AUCinf and Cl/f.
Ctrough corresponded to the plasma concentration measured 12 and 24 hours after drug administration for ranolazine and simvastatin, respectively. AUCinf was computed by measuring AUCtlast and adding Ctlast/Kel. AUCtlast, AUC12 and AUC24h were obtained by applying the linear trapezoidal rule.
An analysis of variance with factors for subject and day was used for ln transformed values of Cmax, AUC24h and AUCinf. 90% confidence intervals for the difference in computed parameters least square means were calculated and expressed as percentage of the reference.

Safety:

Supine and erect systolic and diastolic blood pressure and supine heart rate were determined at the following times:
Screening and admission
Day1, 3-5: Pre-dose each dose
Day 6: Pre-dose a.m.dose, 1, 2, 4, 8 and 12 hours post a.m.dose
Day 7-9 (incl): Pre-dose each dose
Day11: Pre-discharge

Lead 12 and II ECG recordings were obtained at screening and the following times:
Days 1, 6 and 9: Pre a.m. dose, 2, 4, and 12 hours post a.m.dose
Days 3, 4, 5, 7, and 8: 4 hours post a.m. dose
Day 11: Pre-discharge

The ECGs were inspected on site by the principal investigator. Subjects in whom the QTc increased to ≥130% of the baseline value at screening and exceeded 500 msec were to be withdrawn from the study. The final analysis of the ECG parameters PR, QRS, QT, QTc and T-

wave was performed by St. Louis University/Core ECG L aboratory Health Science Center, School of Medicine in St. Louis, MO. The QT intervals were corrected for heart rate using the Bazett formula.

RESULTS:

Eighteen (18) healthy male subjects were enrolled and 16 completed the study. The mean age of the subjects was 32.4 years. One (1) subject was withdrawn by the principal investigator after Day 5 of the study, as a result of non-compliance with clinical procedures. A second subject withdrew consent for personal reasons after the last dose of study medication on Day 9. All subjects were Caucasian males. Data on simvastatin and ranolazine were available for 17 and 16 subjects, respectively.

PK:

The results of the mean parameters of simvastatin, its metabolites and the HMG-CoA reductase inhibitory activity in the presence and absence of ranolazine are listed in the following 3 tables:

Simvastatin Lactone

Parameter	Day 1 Mean	Day 1 Std. Dev.	Day 1 N	Day 6 Mean	Day 6 Std. Dev.	Day 6 N	Day 9 Mean	Day 9 Std. Dev.	Day 9 N
C_{max} (ng/mL)	22.3	19.6	17	40.3	16.4	17	39.1	21.5	17
T_{max} (hours)	1.50	0.87	17	1.32	0.73	17	1.29	0.69	17
C_{trough} (ng/mL)	-	-	-	-	-	-	1.06	1.23	17
K_e (1/hours)	0.154	0.183	17	0.142	0.0965	16	0.156	0.131	17
$t_{1/2}$ (hours)	8.23	4.94	17	6.45	2.71	16	10.90	16.70	17
AUC_{24h} (hr*ng/mL)	75.7	38.9	17	158.	62.1	17	141.	64.5	17
AUC_{inf} (hr*ng/mL)	87.9	44.4	17	166.	66.4	16	-	-	-
CL/F (L/h)	1150.	612.	17	571.	255.	16	770.	573.	17

Simvastatin Acid

Parameter	Day 1 Mean	Day 1 Std. Dev.	Day 1 N	Day 6 Mean	Day 6 Std. Dev.	Day 6 N	Day 9 Mean	Day 9 Std. Dev.	Day 9 N
C_{max} (ng/mL)	8.10	5.22	17	17.9	12.2	17	18.5	15.2	17
T_{max} (hours)	3.09	2.95	16	2.24	1.73	17	2.29	1.08	17
C_{trough} (ng/mL)	-	-	-	-	-	-	0.831	1.04	17
K_e (1/hours)	0.0887	0.0335	15	0.130	0.0598	16	0.102	0.0439	17
$t_{1/2}$ (hours)	9.75	6.11	15	6.64	3.63	16	8.18	4.02	17
AUC_{24h} (hr*ng/mL)	63.7	47.3	17	143.	115.	17	144.	112.	17
AUC_{inf} (hr*ng/mL)	100.	73.1	16	168.	116.	16	-	-	-

6'-Exomethylenesimvastatin Lactone

Parameter	Day 1 Mean	Day 1 Std. Dev.	Day 1 N	Day 6 Mean	Day 6 Std. Dev.	Day 6 N	Day 9 Mean	Day 9 Std. Dev.	Day 9 N
C_{max} (ng/mL)	6.05	14.1	17	3.90	1.64	17	3.70	1.87	17
T_{max} (hours)	1.71	0.97	17	1.56	0.75	17	1.47	0.70	17
C_{trough} (ng/mL)	-	-	-	-	-	-	0.0150	0.0618	17
K_{el} (1/hours)	0.496	0.589	12	0.253	0.163	17	0.260	0.157	17
$t_{1/2}$ (hours)	2.62	1.80	12	3.69	1.83	17	4.03	2.94	17
AUC_{24h} (hr*ng/mL)	6.89	8.10	17	12.3	5.71	17	12.6	6.76	17
AUC_{inf} (hr*ng/mL)	11.2	9.21	12	15.9	5.97	17	-	-	-

3'-Hydroxysimvastatin Lactone

Parameter	Day 1 Mean	Day 1 Std. Dev.	Day 1 N	Day 6 Mean	Day 6 Std. Dev.	Day 6 N	Day 9 Mean	Day 9 Std. Dev.	Day 9 N
C_{max} (ng/mL)	58.2	41.7	17	51.2	26.3	17	45.7	26.2	17
T_{max} (hours)	1.68	0.95	17	1.41	0.67	17	1.38	0.67	17
C_{trough} (ng/mL)	-	-	-	-	-	-	0.0415	0.171	17
K_{el} (1/hours)	0.585	0.317	17	0.470	0.233	17	0.481	0.289	17
$t_{1/2}$ (hours)	1.71	1.46	17	1.90	1.15	17	2.34	2.11	17
AUC_{24h} (hr*ng/mL)	111.	50.1	17	99.5	36.7	17	92.9	37.9	17
AUC_{inf} (hr*ng/mL)	115.	51.7	17	106.	33.5	17	-	-	-

HMG-CoA Reductase Inhibitor Activity (Simvastatin Equivalent)

Parameter	Day 1 Mean	Day 1 Std. Dev.	Day 1 N	Day 6 Mean	Day 6 Std. Dev.	Day 6 N	Day 9 Mean	Day 9 Std. Dev.	Day 9 N
C_{max} (ng/mL)	113.	33.5	17	183.	96.3	17	223.	149.	17
T_{max} (hours)	1.50	0.77	17	1.56	0.63	17	1.53	0.93	17
C_{trough} (ng/mL)	-	-	-	-	-	-	8.82	6.08	17
K_{el} (1/hours)	0.0989	0.0222	17	0.108	0.0244	16	0.0701	0.0229	17
$t_{1/2}$ (hours)	7.39	1.87	17	6.73	1.59	16	11.00	3.91	17
AUC_{24h} (hr*ng/mL)	586.	203.	17	974.	365.	17	1030.	418.	17
AUC_{inf} (hr*ng/mL)	640.	222.	17	1060.	436.	16	-	-	-

Note: Units for HMG-CoA Reductase Inhibitor Activity are ng/mL Simvastatin Equivalent

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The results of the statistical evaluation of the impact of ranolazine co-administration on the exposure measures for simvastatin and its metabolites and on the HMG-CoA reductase inhibition activity is shown in the following 3 tables:

Ratios of Least Squares Means and 90% Confidence Intervals

	Untransformed Data Sample Means		Natural Log Transformed Data Ratio of Least Squares Means (%)	Lower Bound (%)	Upper Bound (%)
	Simvastatin Lactone Day 9/Day 1				
	Day 9	Day 1			
C_{max}	39.1	22.3	191.	151.	241.
AUC_{24h}/Aucinf	141.	87.9	159.	137.	184.
	Simvastatin Lactone Day 6/Day 1				
	Day 6	Day 1			
C_{max}	40.3	22.3	213.	169.	269.
AUCinf/Aucinf	166.	87.9	202.	174.	235.
	Simvastatin Lactone Day 9/Day 6				
	Day 9	Day 6			
C_{max}	39.1	40.3	89.7	71.0	113.
AUC_{24h}/Aucinf	141.	166.	78.7	67.6	91.5
	Simvastatin Acid Day 9/Day 1				
	Day 9	Day 1			
C_{max}	18.5	8.10	208.	178.	244.
AUC_{24h}/Aucinf	144.	100.	139.	114.	171.
	Simvastatin Acid Day 6/Day 1				
	Day 6	Day 1			
C_{max}	17.9	8.10	213.	181.	249.
AUCinf/Aucinf	168.	100.	177.	145.	217.
	Simvastatin Acid Day 9/Day 6				
	Day 9	Day 6			
C_{max}	18.5	17.9	97.9	83.8	114.
AUC_{24h}/Aucinf	144.	168.	78.5	64.5	95.5

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Ratios of Least Squares Means and 90% Confidence Intervals

	Untransformed Data Sample Means		Natural Log Transformed Data Ratio of Least Squares Means (%)	Lower Bound (%)	Upper Bound (%)
	6'-Exomethylenesimvastatin Lactone Day 9/Day 1				
	Day 9	Day 1			
C_{max}	3.70	6.05	128.	91.7	178.
AUC_{24h}/Aucinf	12.6	11.2	132.	104.	167.
	6'-Exomethylenesimvastatin Lactone Day 6/Day 1				
	Day 6	Day 1			
C_{max}	3.90	6.05	140.	101.	196.
AUCinf/Aucinf	15.9	11.2	187.	148.	238.
	6'-Exomethylenesimvastatin Lactone Day 9/Day 6				
	Day 9	Day 6			
C_{max}	3.70	3.90	91.0	65.3	127.
AUC_{24h}/Aucinf	12.6	15.9	70.4	57.1	86.7
	3'-Hydroxysimvastatin Lactone Day 9/Day 1				
	Day 9	Day 1			
C_{max}	45.7	58.2	82.9	66.2	104.
AUC_{24h}/Aucinf	92.9	115.	82.7	69.8	98.0
	3'-Hydroxysimvastatin Lactone Day 6/Day 1				
	Day 6	Day 1			
C_{max}	51.2	58.2	95.1	75.9	119.
AUCinf/Aucinf	106.	115.	97.9	82.6	116.
	3'-Hydroxysimvastatin Lactone Day 9/Day 6				
	Day 9	Day 6			
C_{max}	45.7	51.2	87.2	69.7	109.
AUC_{24h}/Aucinf	92.9	106.	84.4	71.2	100.

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Ratios of Least Squares Means and 90% Confidence Intervals

	Untransformed Data Sample Means		Natural Log Transformed Data Ratio of Least Squares Means (%)	Lower Bound (%)	Upper Bound (%)
HMG-CoA Reductase Inhibitor Activity (Simvastatin Equivalent) Day 9/Day 1					
	Day 9	Day 1			
C_{max}	223.	113.	173.	142.	210.
AUC_{24h}/Aucinf	1030.	640.	159.	145.	174.
HMG-CoA Reductase Inhibitor Activity (Simvastatin Equivalent) Day 6/Day 1					
	Day 6	Day 1			
C_{max}	183.	113.	152.	125.	185.
AUCinf/Aucinf	1060.	640.	165.	150.	181.
HMG-CoA Reductase Inhibitor Activity (Simvastatin Equivalent) Day 9/Day 6					
	Day 9	Day 6			
C_{max}	223.	183.	114.	93.5	138.
AUC_{24h}/Aucinf	1030.	1060.	96.2	87.7	106.

Co-administration of 13 doses of ranolazine increased the arithmetic mean Cmax and AUC of simvastatin lactone on Day 9 relative to Day 1 (no ranolazine) 1.75 and 1.86 fold, respectively. Co-administration of 7 doses of ranolazine increased the arithmetic mean Cmax and AUC of simvastatin lactone on Day 6 relative to Day 1 1.81 and 2.09 fold, respectively. Co-administration of ranolazine increased mean Cmax and AUC of simvastatin acid on Day 9 relative to Day 1 2.28 and 2.26 fold, respectively. The mean Cmax and AUC values of simvastatin acid on Day 6 relative to Day 1 increased 2.21 and 2.24 fold, respectively.

For 6'-exomethylenesimvastatin lactone co-administration of ranolazine decreased mean Cmax by 38.8% and increased mean AUC 1.83 fold on Day 9 relative to Day 1. Relative to Day 1 mean Cmax of 6'- exomethylenesimvastatin lactone was also decreased by 35.5% and mean AUC increased 1.79 fold on Day 6. For 3'-hydroxysimvastatin lactone co-administration of ranolazine decreased Cmax and AUC on Day 9 relative to Day 1 by 21.5% and 16.3%, respectively. Mean Cmax (-12.0%) and AUC (-10.4%) were also slightly decreased on Day 6 relative to Day 1 for 3'-hydroxysimvastatin lactone. Co-administration of ranolazine increased Cmax and AUC of the HMG-Co A reductase inhibition capacity on Day 9 relative to Day 1 1.97 and 1.76 fold, respectively. Co-administration of ranolazine increased mean Cmax and AUC of 1.61 and 1.66, respectively, on Day 6 relative to Day 1 for the HMG-Co A reductase inhibitory activity.

The 90% confidence intervals for the ratios of the least square means of the ln transformed data for Cmax and AUC were not contained in the 80% to 125% range for simvastatin lactone, simvastatin acid and 6'-exoethylenesimvastatin lactone and HMG-Co A inhibitory activity. There were no important differences between the data obtained on Days 9 and 6 for simvastatin, simvastatin metabolites and HMG-CoA reductase inhibitory activity. With the metabolite 3'-hydroxy simvastatin lactone the Day 6 /Day 1 data met the equivalence criteria, whereas the Day 9/Day 1 data did not.

The results on the arithmetic mean parameters of ranolazine in the presence and absence of simvastatin and the statistical evaluations are listed in the following 2 tables:

Parameter	Ranolazine Day 5 Mean	Day 5 Std. Dev.	Day 5 N	Day 9 Mean	Day 9 Std. Dev.	Day 9 N
C_{max} (ng/mL)	2660.	1020.	17	3030.	1110.	17
T_{max} (hours)	3.88	1.80	17	3.29	1.10	17
C_{trough} (ng/mL)	1380.	880.	17	1580.	1150.	17
K_{el} (1/hours)	-	-	-	0.131	0.0390	16
$t_{1/2}$ (hours)	-	-	-	5.96	2.63	16
AUC_{tau} (hr*ng/mL)	23500.	11100.	17	24900.	9470.	17
CL/F (L/h)	49.9	18.5	17	44.9	14.5	17

Ratios of Least Squares Means and 90% Confidence Intervals

	Untransformed Data Sample Means		Natural Log Transformed Data Ratio of Least Squares Means (%)	Lower Bound (%)	Upper Bound (%)
	Ranolazine Day 9/Day 5				
	Day 9	Day 5			
C_{max}	3030	2600.	115.	106.	124.
Ctrough	1580	1330.	112.	105.	120.
AUC12h/Auc12h	24900	22700.	109.	99.4	119.

Co-administration of simvastatin increased arithmetic mean Cmax, Ctrough and AUC of ranolazine on Day 9 after 4 doses of simvastatin relative to Day 5 (no simvastatin) 1.14, 1.14 and 1.06 fold, respectively, and the data met the equivalence criteria.

Safety:

The relationship between the increase in QTc from time specific baseline (equivalent Day 1 time point) plotted against the plasma concentrations of ranolazine is depicted in the following figure:

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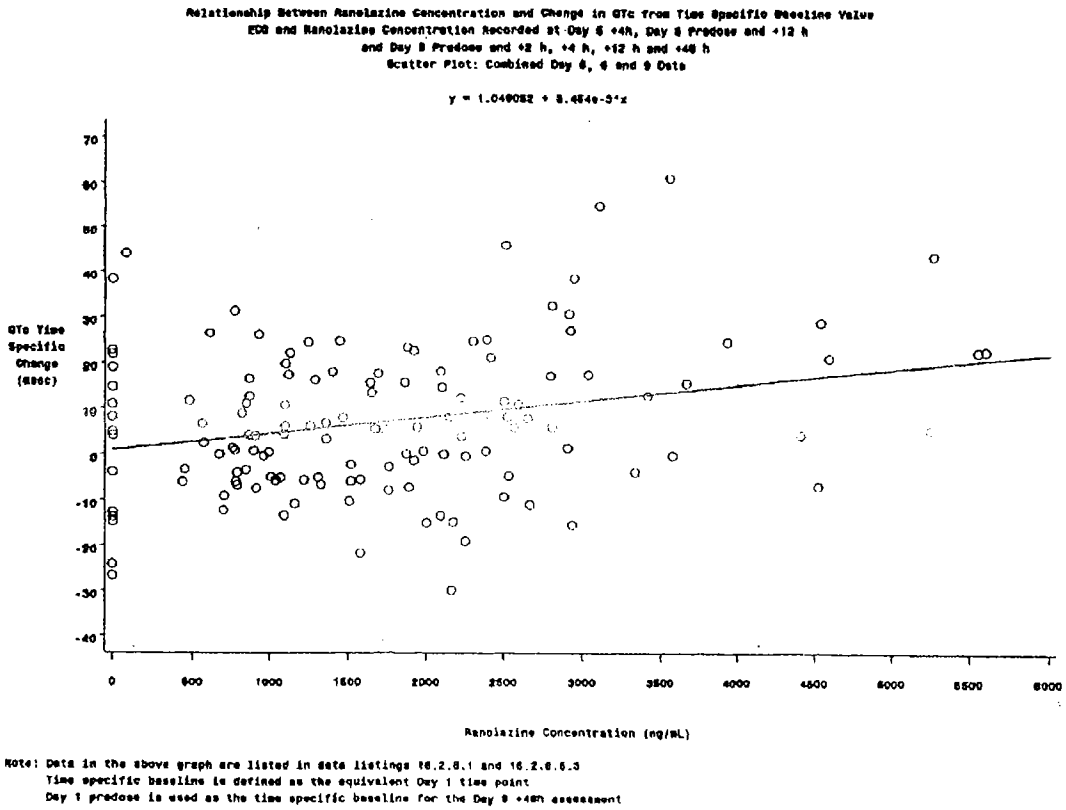

Note: Data in the above graph are listed in data listings 16.2.8.1 and 16.2.8.3
Time specific baseline is defined as the equivalent Day 1 time point
Day 1 predose is used as the time specific baseline for the Day 8 +48h assessment

There is an apparent linear relationship between ΔQTc and the plasma concentrations of ranolazine (ΔQTc(msec)= 1.05 + 0.00345• ranolazine concentration (ng/mL)). The ΔQTc data showed scatter.

The mean change in QTc from baseline (pre-dose Day 1) and the mean time specific change from baseline in QTc (absolute change) are listed in the following table:

ECG: QTc Interval (msec)
Summary Statistics, Change from Baseline and Absolute Change from Baseline: All Subjects

Timepoint		Result					Change From Baseline				Time Specific Change From Baseline			
		Mean	SD	Min	Max	N	Mean	SD	Min	Max	Mean	SD	Min	Max
DAY 1	PREDOSE	394.421	17.217	372.32	428.67	18								
	+2 H	393.852	18.275	363.72	428.67	18	-0.568	13.813	-23.06	25.03				
	+4 H	395.038	16.230	369.10	424.41	18	0.618	14.500	-15.49	30.92				
	+12 H	402.959	16.979	367.19	427.91	18	8.538	15.721	-20.77	30.04				
DAY 3	+4 H	397.982	16.945	364.92	429.64	18	3.562	15.172	-25.54	25.51	2.944	12.411	-18.98	35.63
DAY 4	+4 H	402.812	18.301	372.46	443.65	18	8.391	14.784	-18.80	52.10	7.773	17.380	-20.37	42.88
DAY 5	+4 H	398.742	18.319	367.74	425.09	18	4.322	11.040	-9.71	33.54	3.704	14.233	-29.80	30.50
DAY 6	PREDOSE	399.539	19.333	372.32	446.16	18	5.119	15.662	-13.27	54.61	5.119	15.662	-13.27	54.61
	+2 H	400.235	18.720	368.13	436.53	17	7.185	16.973	-22.11	44.98	7.506	11.258	-13.95	22.74
	+4 H	401.315	22.243	370.65	460.00	17	8.264	19.908	-19.87	68.45	6.804	18.765	-15.41	59.23
	+12 H	412.685	19.565	383.02	461.47	17	19.615	17.533	-9.84	69.92	9.694	15.747	-10.25	45.77
DAY 7	+4 H	402.940	18.245	380.00	447.27	17	9.889	17.735	-19.67	55.72	8.429	20.935	-30.29	46.50
DAY 8	+4 H	401.036	18.969	378.80	444.45	17	7.986	17.158	-17.76	52.90	6.525	20.110	-22.28	43.68
DAY 9	PREDOSE	401.798	20.708	365.14	452.26	17	8.748	18.198	-10.76	60.71	8.748	18.198	-10.76	60.71
	+2 H	403.331	17.259	371.47	444.24	17	10.281	17.240	-24.86	52.69	10.602	13.399	-21.61	28.55
	+4 H	400.997	18.243	372.32	443.98	17	7.946	17.532	-21.03	52.43	6.486	18.489	-18.98	43.21
	+12 H	407.861	18.013	379.84	448.00	16	15.586	18.878	-18.17	56.45	5.265	12.415	-12.16	32.30
	+48 H	398.139	17.046	365.95	435.58	16	5.864	20.863	-26.66	44.03	5.864	20.863	-26.66	44.03

Note: Data summarised in the above table are listed in data listing 16.2.8.5.3
Baseline defined as Day 1 predose
Time specific baseline is defined as the equivalent Day 1 time point - Day 1 predose is used as the time specific baseline for the Day 9 +48h assessment

The mean (SD) increase from baseline in QTc 4 hours post-dose on Days 3-5 during ranolazine alone treatment was ranging between 2.9 (12.4) msec and 7.8 (17.4) msec (mean ΔQTcmax). During co-administration of simvastatin to ranolazine on Days 6 through 9 mean apparent ΔQTc ranged between +5.1 (15.7) msec and +10.6 (13.4) msec (mean ΔQTCmax). Individual apparent ΔQTc values ranged between + 60.7msec and - 30.3msec. Maximum increases in QTc were not necessarily observed at peak concentrations of ranolazine.

During treatment with ranolazine the T-wave amplitude decreased relative to Day 1 pre-dose by between -1.07 mm and -3.02 mm. In the absence of ranolazine (Day 1) the T-wave amplitude ranged between 0.29 and -0.77msec.

There were no serious adverse events reported. Dizziness (2 subjects), constipation (1 subject), diarrhoea (2 subjects), nausea (3 subjects) and vomiting (1 subject) were reported.

CONCLUSIONS:

Co-administration of ranolazine 1000 mg bid affects the pharmacokinetics of simvastatin lactone, the metabolite simvastatin acid and the HMG-Co A reductase inhibitory capacity. The mean AUC values for these entities increase 1.86, 2.26,and 1.76 fold when ranolazine is co-administered indicating an interaction. The exposure measures of the 6'-exo-methylenesimvastatin lactone and 3'-hydroxysimvastatin lactone do not change importantly or consistently and co-administration of ranolazine appears not to affect these simvastatin metabolites.
In vitro data with Caco2 cells and liver micrososmes (Study 303.018-N) indicate that ranolazine inhibits the baso-apical transport by P-glycoprotein and the metabolism of simvastatin and other statins. (Ki >20 μM (21'400 ng/mL). The mean Cmax concentration of ranolazine in the present study is lower (3030 ng/mL) than the respective Ki values (8123 ng/mL and 21400 ng/mL).
There exists a linear relationship of ΔQTc and ranolazine plasma concentrations.
Ranolazine decreases the T-wave amplitude.

COMMENTS:

1. In table 2 (p.140 of report) reference (Day 1) and test treatment for 6'-exomethylenesimvastatin (Day 6) were mixed up and as a result the ratio of the geometric means and the 90% confidence intervals are erroneous. Fortunately this does not affect the conclusion regarding equivalence.
2. The value for R^2 of the regression of ΔQTc and the plasma concentrations of ranolazine should have been provided.
3. The data were obtained in healthy males with QTc ≤ 430 msec and may not be extrapolated to female and male patients with the target disease displaying longer QTc intervals.

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STUDY CVT 301-10 - A STUDY TO INVESTIGATE THE EFFECT OF KETOCONAZOLE ON THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF RANOLAZINE IN HEALTHY SUBJECTS

STUDY INVESTIGATOR AND SITE: [

]

Report No.: CVT 301-10
Volume No.: 36-41, ITEM 6

OBJECTIVES:

Primary: To compare the pharmacokinetics of multiple oral doses of ranolazine SR when administered alone and following the co-administration of ketoconazole under steady state conditions of both drugs
Secondary: 1. To further assess the safety and tolerability of multiple oral doses of ranolazine SR when administered alone and following the co-administration of ketoconazole under steady-state conditions of both drugs 2. To further characterize the relationship between the plasma concentration of ranolazine and the QTc interval, when ranolazine is administered alone and following the co-administration of ketoconazole, under steady-state conditions of both drugs

FORMULATIONS:

SR tablets containing 375 mg ranolazine (Lot No. 5863)
Matching placebos
SR tablets containing 500 mg ranolazine (Lot No. 6202)
Matching placebos
Tablets containing 200 mg ketoconazole (Lot Nos. 01FL110, 00EB568, 00FB573, 00KB287)

STUDY DESIGN:

This was a double-blind, randomized, multiple dose, parallel group study involving at least 42 male and female subjects subdivided in 2 groups of 21, Part A and Part B. Six (6) received placebo and 15 active treatment in each part. In Part A 21 subjects received ranolazine/placebo SR 375mg bid for five days followed by ranolazine/placebo SR 375 mg bid daily co-administered with ketoconazole 200 mg bid for four days, followed by a single morning dose of both ranolazine/placebo SR 375 mg and ketoconazole 200mg on Day 10. In Part B 21 subjects received ranolazine/placebo SR 1000 mg bid for five days followed by ranolazine/placebo SR 1000 mg bid co-administered with ketoconazole 200 mg bid for four days, followed by a single morning dose of both ranolazine/placebo SR 1000 mg and ketoconazole 200 mg on Day 10. The subjects were institutionalized throughout the duration of the study. Drug administration in the morning and evening was about 1 hour after breakfast and dinner, respectively.

ASSAY:

Study site monitoring of ranolazine plasma concentrations was performed at [redacted] A HPLC method with fluorescence detection was used. The calibration curve was linear in the range between 1'000 ng/mL and 24'800ng/mL, when the calibration standards were weighted by $1/X^2$ (R^2 >0.99). Accuracy (bias, %) and precision (CV, %) were within the ± 15% limits.
The definitive plasma concentration measurements of ranolazine and the metabolites RS-88640 (CVT 2512), RS-88390 (CVT-2514) and RS-94287 (CVT-2738) were performed at CV Therapeutics in Palo Alto, CA. A LC/MS/MS method [redacted] d-3 was employed as internal standard. The calibration curve was linear in the range between 50 ng/mL and 10'000 ng/mL for ranolazine.and between 10 ng/mL and 2000 ng/mL for the metabolites. The quantitation range for ranolazine in urine was between 200 ng/mL and 50'000 ng/mL for ranolazine. Mean accuracy (bias %) for ranolazine and the metabolites in urine was within the ± 15% limits. The precision for ranolazine and RS-94287 (CVT 2738) was within the ± 15% limits. For the metabolites RS-88390 (CVT-2514) and RS-88640 (CVT-2512) precision was not determined in urine.

Blood Sample Collection:

Blood samples for the determination of the pharmacokinetics of ranolazine were taken at the following times:
Days 1, 3, 4-6, 8-10: Pre a.m. dose
Day 5: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 7, 9, 12 hours post a.m. dose
Day 10: 0.5, 1, 1.5, 2.5, 3, 3.5, 4, 5, 7, 9, 12, and 16 hours post a.m. dose
Day 11: 24 and 36 hours post a.m. dose Day 10
Day 12: 48 hours post a.m. dose on Day 10

Blood samples for the therapeutic monitoring of ranolazine were taken at the following times:
Days 6-9: Pre a.m. dose

Urine Sample Collection:

Total urine volumes were collected as follows:
Days 5 and 10: from 0-12 hours post a.m. dose.

The steady-state plasma concentration profiles of ranolazine and the three metabolites were analyzed using non-compartment model dependent methods with WinNonlin™ Professional. The parameters Css,min, Cssmax, and the corresponding times, tssmin and tss,max, and C12, AUCτ, PTF (peak to trough fluctuation), λz, t1/2z and Cl_R for ranolazine and the three metabolites were computed. Css,min, Css,max, tssmin, tss,max and C12 were direct experimental observations. AUCτ was obtained by applying the linear trapezoidal rule. PTF was obtained from [(Cssmax-

Css,min)/Cave] •100. Cl_R was computed from Aeτ/AUCτ, where Aeτ correspond to the urinary excreted amounts of ranolazine or metabolites excreted during a dose interval. The metabolic ratio was computed from AUCmetabolite/AUC parent.

The logarithmically transformed Css,max and AUCτ values of ranolazine and metabolites after both doses of ranolazine in the presence (test) and absence (reference) of ketoconazole were compared statistically using ANOVA. Following back-transformation the point estimates and the 90% confidence intervals for the ratio of the least square means of the test treatment/reference treatment expressed as percentage were calculated. The analysis of tss,max used the Wilcoxon matched pairs test.

Safety:

Standard 12 Lead ECGs recordings were performed on the following times:
Day -1: -24, -23, -22, -21, -20, -19, -17, -15, -12 and -8 hours pre a.m. dose Day 1.
Days 1-4 and 6-9: Pre a.m. dose
Day 5: Pre a.m. dose, 1, 2, 3, 4, 5, 7, 9, and 12 hours post a.m. dose
Day 10: Pre a.m. dose, 1, 2, 3, 4, 5, 7, 9, 12, 16, 24, 36, and 48 hours post a.m. dose
Day 11: 24 and 36 hours post a.m. dose of Day 10
Day 12: 48 hours post a.m. dose of Day 10

Supine and standing systolic and diastolic blood pressure and heart rate were determined at the following times:
Day -2: 36 hours pre a.m.dose of Day 1
Day -1: -24 and -12 hours pre a.m. dose of Day 1
Days 1- 10: Pre a.m. dose, 4, and 12 hours post a.m. dose
Day 11: 24 hours post a.m. dose of Day 10
Day 12: 48 hours post a.m.dose of Day 10

The study physician or deputy examined each ECG as measured by the machine.
The final analysis of the ECGs was performed at the ECG Core Laboratory.
Time specific ΔQTc values were calculated from the difference between the post-dose QTc and the QTc at pre-treatment baseline measured at corresponding times of the day.
Data from 43 subjects receiving placebo, ranolazine alone or in combination with ketoconazole were used. To determine the relationship between ΔQTc and the plasma concentrations of ranolazine NONMEM and first order estimation (FOCE) was used. Initially a linear model E=Eo+ Slope• C was fitted to the data, where E is the change in QTc from the baseline, E0 is the change in QTc from baseline at pre-dose and C is the observed ranolazine concentration. Since the 95% confidence intervals included zero a linear model with no intercept was fitted to the data. Inter-subject variability in the slope used an exponential error model.
The magnitude of the residual error variability in QTc form the baseline was modeled using an additive error model and the additive residual variability in the model was an approximation taken as the square root of the additive variance expressed in units of standard deviation (μg/mL). When possible the 95% confidence interval in the parameter estimates was calculated from 95% CI=[P±1.96 • s.e.(P)], where P is the point estimate of the population mean of the

parameter, s.e.(P) is the standard error of P. Precision of each parameter estimate was calculated as the s.e. divided by the parameter estimate multiplied by 100.

The QT values were corrected for heart rate in accordance with $QTc = QT/RR^{0.28}$.

RESULTS:

A total of 50 subjects, 25 males and 25 females, with a mean age of 26 years were recruited for the study. Forty-five subjects were Caucasians, three Blacks, one Asian and one Chinese.

Twenty one (21) subjects received ranolazine SR/placebo in Part A of the study and 20 completed the treatment. One subject was withdrawn on Day 5 after receiving 375mg ranolazine because of an abnormal liver function test. Twenty-two (22) subjects received ranolazine SR/placebo during Part B and 16 completed the treatment Four subjects were withdrawn on Day 6, 8, 5, and 6 respectively, due to adverse events. A fifth subject was withdrawn on Day 5 because of QTc prolongation and a sixth subject withdrew consent on Day 6.

PK:

The mean pharmacokinetic parameters for ranolazine and the three metabolites RS-88640 (CVT-2512), RS 88390 (CVT-1514) and RS-94287 (CVT-2738) and the results of the statistical analysis are listed in the following tables:

Mean (±SD or range for t_{max} and t_{min}) pharmacokinetic parameter estimates for ranolazine following twice daily administration of 375 mg or 1,000 mg ranolazine alone and when co-administered with 200 mg ketoconazole

Pharmacokinetic Parameter	Treatment			
	375 mg Ranolazine	375 mg Ranolazine + 200 mg Ketoconazole	1,000 mg Ranolazine	1,000 mg Ranolazine + 200 mg Ketoconazole
$C_{ss,min}$ (ng/mL)	222.3 (95.7)	936.0 (638.4)	867.7 (350.9)	3930.0 (1406.9)
$t_{ss,min}$ (h)[a]	11.93 (0.00-12.02)	12.00 (0.00-12.05)	11.58 (0.00-12.07)	11.99 (0.00-12.02)
$C_{ss,max}$ (ng/mL)	739.0 (361.4)	1900.2 (972.9)	2320.0 (705.1)	7330.8 (1956.4)
$t_{ss,max}$ (h)[a]	2.53 (2.00-5.00)	3.74 (2.00-7.05)	3.50 (1.02-7.00)	3.50 (2.00-7.00)
C_{12} (ng/mL)	235.5 (91.7)	968.1 (668.5)	946.4 (429.1)	4182.5 (1623.4)
C_{av} (ng/mL)	440.6 (183.1)	1420.7 (795.6)	1591.3 (471.7)	5796.2 (1656.5)
PTF (%)	111.83 (28.94)	75.54 (19.83)	91.89 (20.58)	61.58 (20.35)
AUC_τ (ng·h/mL)	5286.6 (2197.1)	17047.8 (9546.8)	19095.4 (5660.5)	69554.9 (19877.6)
$t_{1/2}$ (h)	–	6.30 (1.82)	–	5.33 (1.33)
CL_R (L/h)	–	–	2.40 (1.44)	1.48 (0.79)

[a] Median (range)

Mean (±SD or range for t_{max} and t_{min}) pharmacokinetic parameter estimates for CVT-2512 (RS-88640) following twice daily administration of 375 mg or 1,000 mg ranolazine alone and when co-administered with 200 mg ketoconazole

Pharmacokinetic Parameter	Treatment			
	375 mg Ranolazine	375 mg Ranolazine + 200 mg Ketoconazole	1,000 mg Ranolazine	1,000 mg Ranolazine + 200 mg Ketoconazole
$C_{ss,min}$ (ng/mL)	73.36 (28.73)	63.57 (27.59)	125.6 (74.1)	84.78 (61.80)
$t_{ss,min}$ (h) [a]	1.00 (0.00-12.02)	2.50 (0.00-9.00)	3.01 (0.00-12.07)	4.00 (0.50-12.02)
$C_{ss,max}$ (ng/mL)	99.38 (40.68)	80.47 (34.60)	159.9 (92.7)	103.00 (68.14)
$t_{ss,max}$ (h) [a]	7.00 (0.00-11.93)	4.51 (0.00-12.00)	5.00 (0.00-9.05)	8.00 (0.00-12.00)
C_{12} (ng/mL)	83.93 (37.42)	73.73 (35.37)	128.7 (73.3)	94.88 (64.24)
C_{av} (ng/mL)	87.79 (37.46)	72.60 (31.08)	143.2 (84.7)	92.51 (66.70)
PTF (%)	29.98 (7.01)	23.35 (8.03)	24.09 (6.81)	28.95 (19.26)
AUC_τ (ng-h/mL)	1053.4 (449.5)	871.2 (373.0)	1718.7 (1016.2)	1110.1 (800.4)
MR	0.233 (0.140)	0.081 (0.073)	0.100 (0.080)	0.020 (0.021)
CL_R (L/h)	–	–	8.34 (2.78)	5.81 (1.28)

[a] Median (range)

Mean (±SD or range for t_{max} and t_{min}) pharmacokinetic parameter estimates for CVT-2514 (RS-88390) following twice daily administration of 375 mg or 1,000 mg ranolazine alone and when co-administered with 200 mg ketoconazole

Pharmacokinetic Parameter	Treatment			
	375 mg Ranolazine	375 mg Ranolazine + 200 mg Ketoconazole	1,000 mg Ranolazine	1,000 mg Ranolazine + 200 mg Ketoconazole
$C_{ss,min}$ (ng/mL)	205.9 (66.6)	575.0 (148.3)	359.1 (195.6)	686.8 (398.6)
$t_{ss,min}$ (h) [a]	11.92 (0.00-12.02)	11.96 (0.00-12.05)	11.88 (0.00-12.07)	6.52 (0.00-12.02)
$C_{ss,max}$ (ng/mL)	415.1 (142.3)	874.4 (223.2)	627.7 (367.3)	1017.0 (630.2)
$t_{ss,max}$ (h) [a]	3.52 (2.50-5.00)	4.00 (3.00-5.00)	4.00 (2.00-7.00)	3.75 (2.00-7.00)
C_{12} (ng/mL)	225.8 (88.3)	600.6 (165.5)	372.6 (202.0)	720.6 (418.0)
C_{av} (ng/mL)	312.0 (109.1)	735.9 (176.9)	506.2 (292.1)	862.7 (521.3)
PTF (%)	101.23 (45.53)	51.50 (24.37)	73.10 (34.21)	45.15 (21.00)
AUC_τ (ng-h/mL)	3744.2 (1309.0)	8830.5 (2122.2)	6074.9 (3505.0)	10352.1 (6255.1)
$t_{1/2}$ (h)	–	13.18 (4.99)	–	12.10 (4.46)
MR	0.807 (0.401)	0.692 (0.395)	0.332 (0.220)	0.175 (0.152)
CL_R (L/h)	–	–	1.50 (0.86)	1.06 (0.42)

[a] Median (range)

Mean (±SD or range for t_{max} and t_{min}) pharmacokinetic parameter estimates for CVT-2738 (RS-94287) following twice daily administration of 375 mg or 1,000 mg ranolazine alone and when co-administered with 200 mg ketoconazole

Pharmacokinetic Parameter	Treatment			
	375 mg Ranolazine	375 mg Ranolazine + 200 mg Ketoconazole	1,000 mg Ranolazine	1,000 mg Ranolazine + 200 mg Ketoconazole
$C_{ss,min}$ (ng/mL)	136.7 (44.0)	107.54 (52.54)	470.4 (106.1)	415.9 (112.8)
$t_{ss,min}$ (h)[a]	11.92 (0.00-12.02)	3.50 (0.00-12.05)	11.98 (0.00-12.07)	3.26 (2.00-12.02)
$C_{ss,max}$ (ng/mL)	210.7 (77.3)	131.49 (70.01)	664.0 (153.4)	521.8 (145.3)
$t_{ss,max}$ (h)[a]	4.00 (2.00-5.00)	7.00 (0.00-12.00)	4.00 (0.00-7.00)	9.00 (0.00-12.00)
C_{12} (ng/mL)	143.3 (45.8)	118.89 (63.93)	483.9 (121.8)	494.4 (144.2)
C_{av} (ng/mL)	173.1 (59.9)	119.71 (61.28)	580.9 (129.9)	468.1 (132.7)
PTF (%)	41.22 (12.81)	18.66 (7.48)	33.13 (9.47)	22.26 (5.09)
AUC_τ (ng·h/mL)	2076.6 (718.8)	1436.5 (735.4)	6971.2 (1558.2)	5617.7 (1592.9)
$t_{½z}$ (h)	–	13.37 (3.40)	–	9.46 (2.85)
MR	0.409 (0.110)	0.095 (0.041)	0.390 (0.113)	0.085 (0.026)
CL_R (L/h)	–	–	13.20 (4.51)	9.72 (2.40)

[a] Median (range)

Statistical Analysis of the Effect of 200 mg Ketoconazole on the Pharmacokinetics of Ranolazine

Summary of the 90% confidence intervals and the statistical comparison of the pharmacokinetic parameters of ranolazine alone and in the presence of 200 mg ketoconazole

Treatment	Parameter	90% Confidence Intervals			p-value
		Lower Limit	Point Estimate[a]	Upper Limit	
375 mg Ranolazine + 200 mg Ketoconazole	C_{max}	222.55	256.56	295.80	<0.0001
	AUC_τ	258.26	299.97	348.37	<0.0001
1,000 mg Ranolazine + 200 mg Ketoconazole	C_{max}	320.43	348.72	379.51	<0.0001
	AUC_τ	347.99	387.40	431.29	<0.0001

[a] Test (ranolazine + 200 mg ketoconazole)/reference (ranolazine alone)

Summary of the 90% confidence intervals and the statistical comparison of the pharmacokinetic parameters of CVT-2512 (RS-88640) alone and in the presence of 200 mg ketoconazole

Treatment	Parameter	90% Confidence Intervals			p-value
		Lower Limit	Point Estimate[a]	Upper Limit	
375 mg Ranolazine + 200 mg Ketoconazole	C_{max}	68.00	76.03	85.00	0.0008
	AUC_τ	68.94	76.82	85.62	0.0008
1,000 mg Ranolazine + 200 mg Ketoconazole	C_{max}	63.39	70.90	79.30	0.0002
	AUC_τ	43.25	60.49	84.60	0.0210

[a] Test (ranolazine + 200 mg ketoconazole)/reference (ranolazine alone)

Summary of the 90% confidence intervals and the statistical comparison of the pharmacokinetic parameters of CVT-2514 (RS-88390) alone and in the presence of 200 mg ketoconazole

Treatment	Parameter	90% Confidence Intervals			p-value
		Lower Limit	Point Estimate*	Upper Limit	
375 mg Ranolazine + 200 mg Ketoconazole	C_{max}	187.95	206.33	226.51	<0.0001
	AUC_τ	208.74	231.29	256.31	<0.0001
1,000 mg Ranolazine + 200 mg Ketoconazole	C_{max}	177.46	201.15	228.01	<0.0001
	AUC_τ	187.50	212.17	240.08	<0.0001

* Test (ranolazine + 200 mg ketoconazole)/reference (ranolazine alone)

Summary of the 90% confidence intervals and the statistical comparison of the pharmacokinetic parameters of CVT-2738 (RS-94287) alone and in the presence of 200 mg ketoconazole

Treatment	Parameter	90% Confidence Intervals			p-value
		Lower Limit	Point Estimate*	Upper Limit	
375 mg Ranolazine + 200 mg Ketoconazole	C_{max}	53.06	59.65	67.07	<0.0001
	AUC_τ	58.01	64.73	72.22	<0.0001
1,000 mg Ranolazine + 200 mg Ketoconazole	C_{max}	77.19	84.97	93.53	0.0111
	AUC_τ	79.03	85.93	93.45	0.0078

* Test (ranolazine + 200 mg ketoconazole)/reference (ranolazine alone)

Relative to treatment with ranolazine/placebo, co-administration of 200 mg qd ketoconazole and ranolazine 375 mg bid increased arithmetic mean Css,max and AUCτ of ranolazine 2.57 and 3.22 fold, respectively. The mean Css,max and AUCτ values for RS-88390 (CVT-2514) increased 2.11 and 2.35 fold, respectively. In contrast, the exposure measures for the metabolites RS-88640 (CVT-2512) and RS-94287 (CVT-2738) decreased in the presence of ketoconazole. The mean Css,max and AUCτ -values for RS-88640 (CVT-2512) decreased by 19.0% and 17.0%, respectively, and the respective values for RS-94287 (CVT-2738) decreased by 37.6% and 30.8%.

Relative to treatment with ranolazine/placebo, co-administration of 200 mg qd ketoconazole and ranolazine 1000 mg bid increased the mean Css,max and AUCτ values of ranolazine 3.16 and 3.64 fold, respectively, relative to treatment with ranolazine/placebo. The mean Css,max and AUCτ values for RS-88390 (CVT-2514) increased 1.62 and 1.70 fold, respectively. In contrast, the exposure measures for RS-88640 (CVT-2512) and RS-94287 CVT-2738) decreased in the presence of ketoconazole. The mean Css,max and AUCτ values for RS-88640 (CVT-2512) decreased by 35.6% and 35.4%, respectively, and the respective values for RS-94287 (CVT-2738) decreased by 21.4% and 19.4%.

In the presence of ketoconazole the 90% confidence intervals for either exposure measure with all 4 analytes exceed the 80% to 125%. Range. This was true for both dose levels of ranolazine.

The values for tss,max for ranolazine and the metabolites did not change when ketoconazole was co-administered.

Safety:

The summary changes in QTc (msec) from baseline on Days 5 or 10 with the different treatments are shown in the following tables:

375 mg ranolazine bid, Day 5:

Nominal Time (h)	Descriptive Statistics					
	N	Mean	SD	Min	Median	Max
0	14	-5.4	15.7	-31	-3	19
1	15	-5.1	9.8	-17	-5	16
2	15	-4.0	11.0	-18	-7	17
3	15	1.1	14.6	-22	0	23
4	15	-0.9	11.8	-23	-1	23
5	15	1.2	11.7	-15	-2	33
7	15	-4.2	11.7	-22	-3	17
9	15	0.8	7.6	-12	-1	14
12	15	3.3	14.7	-16	2	29
16	15	0.1	12.2	-22	2	21
24	14	-2.2	17.0	-38	2	21

375 mg ranolazine bid & 200 mg ketoconazole qd, Day 10:

Nominal Time (h)	Descriptive Statistics					
	N	Mean	SD	Min	Median	Max
0	14	4.4	14.4	-32	6	25
1	14	0.4	11.0	-22	1	22
2	14	5.5	14.6	-20	7	38
3	14	6.1	18.1	-20	5	45
4	14	4.1	14.0	-30	6	23
5	14	5.5	18.8	-32	6	38
7	14	6.6	10.6	-10	6	30
9	14	5.4	13.2	-19	8	24
12	14	8.1	13.3	-11	10	34
16	14	8.4	14.0	-18	8	41
24	14	4.9	9.9	-16	8	21
36	14	3.6	12.7	-17	2	27
48	14	-1.7	17.2	-36	2	29

375 m placebo bid, Day 5:

Nominal Time (h)	Descriptive Statistics					
	N	Mean	SD	Min	Median	Max
0	6	2.5	6.1	-5	2	10
1	6	-12.8	14.0	-28	-17	4
2	6	-5.7	19.6	-37	-1	20
3	6	2.7	10.1	-7	2	14
4	6	0.7	13.5	-22	2	19
5	6	-1.3	19.8	-32	1	23
7	6	-4.5	17.8	-37	1	10
9	6	-3.2	9.9	-16	1	6
12	5	-3.6	4.7	-9	-5	3
16	6	-5.7	21.4	-40	-5	22
24	6	9.0	19.7	-12	9	41

375 mg placebo bid & ketoconazole 200 mg qd, Day 10:

Nominal Time (h)	Descriptive Statistics					
	N	Mean	SD	Min	Median	Max
0	6	0.3	19.7	-34	5	22
1	6	-12.0	12.2	-32	-7	-2
2	6	2.0	12.6	-15	5	13
3	6	13.0	5.6	6	12	21
4	6	4.2	8.9	-12	5	14
5	6	1.5	18.0	-16	-3	32
7	6	-11.8	16.2	-37	-11	9
9	6	3.7	9.8	-7	2	21
12	5	4.2	9.3	-11	5	13
16	6	-7.0	20.7	-36	-4	21
24	6	4.2	19.5	-15	-2	36
36	5	9.8	19.3	-18	18	29
48	6	1.0	19.9	-28	4	31

1000 mg ranolazine bid, Day 5:

Nominal Time (h)	Descriptive Statistics					
	N	Mean	SD	Min	Median	Max
0	16	-2.6	14.7	-29	-1	26
1	16	0.2	11.3	-28	4	15
2	16	8.5	15.6	-17	8	46
3	16	7.1	17.9	-27	11	36
4	16	11.3	15.7	-8	10	57
5	15	13.1	17.4	-17	19	39
7	16	4.4	15.2	-22	8	26
9	16	7.5	16.5	-23	12	36
12	16	2.6	8.5	-10	1	22
24	15	6.7	14.4	-14	7	32

1000 mg ranolazine & 200 mg ketoconazole, Day 10:

Nominal Time (h)	Descriptive Statistics					
	N	Mean	SD	Min	Median	Max
0	12	14.2	14.1	-15	16	37
1	12	19.1	14.7	-7	22	42
2	12	26.3	17.4	3	25	61
3	12	32.1	16.8	-14	36	49
4	12	30.0	18.9	4	26	77
5	12	34.3	24.2	6	31	84
7	12	16.9	21.6	-33	18	50
9	12	24.1	12.7	4	26	42
12	12	21.6	12.6	5	21	45
16	12	14.1	16.6	-24	14	39
24	12	20.8	20.8	-11	16	59
36	12	10.0	8.3	-5	13	21
48	12	-1.2	21.6	-33	3	41

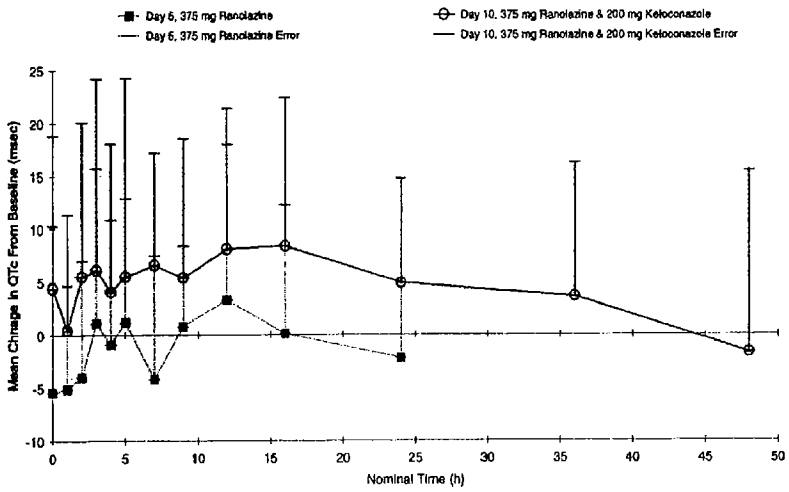
1000 mg placebo bid, Day 5:

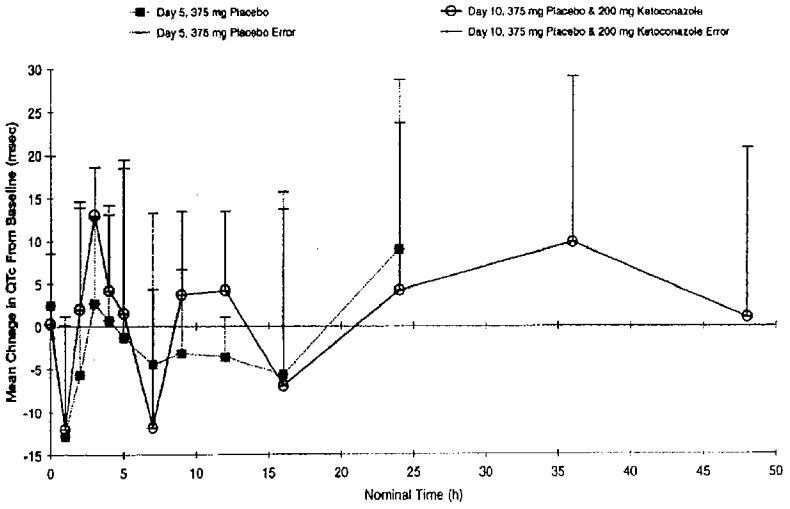
Nominal Time (h)	Descriptive Statistics					
	N	Mean	SD	Min	Median	Max
0	6	-11.3	8.7	-24	-12	0
1	6	-9.8	12.1	-27	-11	10
2	6	2.5	10.8	-7	0	22
3	6	8.2	11.9	-13	14	17
4	6	0.8	8.3	-10	1	14
5	6	2.5	13.7	-12	1	22
7	6	-4.2	17.9	-24	-12	21
9	6	-9.3	13.0	-27	-8	7
12	6	-5.5	7.1	-14	-6	6
16	6	-8.8	10.0	-21	-9	6
24	5	-6.2	12.9	-18	-11	10

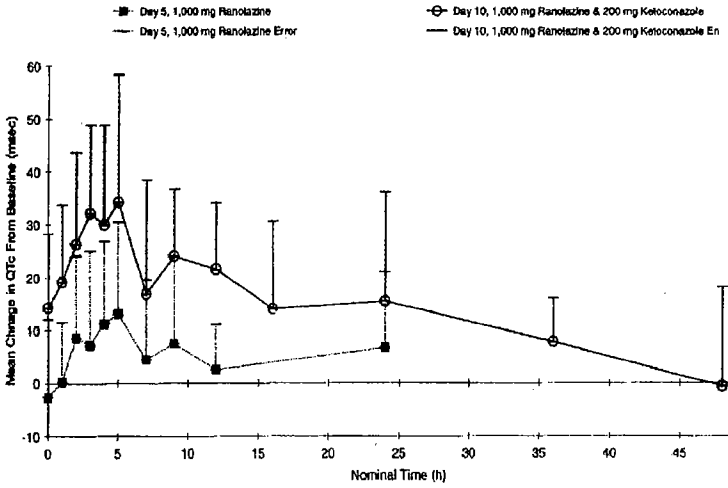
1000 mg placebo bid & 200 mg ketoconazole qd, Day 10:

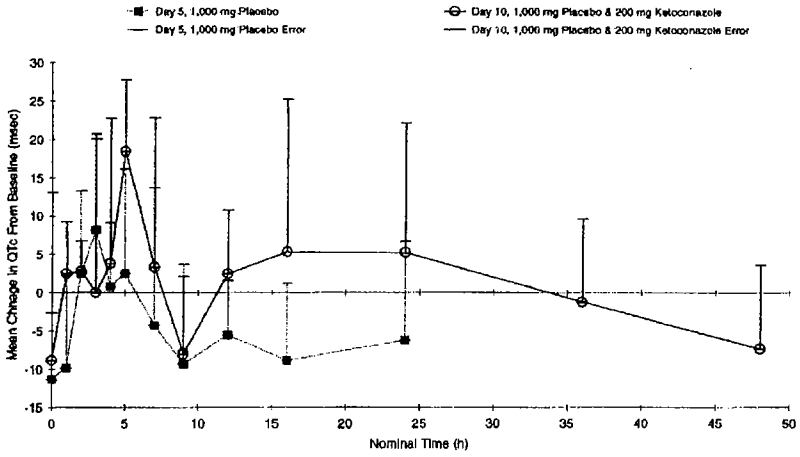
Nominal Time (h)	Descriptive Statistics					
	N	Mean	SD	Min	Median	Max
0	4	-8.8	21.9	-40	-2	9
1	4	2.5	6.8	-5	2	11
2	4	2.8	4.0	-3	4	6
3	4	0.0	20.8	-26	1	25
4	4	3.8	19.0	-21	6	24
5	4	18.5	9.3	5	22	26
7	4	3.3	19.6	-12	-2	29
9	4	-8.0	10.1	-23	-4	-1
12	4	2.5	8.3	-5	1	14
16	4	5.3	20.0	-14	2	32
24	4	-1.5	9.3	-10	-3	10
36	4	-1.3	12.0	-14	0	9
48	4	-11.3	11.6	-27	-10	1

Plots of the mean changes in QTc are shown in the following figures:



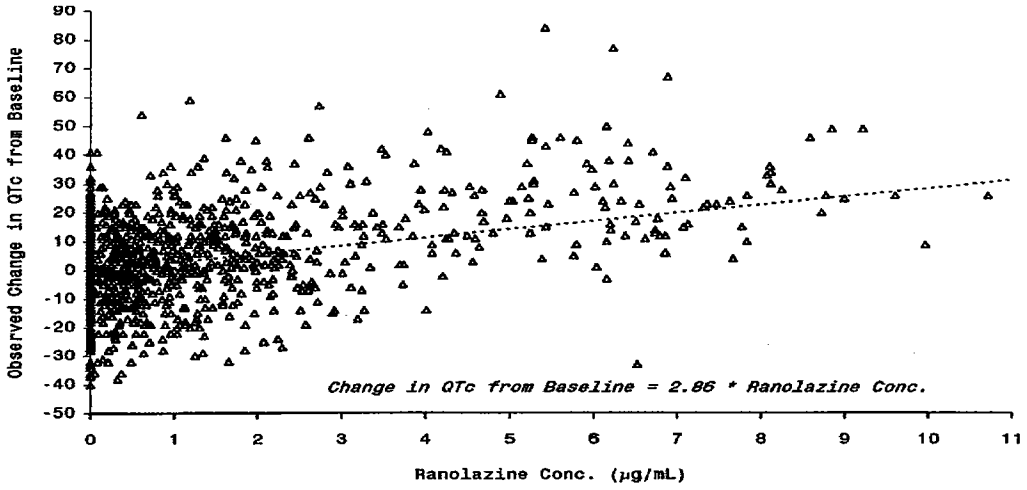






The standard deviation about the mean ΔQTc values were large. The number of subjects in the placebo receiving groups was small (n=4-6). At the 375 mg dose level of ranolazine the mean (SD) apparent ΔQTmax values in the absence of ketoconazole was 3.3 (14.7) msec and increased to 8.4 (14.0) msec in the presence of ketoconazole. At the 1000 mg ranolazine level the mean apparent ΔQTc was 13.1 (17.4) msec in the absence of ketoconazole and increased to 34.3 (24.2) msec in the presence of ketoconazole. The mean apparent ΔQTcmax values during the placebo treatments were 9.0 (19.7) msec (375 mg placebo) and 8.2 (11.9) msec (1000 mg placebo). The respective values increased in the presence of ketoconazole to 13.0 (5.6) msec and 18.5 (9.3) msec. The co-administration of ketoconazole to the different treatments resulted consistently in an increase of apparent ΔQTcmax that was greatest (+ 21.2msec) when ketoconazole was co-administered with 1000 mg ranolazine.

A plot of the individual ΔQTc on the plasma ranolazine concentrations using an empirical linear model is shown in the following figure:



The final estimates for the population point estimate and precision for the slope of the linear relationship between ΔQTc and plasma ranolazine concentrations are shown in the following table:

Parameter	Estimate [95% CI]	Precision (%CV)[§]
Slope (msec per 1000 ng/mL (1 µg/mL) of ranolazine)	2.86 [1.43 – 4.28]	25.4
Inter-patient variability in Slope (%CV)*	100.5 [50.7 – 176.3]	38.0
Additive residual variability (msec)	13.6	9.3

[§]Precision was calculated as the s.e. 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. The approximation is due to the expansion of the exponential function only to first-order.

An increase of 2.86 msec in QTc per 1000 ng/mL ranolazine and an inter-patient variability about the slope of 100% were estimated. The estimated residual variability of 13.6 msec was large. The impact of gender or ketoconazole co-administration on the slope of the ΔQTc to ranolazine concentration relationship was not statistically significant.
Administration of 1000 mg ranolazine in the presence and absence of ketoconazole was sometimes associated with changes in the amplitude and morphology of the T-wave.

No serious adverse events or death occurred in the study. Six subjects were withdrawn because of AEs. One subject on 375 mg ranolazine had an abnormal liver function test. A second subject on 1000 mg ranolazine experienced nausea. A third subject on placebo 1000 mg and ketoconazole 200 mg had chest pain. The ECG recordings of a fourth subject on 1000 mg ranolazine and 200 mg ketoconazole exceeded the limits stated in the protocol (QTc>130% QTc at baseline or QTc>500 msec, whichever is lower). A fifth and a sixth subject both receiving 1000 mg ranolazine and 200 mg ketoconazole experienced dizziness and visual disturbance. Compared to treatment with placebo, a much greater incidence of AEs was noted in the treatments with ranolazine 1000 mg + ketoconazole 200mg, ranolazine 1000mg, and ranolazine 375 mg + ketoconazole 200mg. The most frequent AEs associated with the ranolazine treatments were headache, dizziness, nausea, somnolence and constipation.

CONCLUSION:

Co-administration of ketoconazole 200 mg qd to ranolazine 375 mg or 1000 mg bid results in statistically and clinically significant increases of the exposure measures of ranolazine: At the lower ketoconazole dose level mean arithmetic Css,max and AUCτ of ranoolazine increased 2.57 and 3.22 fold, respectively, and at the higher dose level Css,max and AUCτ increased 3.16 and 3.64 fold, respectively. The extent of the interaction appears not to depend on the ratio of the doses of ketoconazole and ranolazine. The exposure measures for the metabolite, RS-88390 (CVT-2514), are also enhanced after co-administration of ketoconazole. In contrast, the Css,max and AUCτ values for the other 2 measured metabolites, RS-88340 (CVT-2512) and RS-94287 (CVT-2738), are smaller in the presence than in the absence of ketoconazole. Ketoconazole is known to primarily inhibit CYP 3A4. In vitro data indicate that ketoconazole inhibits the metabolism of ranolazine (Study CVT 303.011-N). In vitro data (CVT 303.009-N) indicate that the formation of RS-88640 (CVT-2514) and RS-94287 (CVT-2738) is CYP 3A4 catalyzed, whereas RS-88390 (CV-2514) is presumably generated by CYP 2D6.

Co-administration of 200 mg ketoconazole to ranolazine 375 mg or 1000 mg results in an increase in mean apparent ΔQTcmax of 5.1 msec and 21.2 msec, respectively. However, co-administration of ketoconazole 200 mg to placebo is associated with an increase in apparent ΔQTcmax of 10.3msec. On the assumption that ketoconazole does not affect the QTc interval, the data suggest that only the increase in ΔQTcmax observed at the 1000 mg dose level of ranolazine may be real. However, the large inter and intrasubject variation in ΔQTc must be considered.

ΔQTc is linearly related to the plasma concentration of ranolazine and the slope of the relationship indicates an increase in ΔQTc of 2.86 msec/1000 ng/mL ranolazine.
Compared to treatment with placebo an important increase in the incidence of AEs was noted in the treatments with 1000 mg ranolazine + ketoconazole, 1000 mg ranolazine alone, and 375 mg ranolazine 375 mg + ketoconazole. The most frequent AEs associated with the ranolazine treatments were headache, dizziness, nausea, somnolence and constipation.

COMMENTS:

1. The precision of the assay in urine for the metabolites RS-88390 (CVT-2514) and 886410 (CVT-2512) was not provided.
2. The results obtained in subjects receiving 200 mg ketoconazole qd co-administered with ranolazine 1000mg bid cannot be extrapolated to subjects receiving 400 mg ketoconazole qd, the highest labeled dose.
3. The data were obtained in healthy subjects with QTc $\leq$ 420 msec in males and $\leq$ 437 msec in females and may not be extrapolated to patients with the target disease and longer QTc intervals.

Appears This Way
On Original

STUDY CVT 301-13 - AN OPEN-LABEL, MULTIPLE DOSE STUDY TO EVALUATE THE EFFECT OF PAROXETINE ON THE PHARMACOKINETICS OF RANOLAZINE SR AND MAJOR METABOLITES DURING STEADY-STATE CONDITIONS FOR BOTH DRUGS, AND TO EVALUATE THE EFFECT OF RANOLAZINE SR MONOTHERAPY ON THE PHENOTYPE FOR CYP2D6

STUDY INVESTIGATOR AND SITE: [ ]

Report No.: 301-13
Volume No.: 44-48, ITEM 6

OBJECTIVES:

Primary: To evaluate the effect of paroxetine at steady state on the pharmacokinetics of ranolazine and major metabolites at steady state
Secondary: To evaluate: 1. The effect of ranolazine at steady state on the phenotype for CYP 2D6 2. The effect of paroxetine administered in combination with ranolazine on the QTc interval 3. The safety and tolerability of ranolazine when administered in combination with paroxetine

FORMULATIONS:

SR tablets containing 500 mg ranolazine (Lot No.9G2714A)
Paxil® tablets containing 20 mg paroxetine hydrochloride (Lot No. 20261B11, SmithKlineBeecham)
Benylin® containing 30 mg/mL dextrometorphan hydrobromide (Lot No.33480L/58351L, Parke-Davis)

STUDY DESIGN:

This was a single-center, open-label, multi-dose pharmacokinetic study. Subjects received repeated dosing of ranolazine SR 1000 mg bid to steady state. Paroxetine, 20 mg qd was then added with multiple dosing to steady state for both drugs. Pharmacokinetic profiles for ranolazine were documented on Day 4 at steady state, before commencing the repeated paroxetine dosing, and after the last dose on Day 12 at steady state for both drugs. The subjects were to be healthy male or non-pregnant, non-breast feeding female subjects in the age between 18 and 60 years.
The dose regimen for ranolazine and paroxetine is shown in the following scheme:

Study Medication	Time of Day	Dosing Regimen (Days)											
		1	2	3	4	5	6	7	8	9	10	11	12
Ranolazine (mg)	0800	1500	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
	2000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Paroxetine (mg)	0800					20	20	20	20	20	20	20	20

The subjects were instructed to take the ranolazine and paroxetine tablets with 150 ml water while sitting, semi-recumbant, or standing. The subjects fasted overnight (minimum of 10 hours). The subjects received 30 mg dextrometorphan with 240 mL of water in the evening of Days-1, 4 and 11.

ASSAY:

Ranolazine and metabolites:

The plasma concentrations of ranolazine, RS-88390 (CVT-2514), RS-88640 (CVT-2512) and RS-94287 (CVT-2738) were measured at CV Therapeutics, Palo Alto, CA, using a LC/MS/MS method with positive ion electronspray ionization interface with multiple reaction-monitoring. d3-ranolazine was used as internal standard. The respective quantitation range for ranolazine was 50 ng/mL to10'000 ng/mL and for the metabolites 10 ng/mL to 2000 ng/mL (R>0.9939). Accuracy (bias, %) and precision (CV, %) determined from the QC samples for ranolazine and the metabolites were within the ± 15% limits.

Paroxetine:

The plasma concentrations of paroxetine were determined by [ ] a LC/MS/MS method. The quantitation range was 0.2 ng/mL to 100 ng/mL (R^2 >0.997). Between batch accuracy (bias, %) and precision (CV, %) determined from the QC samples were within the ± 15% limits.

Dextrometorphan and Dextrorphan:

Urine concentrations of dextrometorphan and dextrorphan were determined by LC/MS/MS at [ ]. The quantitation range for dextrometorphan was between 1.0 ng/mL and 1000 ng/mL and for dextrorphan between 20 ng/mL and 20'000 ng/mL (R>0.999). The inter-assay precision and accuracy determined from the QC samples were for both analytes in the presence of paroxetin, ranolazine and its metabolites within the ± 15% limits.

Blood Sample Collection:

Separate blood samples were taken for the determination of ranolazine and metabolites and paroxetine as follows:

Ranolazine and Metabolites:

Days 1-3: Pre a.m. and p.m. doses
Day 4: Pre-dose, and 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 7, 9 and 12 hours post a.m. dose
Days 5-11: Pre a.m. and p.m. doses
Day 12: Pre-dose, and 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 7, 9, 12 and 16 hours after last dose
Day 13: 24 and 36 hours after last dose
Day14: 48 hours after last dose

Paroxetine:

Days 5-11: Pre-dose
Day 12: Pre-dose and 12 hours after last dose
Day13: 24 hours after last dose

Urine Sample Collection

Dextrometorphan and Dextrorphan:

Days-1, 4 and 11: Urine was sampled prior to each dextrometorphan dose and total urine volumes were collected for 8 hours following dextrometorphan dosing.

PK and Statistical Analysis:

Morning and evening trough concentrations of ranolazine and the metabolites were determined daily. Cmax, Tmax and AUC0-tau for ranolazine and the metabolites were determined on Days 4 and 12. The Kel and t1/2 were computed on Day 12. Standard compartment model independent methods were used.
Daily trough concentrations were determined for paroxetine.
Dextrometorphan and dextrorphan concentrations and drug/metabolite ratios were determined in defined pre-dose and 8 hour post-dose urine collection. CYP 2D6 metabolic status (fast or slow) was reported for each collection. A drug/metabolite ratio of < 0.3 indicated fast/extensive metabolism and a ratio of > 0.3 indicated slow/poor metabolism.
A parametric normal theory general linear model was applied to the ln transformed Cmax and AUC0-tau parameter values of ranolazine. The geometric least squares mean Cmax and AUC0-tau ratios and associated 90% confidence intervals (Day 12 versus Day 4) for ranolazine were calculated. The Wilcoxon Signed Rank test was used to compare ranolazine Tmax between Days 4 and 12. Attainment of steady state on Days 4 and 12 for ranolazine was tested by determining whether the mean slope of the trough concentrations was statistically significantly different from

zero. The attainment of steady state for paroxetine on Day 12 was evaluated by performing a paired t-test with the trough concentrations on Days 12 and 13.

Safety:

Standard 12 Lead ECG recordings were performed:
Day –1:12 hours prior to first dose
Day 1: Pre a.m. dose and 2, 4, 8, and 12 hours post a.m. dose
Days 2, 3: 4 hours post a.m. dose
Day 4: Pre a.m. dose and 2, 4, 8 and 12 hours post a.m. dose
Days 5-11: 4 hours post a.m. dose
Day12: Pre a.m. dose and 2, 4, 8, 12 hours after last dose
Day 13: 24 hours after last dose
Day 14: 48 hours after last dose

Blood pressure and heart rate were recorded:

Day 1: Pre a.m. dose and 4, 8, and 12 hours post a.m. dose
Days 2, 3: 4 hours post a.m. dose
Day 4: Pre a.m. dose and 2, 4, 8, and 12 hours post a.m. dose
Days 5-11: Pre a.m. dose, and 4 hours post a.m. dose
Days 12: Pre a.m. dose, and 2, 4, 8, 12 hours after last dose
Day 13: 24 hours after last dose
Day 14: 48 hours after last dose

The ECG recordings were inspected on site by the Investigator.
The definitive evaluation of the ECG recordings including PR interval, QRS duration, QT interval and QTc was performed by the ECG Core Laboratory.
The effect on QTc of co-administration of paroxetine and ranolazine versus ranolazine alone was investigated by applying a paired t-test.

RESULTS:

Fifteen subjects, 14 males and 1 female, were enrolled and completed the study. There were 10 Caucasians, 3 Hispanics, one Black and one Asian. The mean age of the subjects was 36 years.

PK:

Ranolazine and metabolites:
The pharmacokinetic parameters of ranolazine, RS-88390 (CVT-2514), RS-88940 (CVT-2512) and RS-94287 (CVT-2738) on Days 4 (absence of paroxetine) and 12 (presence of paroxetine) are shown in the following 4 tables:

Pharmacokinetic Parameters	Plasma Ranolazine Day 12 N	Day 12 Arithmetic Mean	Day 12 SD	Day 4 N	Day 4 Arithmetic Mean	Day 4 SD	90% CI**	% Mean Ratio**
Cmax(ng/mL)	15	3479	734	15	2969	1045	104.2-144.5	122.7
Tmax(hr)*	15	3.00	.	15	3.00	.	. - .	.
AUC(0-tau) (ng*hr/mL)	15	29657	8690.2	15	24839	8857.0	101.0-151.1	123.5
T1/2(hr)	6	7.03	1.34	.	.	.	. - .	.
Kel(1/hr)	6	0.101	0.0180	.	.	.	. - .	.

* Values for Tmax are the medians (P = 0.241).
** 90% CI and % mean ratios are from the ANOVA of log-transformed Cmax and AUC(0-tau) values (Table 14.2.1.8).

Pharmacokinetic Parameters	Plasma RS-88390 Day 12 N	Day 12 Arithmetic Mean	Day 12 SD	Day 4 N	Day 4 Arithmetic Mean	Day 4 SD
Cmax(ng/mL)	15	200	56	15	859	377
Tmax(hr)*	15	2.04	.	15	3.50	.
AUC(0-tau) (ng*hr/mL)	15	1827.3	629.67	15	8335.8	3802.6
T1/2(hr)	3	12.7	3.44	.	.	.
Kel(1/hr)	3	0.0580	0.0186	.	.	.

* Values for Tmax are the medians.

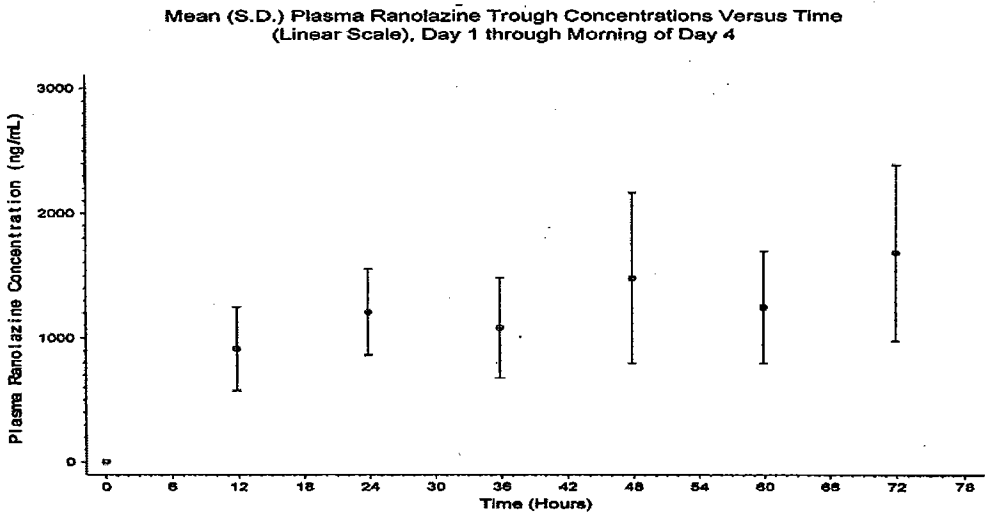
Pharmacokinetic Parameters	Plasma RS-88640 Day 12 N	Day 12 Arithmetic Mean	Day 12 SD	Day 4 N	Day 4 Arithmetic Mean	Day 4 SD
Cmax(ng/mL)	15	68	17	15	191	82
Tmax(hr)*	15	3.54	.	15	4.99	.
AUC(0-tau) (ng*hr/mL)	15	720.08	190.60	15	2023.7	855.43
T1/2(hr)	13	23.3	4.68	.	.	.
Kel(1/hr)	13	0.0310	0.00657	.	.	.

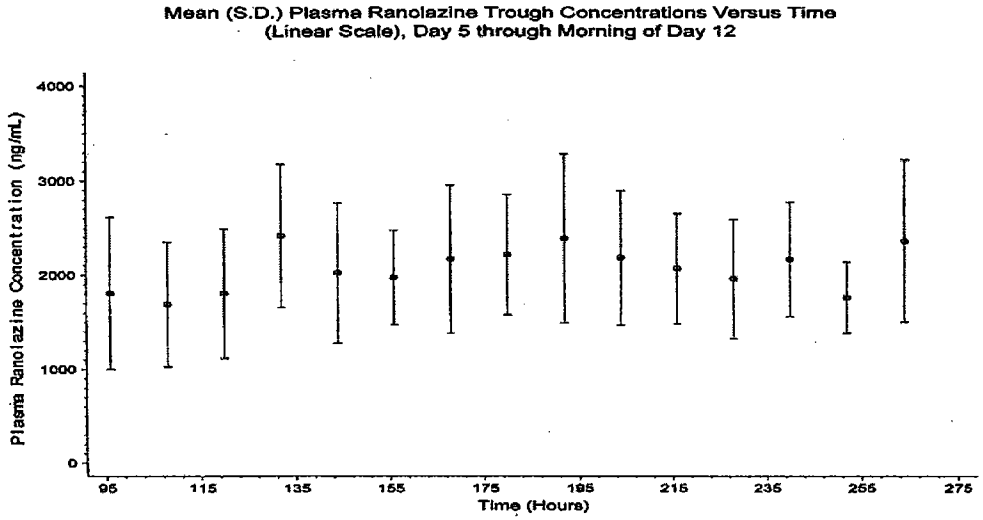
* Values for Tmax are the medians.

Pharmacokinetic Parameters	Plasma RS-94287 Day 12 N	Day 12 Arithmetic Mean	Day 12 SD	Day 4 N	Day 4 Arithmetic Mean	Day 4 SD
Cmax(ng/mL)	15	1095	188	15	776	219
Tmax(hr)*	15	3.53	.	15	5.00	.
AUC(0-tau) (ng*hr/mL)	15	11433	2201.7	15	8105.7	2263.3
T1/2(hr)	15	10.3	2.42	.	.	.
Kel(1/hr)	15	0.0700	0.0114	.	.	.

* Values for Tmax are the medians.

The mean plasma concentrations of ranolazine in the presence and absence of paroxetine are shown in the following 2 figures:



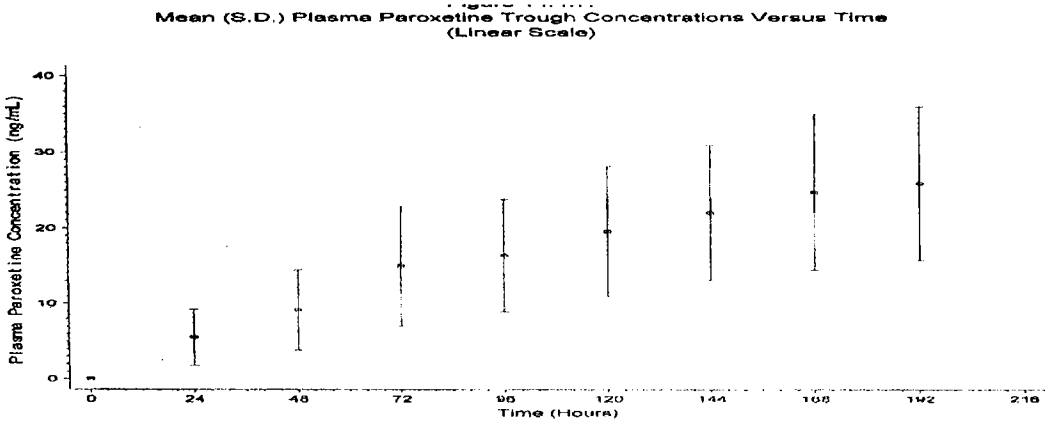


The trough plasma concentrations of ranolazine in the absence of paroxetine show evidence for a circadian rhythm. In the presence of paroxetine the circadian rhythm appears to be less evident. The exposure measures, arithmetic mean Cmax and AUC0-tau of ranolazine, increased slightly 1.17 and 1.19 fold, respectively, in the presence of paroxetine. Similar increases for Cmax (1.23 fold) and AUC0-tau (1.19 fold) were obtained when the logarithmically transformed data were used.. The 90% confidence intervals exceeded the limits of 80%-125% indicating that paroxetine

interacted with ranolazine. Tmax was not affected by the co-administration of paroxetine. Co-administration of paroxetine affected also the exposure to the metabolites, although qualitatively and quantitatively differently. The arithmetic mean Cmax and AUC0-tau of RS-88390 decreased by 76.7% and 78.0 %, respectively, in the presence of paroxetine. Mean Cmax and AUC0-tau of RS-88640 (CVT-2512) also decreased, both by 64.4 %. In contrast, the mean Cmax and AUC-tau for RS-94287 (CVT-2738) increased 1.41 and 1,41 fold, respectively, in the presence of paroxetine .

Ranolazine:

The mean plamsma concentrations of paroxetine at trough are shown in the following figure:



Although the mean trough levels on Days 12 and 13 were not statistically significantly different from each the data appears to indicate a trend for a further increase with time.

Dextrometorphan/Dextrorphan Ratio:

The results on the ratios of dextrometorphan to dextrorphan measured in urien are atbulated in the following table:

Descriptive statistics for the ratio dextromethorphan/dextrorphan by study day (N=14)

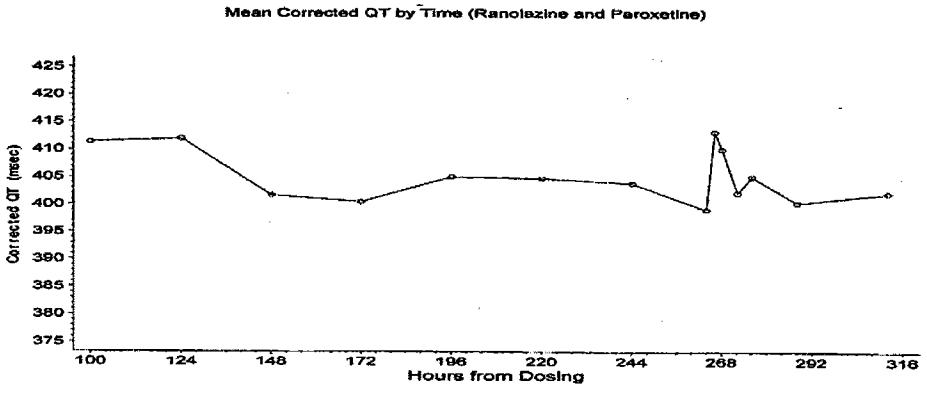
Data for urine collection 0-8 hours after intake of dextromethorphan

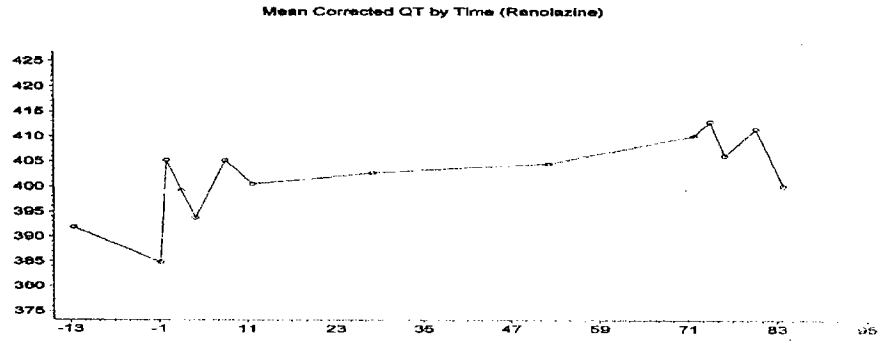
Day	Mean	Geometric mean	Median	Min	Max	SD
1	0.01268	0.00674	0.00628			0.02514
4	0.31029	0.05674	0.03586			0.94324
11	0.84853	0.59441	0.53480			1.05336

The results on the drug/metabolite ratio (geometric mean ratio =0.00674, n=14) on Day-1 indicated that 14 of the 15 subjects were extensive metabolizers of CYP 2D6. On Day 4 of the ranolazine alone treatment the drug/metabolite ratio increased to 0.05674 and one of the subjects became a phenotypically poor metabolizer and on Day 11 after co-administration of 6 daily doses of paroxetine the drug/metabolite ratio further increased to 0.59441 and 12 of the 14 subjects had become phenotypically poor metabolizers.

Safety:

Following dosing with ranolazine alone or in combination with paroxetine none of the subjects experienced a QTc interval exceeding 130% of the baseline value and 500 msec.
The time course of the mean QTc interval prior to and following dosing with ranolazine in the presence or absence of paroxetine is shown in the following 2 figures:





Compared to the 2 baseline values the mean apparent QTc intervals tend to increase over time following dosing with ranolazine alone and after co-administration of paroxetine.

One subject experienced a single episode of syncope approximately 8 hours following dosing with ranolazine together with paroxetine. The subject was standing to urinate, felt lightheaded, and sat down on stool. The blood pressure was 100/55 mmHg and the pulse 60 bpm. Subsequent ECG recordings were normal. All the symptoms resolved within 3 hours. No further episodes of syncope occurred for this subject during the study. The Investigator considered the event as possibly related to study tretament.
After co-administration of paroxetine more AEs were reported than during ranolazine alone treatment. Dizziness was the most common event reported (8 subjects) followed by headache (5 subjects) and nausea (4 subjects).

CONCLUSIONS:

Co-administration of 20 mg qd paroxetine with ranolazine 1000 mg bid results increased the arithmetic mean Cmax and AUC0-tau of ranolazine 1.17 and 1.19 fold, respectively. Co-administration of paroxetine and ranolazine impact the metabolites more than the parent drug. RS-88390 (CVT-2514) is affected the most. Mean Cmax and AUC0-tau of RS-88390 (CVT-2514) decrease by 76.7% and 78.0%, respectively, in the presence of paroxetine. Mean Cmax and AUC-tau of RS 88640 (CVT-2512) decrease also, both by 64.4% in the presence of paroxetine. In contrast, mean Cmax and AUC0-tau for RS-94287 (CVT-2738) are modestly increased 1.41 and 1.41 fold, respectively. Paroxetine is a known inhibitor of CYP2D6. In vitro data obtained with human liver microsomes and cDNA CYP 450 (CVT 303.009-N) suggest that the formation of RS-88390 (CVT-2514) and RS-94287 (CVT2738) is catalyzed by CYP2D6 and CYP 3A4, respectively. The in vivo data of the present study show a decrease in the formation of RS-88390 (CVT-2514) and an increase in the formation of RS-94287 (CVT-2378) in the presence of paroxetine, in agreement with the in vitro data. The decreased formation of RS-88640 (CVT-2512) suggests involvement of CYP 2D6 in the generation of this metabolite as well.

The formation of dextrorphan from dextrometorphan is catalyzed by CYP 2D6. The dextrometorphan/dextrorphan ratio in the 14 extensive metabolizers appears to increase after administration of ranolazine alone on Day 4 suggesting that ranolazine and/or its metabolites inhibit CYP2D6. Co-administration of paroxetine and ranolazine increases the dextrometorphan/dextrorphan ratio substantially confirming 2D6 inhibition by multiple doses of paroxetine 20 mg qd.

Compared to baseline the mean QTc intervals appear to increase from Day 1 to Day 14 of treatments with 1000 mg ranolazine bid given alone or together with 20 mg paroxetine qd. One patient receiving ranolazine together with paroxetine experienced a syncope about 8 hours following dosing.

COMMENTS:

1. A justification for weighting the calibration standards by 1/X was not provided.
2. ECG recordings should have been performed prior to dosing over an entire day in order to evaluate time specifically the impact of ranolazine on QTc in the presence and absence of paroxetine co-administration.
3. The relationship between QTc and plasma concentration of ranolazine was not evaluated.
4. The dextrometorphan to dextrorphan ratio increased slightly after ranolazine alone treatment suggesting that ranolazine and/or one of its metabolites inhibits CYP 2D6. However, the dextrometorphan to dextrorphan ratio could have been perturbed by a lack of control of the urine pH during the collection periods. It is known that changes in urine pH can affect the drug/metabolite ratio of dextrometorphan to dextrorphan importantly. There is substantial intersubject variation in the data. Furthermore, both dextrometorphan and dextrorphan are known to be also metabolized by CYP 3A4. Differential inhibition of the CYP 3A4 catalyzed metabolism of dextrometorphan and dextrorphan by ranolazine and/or a metabolite would affect the ratio as well. In vitro data (CVT 303.22-N, p.106) suggest that RS-88930 can weakly inhibit the CYP 3A4 catalyzed metabolism of ranolazine. Also, two of the EM subjects were not transformed into phenotypical PM by co-administration of paroxetine.
4. The enrollment of more than 1 female in the study would have been desirable.
5. It is questionable whether data from subjects with QTc intervals ($\leq$420 msec in males, $\leq$ 437 msec in females) can be extrapolated to patients with greater QTc intervals.
6. The data obtained in subjects receiving 20 mg paroxetine mg qd and 1000 mg ranolazine bid may not be extrapolated to subjects receiving 60 mg paroxetine qd, the highest labeled dose.
7. In the presence of a circadian rhythm only trough values measured 24 hours apart should have been considered for the evaluaton of attainment of steady state of ranolazine.

STUDY CVT 301-11- AN OPEN LABEL DOSE STUDY TO ASSESS THE POTENTIAL EFFECT OF VERAPAMIL ON THE PHARMACOKINETICS OF RANOLAZINE SR DURING STEADY STATE CONDITIONS FOR BOTH DRUGS

STUDY INVESTIGATOR ANDE SITE: C

J

Report No.: CVT 301-11
Volume No.: 42,43, ITEM 6

OBJECTIVES:

Primary: To evaluate the potential effect of verapamil at steady state on the pharmacokinetics of ranolazine at steady state
Secondary: To evaluate:
1) The effect of verapamil administered in combination with ranolazine on the QTc interval
2) The safety and tolerability of ranolazine when administered in combination with verapamil

FORMULATIONS:

SR tablets containing 375 mg ranolazine (Lot No.0H2761A)
Capsules containing 120 mg verapamil (Lot No.0004, Knoll France, France)

STUDY DESIGN:

This was a single center, open-label, multiple dose, pharmacokinetic study. Subjects were to receive repeated dosing of ranolazine SR to reach steady state. Verapamil was to be added with multiple dosing to reach steady state for both drugs. The initial dose of ranolazine (1125 mg) will be 50% higher then the subsequent doses to ensure that steady state is achieved within 2 days of dosing. The doses and dosing regimens are shown in the following scheme:

		Dosing Regimen							
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Verapamil	(8am)	X	X	X	120 mg	120 mg	120 mg	120 mg	120 mg
Verapamil	(2pm)	X	X	X	120 mg	120 mg	120 mg	120 mg	X
Verapamil	(8pm)	X	X	X	120 mg	120 mg	120 mg	120 mg	X
Ranolazine SR	(8am)	1125 mg	750 mg	750 mg	750 mg	750 mg	750 mg	750 mg	750 mg
Ranolazine SR	(8pm)	750 mg	750 mg	750 mg	750 mg	750 mg	750 mg	750 mg	X

The subjects fasted for >10 hours before the morning dosing. Both drugs were taken by the subjects with approximately 150 mL water either in a sitting, semi-recumbant or standing position. Healthy, female and male subjects in the age between 18 and 60 years of age were to be enrolled in the study

ASSAY:

The plasma concentrations of ranolazine were measured at CV Therapeutics, Palo Alto, CA using a LC/MS/MS method in the Multiple Reaction Monitoring mode. CVT-3023 was used as internal standard. The quantitation range of the method was between 50 ng/mL and 10 000ng/mL. When the calibration standards for ranolazine were weighted by 1/X the R value of the regressions exceeded 0.999. Accuracy (bias, %) and precision (CV, %) for ranolazine determined from the QC samples were within the ± 15% limits.

Blood Sample Collection:

Days 1 and 2: Pre a.m. and p.m. doses
Day 3: Pre-dose, and 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours post a.m. dose
Days 4-7: Pre a.m.and p.m. doses
Day 8: Pre- dose and 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, 48 hours after the last dose

PK and Statistical Analysis:

The parameters Cmax, Tmax, AUC0-t, Kel, and t1/2 were determined for ranolazine using non-compartment model independent standard methods. Trough concentrations from Days 1-3 and 3-8 were evaluated using Dunnet's test. To ensure steady state for ranolazine was reached on Days 3 and 8. An analysis of variance (ANOVA) model was used to test the differences between the parameters obtained during the test (Day 8) and reference (Day 3) data. Following logarithmic

transformation Cmax and AUC0-12 were subjected to an analysis of variance (ANOVA). Point estimates and 90 % confidence intervals for pairwise differences between test and reference treatments were calculated for Cmax and AUC0-12 and then transformed back to the original scale to give estimates of the ratio of Day 8 to Day 3. The Tmax values on Days 3 and 8 were compared by Wilcoxon's signed rank test of the untrasformed data.

Safety:

Standard 12 lead ECG recordings were performed with the subjects in the supine position at the following times:

Screening
Day1: Pre a.m. dose, and 2, 4 and 12 hours post a.m. dose
Day 2: Pre a.m. dose, and 4 hours post a.m. dose
Day3: Pre a.m. dose, and 2, 4, 8, and 12 hours post a.m. dose
Days: 4-7: 4 hours post a.m. dose
Day 8: Pre a.m. last dose
Day 9: 24 hours after last dose
Day 10: 48 hours after last dose
Post study visit: 14 days after last dose

A Holter ECG was recorded at Screening and continuous cardia rhythm monitoring was conducted during Days 4 and 5

Blood pressure and heart rate monitoring was performed at the same times as the 12 lead ECG monitoring with one exception: on Day 1 blood pressure and heart rate were not recored 2 hours after the a.m. dose.

RESULTS:

Fifteen subjects were enrolled and completed the study. There were 7 females and 8 males with a mean age of 29.8 years. Of the 15 subjects 11 were Caucasians and 4 Blacks.

PK:

The arithmetic mean parameters for ranolazine on Day 3 (ranolazine treatment) and Day 8 (combined ranolazine and verapamil treatment) are listed in the following table:

		C_{max} (ng/mL)	T_{max}* (h)	$AUC_{(0-t)}$ (ng·h/mL)	$AUC_{(0-12)}$ (ng·h/mL)	$T_{½}$ (h)
Day 3	Mean	1649	3.00	-	13918	10.05[3]
	SD	(676)	1.00-5.00	-	(6379)	(7.87)
Day 8	Mean	3171	4.00	47363	30153	7.22
	SD	(925)	1.00-10.00	(18475)	(9959)	(3.07)
Analysis of Variance		p<0.0001[1]	p=0.0146[2]	-	p<0.0001[1]	-
Point Estimate (Day 8/Day 3)		1.98			2.25	
90% Confidence Interval		1.79 - 2.20			2.03 - 2.50	

* Median and range

The trough concentrations of ranolazine are listed in the following table:

Table 8 Mean Trough Plasma Concentrations of Ranolazine (ng/ml) Obtained During a Study of 15 Healthy Subjects

	Trough Plasma Concentrations (ng/mL)															
Day	1		2		3		4		5		6		7		8	
Hour	0[1]	12[2]	0[2]	12[2]	0[2]	12[2]	0[3]	12[3]	0[3]	12[3]	0[3]	12[3]	0[3]	12[3]	0[3]	12
Mean	0	750	808	784	966	723	921	1345	1377	1697	1929	1894	1990	1909	2017	1830
SD	0	456	415	403	497	374	424	721	817	824	949	808	924	819	876	855

(1): administration of 1125 mg of ranolazine SR.
(2): administration of 750 mg of ranolazine SR.
(3): administration of 750 mg of ranolazine SR and 120 mg of verapamil.

The arithmetic mean Cmax and AUC0-12 values of ranolazine at the 750 mg dose level increased 1.92 and 2.17 fold, respectively, after co-administration of verapamil 120 mg tid. The 90% confidence intervals for both parameters were not contained in the 80% to 125% range indicating that verapamil interacts with ranolazine. The mean terminal phase t1/2 of ranolazine in the presence of verapamil did not increase. The median Tmax values for ranolazine in the presence and absence of verapamil were similar. The mean trough concentrations of ranolazine on Days 2, 3, and 6-8 were greater in the morning than in the evening.

Safety:

The mean QTc data and the ΔQTc from the pre-dose baseline are listed in the following table:

			Observed values						Changes from baseline data						
Visit			N	Nmiss.	Mean	SD	SEM	Min.	Max.	N	Mean	SD	SEM	95% CI Lower bound	95% CI Upper bound	Min.	Max.
Screening			14	0	405.7	20.3	5.4	355	431	0							
Day 1	Pre-dose	1	15	0	412.1	20.1	5.2	382	457	0							
	Pre-dose	2	15	0	416.3	17.0	4.4	374	453	0							
	Pre-dose	3	15	0	417.9	22.9	5.9	370	452	0							
Day 1	H2		15	0	415.7	16.2	4.2	392	449	15	-2.1	17.3	4.5	-11.7	7.4	-23	45
Day 1	H4		15	0	414.5	26.9	7.0	364	462	15	-3.4	26.4	6.8	-18.0	11.2	-54	50
Day 1	H12		15	0	401.8	15.3	3.9	379	429	15	-16.1	22.4	5.8	-28.5	-3.6	-68	17
Day 2	H4		15	0	412.0	15.2	3.9	383	433	15	-5.9	16.8	4.3	-15.2	3.4	-48	13
Day 3	Pre-dose		15	0	412.5	22.1	5.7	370	455	15	-5.4	20.5	5.3	-16.7	5.9	-28	39
Day 3	H2		15	0	420.9	22.3	5.8	392	458	15	3.1	18.1	4.7	-7.0	13.1	-33	41
Day 3	H4		15	0	412.5	15.7	4.1	375	430	15	-5.3	17.0	4.4	-14.7	4.1	-29	28
Day 3	H8		15	0	413.6	13.8	3.6	378	432	15	-4.3	22.5	5.8	-16.7	8.2	-37	51
Day 3	H12		15	0	413.4	19.5	5.0	364	450	15	-4.5	21.1	5.5	-16.2	7.2	-36	29
Day 4	H4		15	0	421.1	19.2	5.0	380	447	15	3.3	13.1	3.4	-4.0	10.5	-22	21
Day 5	H4		15	0	423.5	16.1	4.2	401	449	15	5.7	13.4	3.5	-1.8	13.1	-11	37
Day 6	H4		15	0	422.3	20.3	5.2	391	468	15	4.4	17.1	4.4	-5.0	13.8	-17	40
Day 7	H4		15	0	424.3	17.2	4.5	383	447	15	6.5	16.9	4.9	-4.0	16.9	-18	36
Day 8	Pre-dose		15	0	426.5	21.4	5.5	371	451	15	8.7	17.8	4.6	-1.2	18.5	-19	37
Day 8	H2		14	1	432.0	16.7	4.5	398	459	14	15.1	25.2	6.7	0.5	29.6	26	69
Day 8	H4		14	1	423.7	15.3	4.1	393	448	14	6.8	18.6	5.0	-4.0	17.6	-28	35
Day 8	H8		15	0	426.1	19.4	5.0	384	453	15	8.3	16.7	4.3	-1.0	17.5	-16	51
Day 8	H12		15	0	424.9	20.8	5.4	393	472	15	7.1	19.8	5.1	-3.8	18.1	-25	36
Day 9	H24		15	0	416.7	23.0	5.9	371	444	15	-1.2	22.1	5.7	-13.5	11.1	-47	28
Day 10	H48		15	0	410.5	16.0	4.1	387	432	15	-7.3	22.2	5.7	-19.6	4.9	-40	27
Post study visit			15	0	416.0	13.9	3.6	400	442	14	11.4	17.3	4.6	1.5	21.4	-20	48

Baseline is the last evaluation of day 1 H0 for the study or screening for post study evaluation
Post study visit is 14 days after the last dosing
From day 1 morning to day 8 morning : Administration of ranolazine SR b.i.d
From day 4 morning to day 8 morning : Administration of verapamil t.i.d

None of the QTc values recorded exceeded 130 % of the baseline value and was > 500 msec at the same time. On Day 3 of the ranolazine alone treatment the maximum increase in mean (SD) apparent QTc relative to the baseline (QTc measured at pre-dose on Day 1) was 3.1(18.1) msec. The maximum increase of mean apparent QTc relative to baseline on Day 8 of the combined treatment with ranolazine and verapamil was 15.1 (25.2) msec. This was the only value whose 95% confidence intervals did not include zero. All the QTc values measured during the combination treatment tended to be greater than the baseline values. The time specific increase in apparent QTc at pre-dose on Days 3 and 8 relative to baseline were -5.4 (20.5) msec and 8.7 (17.8) msec, respectively.

The PR interval was not prolonged during the ranolazine alone treatment but increased as expected after co-administration of verapamil. Similarly, after co-administration of verapamil a decrease in mean standing and supine systolic and diastolic blood pressure (-5 mmHg to 10mmHg) occurred. The AEs noted during the ranolazine alone treatment included headache (2 subjects), vasodilation (2 subjects) and constipation (5 subjects). The AEs reported during the coadministration of ranolazine and verapamil included headache (3 subjects), palpitation (2 subjects), postural hypotension (1 subject), dizziness (1subject) and constipation (5 subjects).

CONCLUSIONS:

The exposure measures, mean Cmax and AUC0-12, of ranolazine when co-administered with verapamil increase 1 92 and 2.17 fold respectively, indicating a clinically relevant drug interaction. Verapamil is known to be a substrate/inhibitor of CYP 3A4 and P-glycoprotein and in vitro data obtained with human tissues suggest that ranolazine is also a substrate/inhibitor of CYP 3A4 and P-glycoprotein (CVT 303.010-N, CVT 303.018-N and CVT 303.009-N). Hence,

the increased exposure to ranolazine in the presence of verapamil can be explained by an inhibition of ranolazine's interaction with CYP 3A4 and/or P-glycoprotein by verapamil.

COMMENTS:

1. The QTc interval should have been meausred during a 24 hour interval at baseline so that time specific changes in this parameter could have been determined.
2. A rationale for the heart rate correction algorithm applied to then QT intervals was not provided.
3. Previous studies have demonstrated that the trough plasma concentrations of ranolazine in the morning are greater than in the evening. Hence the morning and evening trough levels should have been separately evaluated in determining whether steady-state of ranolazine was reached.
4. A justification for weighting of the calibration standards by 1/X was not provided

Appears This Way
On Original

STUDY RAN032 (CL 6886) - A STUDY TO INVESTIGATE THE POTENTIAL PHARMACOKINETIC INTERACTION BETWEEN RANOLAZINE AND CIMETIDINE IN HEALTHY YOUNG MEN

STUDY INVESTIGATOR AND SITE: [

]

Report No.: RAN032 (CL 6886)
Volume No.: 184, ITEM 6

OBJECTIVES:

To determine if there is a pharmacokinetic interaction when ranolazine and cimetidine are co-administered.

FORMULATIONS:

IR capsules containing 200 mg ranolazine hydrochloride (171 mg ranolazine base) (Lot No.: CT1119 12263/4175)
Tablets containing 400 mg cimetidine (Tagamet®, SmithKlineBeecham) (Lot No. CT119SC32D)

STUDY DESIGN:

This was a randomized, opem-label, two-way crossover design, in which subjects received 171 mg ranolazine free base tid with or without 400 mg cimetidine tid for five days with a single dose on Day 6. It was expected that steady-state levels of both ranolazine and cimetidine would be reached by Day 3. There was a washout period of at least six days between phases, based on the elimination half-life of two hours for each drug and allowing sufficient time for any effect on drug metabolizing enzymes to return to baseline. Ranolazine pharmacokinetics and hemodynamic effects were examined on Day 6 of each phase. Twelve subjects were to be enrolled in the study. This number of subjects was calculated from the results of previous studies to provide 80 % power to detect a 20 % difference in ranolazine AUC and a 30% change in Cmax using a two-sided test of significance at the 5% level.
Meals were provided to the subjects each day 1, 5, 10 and 14 hours after the morning dosing. On Day 6 the subjects did not receive breakfast.

ASSAY:

The plasma concentrations of ranolazine were measured using a HPLC method with fluorimetric detection. The calibration range was from 5 ng/mL to 1039 ng/mL. RS-87986 was used as

internal standard. Precision (CV, %) determined from the QC samples was within the ± 15% limits. Recovery ranged between 101% to 107%.

Blood Sample Collection:

Blood samples for pharmacokinetic purposes were collected at the following times:
Day 6: Pre-dose, 20 and 40 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours after the last dose

PK and Statistical Analysis:

The parameters Cmax, Tmax, AUC120-128, Ctrough, Clpo and t1/2 were determined for ranolazine using standard compartment model independent methods. AUC 120-128 was obtained on application of the linear trapezoidal rule. The Clpo was obtained from Dose/AUC120-128. Cmax, AUC120-128, Ctrough, Clpo and t1/2 were analyzed using a mixed effect analysis of variance (ANOVA) model. The fixed effects were sequence (ranolazine/cimetidine to ranolazine, ranolazine to ranolazine/cimetidine), phase (Phase 1, Phase 2) and treatment (ranolazine/cimetidine, ranolazine). The random effects were subject (within sequence) and the residual. Carryover was tested for by testing the sequence effect against the subject (within sequence) effect. Phase and treatment effects were tested against the residual. The analysis was performed using untransformed and log transfomed data. All treatment comparisons were performed via two-sided tests using estimates of variability from the ANOVA model. The 90% and 95% confidence intervals were calculated for treament comparisons. Ranolazine tmax data were analyzed using the Wilcoxon rank sum test and non-parametric 90% and 95% confidence intervals were calculated for the median difference between treatments.

Safety:

Standard 12 lead ECG recordings and supine and erect systolic and diastolic blood pressure and heart rate readings were taken at the following times:
Days 1-5: Pre morning dosing and 1 hour after morning dosing
Day 6: Pre-last dose and 1 after last dose
Day 7: 24 hours after last dose

RESULTS

Thirteen subjects entered and eleven completed the study. Two subjets withdrew from the study for personal reasons. All 11 subjects were males of an average age of 29.3 years. All were Caucasian.

The arithmetic mean values of the pharmacokinetic parameters of ranolazine with and without co-administration of cimetidine and the results of the statistical analysis are shown in the following 2 tables:

DAY 6 MEAN ± SD RANOLAZINE PHARMACOKINETIC PARAMETERS (n =11)

Parameter	Treatment		RAN/CIM - RAN	
	Ran	Ran/Cim	p value	90 % CI
C_{max} (ng/ml)	1374 ± 572	1542 ± 388	0.230	-66.5, 380.6
t_{max} (h)	1.00*	1.00*	0.457	-0.2500, 0.4165
C_{trough} (ng/ml)	148 ± 89.1	208 ± 73.1	0.017	21.2, 92.4
$AUC_{120-128h}$ (ng.h/ml)	4383 ± 1947	5477 ± 1505	0.005	533.4, 1553.8
Cl_{po} (ml/min/kg)	10.6 ± 4.51	7.68 ± 1.67	0.014	-4.463, -1.098
$t_{1/2}$ (h)	2.12 ± 0.335	2.24 ± 0.349	0.347	-0.083, 0.279

Pharmacokinetic parameters are given in terms of ranolazine base.
* = Median t_{max}

Ranolazine IR Pharmacokinetic Parameters : Day 6
Log-transformed Data

Treatment		Parameter				
		C_{max} (ng/ml)	$AUC_{120-128h}$ (ng.h/ml)	C_{trough} (ng/ml)	Oral Clearance (ml/min/kg)	$t_{1/2}$ (h)
Ran/Cim	mean	1521.0	5366.3	197.7	7.480	2.201
	n	11	11	11	11	11
Ran	mean	1311.6	4158.5	128.1	9.659	2.104
	n	11	11	11	11	11
(Ran/Cim)/Ran	ratio	116.0%	129.0%**	154.4%*	77.4%**	104.6%
	p	0.138	0.006	0.011	0.005	0.339
	95% CI	(94.4%,142.5%)	(110.1%,151.3%)	(113.4%,210.1%)	(66.1%,90.8%)	(94.6%,115.8%)
	90% CI	(98.1%,137.0%)	(113.4%,146.8%)	(120.2%,198.2%)	(68.1%,88.1%)	(96.4%,113.6%)

Key: mean = least square mean; n = number of subjects; ratio = ratio of least square geometric means; p = probability * p<0.05, ** p<0.01, *** p<0.001; 95% CI = 95% Confidence Interval for mean difference; 90% CI = 90% Confidence Interval for ratio of means; Ran/Cim = Ranolazine 200 mg IR tid/Cimetidine 400 mg tid; Ran = Ranolazine 200 mg IR tid

The arithmetic mean exposure parameters of ranolazine, Cmax and AUC120-128, increased after co-administration of cimetidine slightly 1.12 and 1.25 fold, respectively. Similar results were obtainmed when the geometric means were used. Cmax and AUC increased 1.26 and 1.29 fold in the presence of cimetidine. The 90% confidence intervals of the ln transformed data were not contained in the 80% to 125% range indicating that cimetidine interacts with ranolazine. The Clpo of ranolazine in the presence of cimetidine was decreased, wheras tmax and t1/2 were similar in the presence and absence of cimetidine.

Safety:

The mean QTc values in the presence and absence of cimetidine are listed in the following table:

MEAN ECG DATA
QTc Interval (msec)

Day	Time Post-Dose	Treatment					
		Ran/Cim			Ran		
		n	mean	se	n	mean	se
1	Pre-dose	12	398.3	4.4	12	398.9	4.6
	1 h	12	399.4	7.4	12	394.6	4.8
2	Pre-dose	12	392.5	6.4	12	388.4	6.1
	1 h	11	399.7	5.1	12	393.9	6.7
3	Pre-dose	11	395.5	5.1	12	390.4	5.0
	1 h	11	391.7	4.8	12	390.2	5.5
4	Pre-dose	11	398.7	5.9	12	390.8	5.9
	1 h	11	394.6	6.4	12	385.5	4.5
5	Pre-dose	11	392.6	6.0	12	385.9	5.5
	1 h	11	394.3	6.4	12	389.8	5.7
6	Pre-dose	11	391.4	5.3	12	393.0	5.4
	1 h	11	394.8	4.1	12	385.6	5.2
	24 h	11	389.9	4.6	12	388.8	4.6

Key: n = number of subjects
mean = raw (unadjusted) mean
se = standard error of the mean
Ran/Cim = Ranolazine 200 mg IR tid/Cimetidine 400 mg tid
Ran = Ranolazine 200 mg IR tid

A comparison of the time specific mean QTc values obtained at pre–morning dosing on Day 1 (baseline) with the corresponding values on Days 2-6 indicates no overt increase in the QTc interval during the treatments with ranolazine alone or in combination with cimetidine.
The most common AE reported was headache with the combination (5 subjects) and ranolazine alone treatments (8 subjects).

CONCLUSIONS:

Co-administration of cimetidine 200 mg tid to 171 mg ranolazine tid increases the exposure measures, mean Cmax and AUC120-128, of ranolazine 1.12 and 1.25 fold, respectively.
Cimetidine is known to inhibit CYP 3A4, 2D6 and 2C19. In vivo data
(CVT 301-10, and CVT-301-13) and in vitro data (CVT 303.009-N) indicate that CYP 3A4 and to a smaller extent CYP 2D6 are the two main CYPs known to metabolize ranolazine, but other enzymes are also involved in the multiple metabolic pathways of the drug.
The comparison of the time specific mean QTc values measured prior to the morning dosing on Days 2-6 and Day 1 (=baseline) appears not to suggest a treatment related increase of the intervals. Headache is the most frequent reported AE.

COMMENTS:

1. A detailed description of the assay with information on the characteristics of the calibration curve and an estimate for the accuracy of the assay determined with QC samples were not provided.
2. Information on the cross-validation of the HPLC assay with fluorimetric detection used in the present study and the HPLC/MS/MS assay used in other studies was not given.
3. The results obtained with 171 mg ranolazine tid and cimetidine 400 mg tid cannot necessarily be extrapolated to combination regimens with effective dose levels of ranolazine and higher doses of cimetidine such as 800 mg bid.
4. Females should have been enrolled in the study.

STUDY RANS0110 (CL6982), CVT 303.005 - A STUDY TO INVESTIGATE THE POTENTIAL PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTION BETWEEN RANOLAZINE AND WARFARIN IN HEALTHY YOUNG MEN

STUDY INVESTIGATOR AND SITE: [ ]

Report No: RANS0110 AND CVT 303.005
Volume No.: 218, 219, ITEM 6

OBJECTIVES:

To determine if there is a pharmacokinetic and /or pharmacodynamic interaction when ranolazine and warfarin are co-administered.

FORMULATIONS:

IR capsules containing 400 mg ranolazine hydrochloride (342 mg ranolazine free base) (Lot No. CT1118 SC987H)
Matching placebo capsules (Lot No.CT1118SC272J)
Tablets containing 5 mg warfarin (Boehringer Ingelheim Ltd) (Lot No. CT1118 11813/3742)

STUDY DESIGN:

This was a randomized, double-blind, placebo controlled, two-way crossover study. Subjects received either 342 mg ranolazine or placebo ranolazine tid, with a single dose of warfarin on Day 4. It was expected that steady state levels of ranolazine would be reached by Day 3. There was a washout period of at least six days between the last day of Phase 1 and the first dose of Phase 2. Prothrombin times were assessed prior to the start of the second phase to ensure these had returned to normal levels. Warfarin pharmacokinetic parameters and prothrombin times were monitored at intervals until 168 hours and 144 hours after the warfarin dose, respectively. Hemodynamic, ECG and adverse event data were collected at regular time intervals during the dosing period.
The dose of ranolazine (free base) was 342 mg tid for ten days. On Day 4 of both phases of the study the subjects received a single dose of five 5 mg warfarin tablets in the morning. Warfarin was administered in an open design, but ranolazine IR capsules and matching placebo were given in a double-blind manner. The subjects were to avoid aspirin, laxatives and vitamin supplements for fourteen days prior to study start and throughout the study. There were restrictions on alcohol consumption before and during the dosing periods.
Prothrombin time (PT) and Activated Partial Thromboplastin Time (APTT) were determined in the month prior to study start. Except for a period of 8 hours (8:00 to 16:00) on Days 2 and 3 and 5 to 10 the subjects were institutionalized during the treatments.

It was planned to have 12 subjects participating in the study to provide 80% power to detect a 25% change in AUC of warfarin for both the R- and S- enantiomers in the presence of ranolazine IR, at the 5% level.

ASSAY:

Plasma concentrations of (+) R- and (-) S warfarin were determined at [redacted]. A HPLC method with fluorimetric detection was used. The calibration range was between 0.1 μg/mL and 3.0 μg/mL. Precision (CV, %) determined from the QC samples ranged between 16.2% and 19.6% for the two enantiomers and was outside the ±15% limits for both. Recovery of the two enantiomers ranged between 96.4 % and 107 %.

PT was determined by the one-stage test according to the method of Quick at the Pathology Department at Syntex Research Scotland.

Blood Sample Collection:

Blood samples for the determination of the plasma concentrations of the warfarin enantiomers were collected at the following times:
Pre-dose and 20 and 40 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144 and 168 hours after dosing on Day 4.

Blood samples for the determination of PT were collected at the following times:
Pre-study
Days 4-7: Pre- and 12 hours post morning dose of ranolazine
Days 8-10: Pre morning dose of ranolazine

PK and Statistical Analysis:

Cmax, tmax, AUC0-∞, CL/F, k and t1/2 of the warfarin enantiomers were calculated using standard compartment model independent methods. The AUC0-∞ was calculated by applying the linear trapezoidal rule using actual sampling times and extrapolating to infinity. Oral clearance was computed from Dose/AUC0-∞ • weight, where the dose is the dose of either (+)R or (-)S warfarin (12.5 mg) and weight is the subject's pre-trial body weight. The pharmacodynamic parameters, maximum prothrombin time, PTmax, the corresponding time, tmax PT and the prothrombin time versus time curve up to 144 hours after administartion, AUC0-144PT, were computed. The AUC0-144 was computed by the linear trapezoidal rule.
Except for Tmax and TmaxPT, the pharmacokinetic and pharmacodynamic parameters were analyzed using a mixed effect analysis of variance (ANOVA) model. The pharmacokinetic parameters for (+)R warfarin and (-)S warfarin were analyzed separately. The fixed effects were sequence (ranolazine/placebo, placebo ranolazine), phase (Phase 1/Phase 2) and treatment (ranolazine, placebo). The random effects were subject (within sequence) and the residual. Carryover was tested for by testing the sequence effect against the (within sequence effect). The analysis was performed using untransformed and log transformed data. All treatment comparisons were performed via two-sided tests using estimates of variability from the ANOVA

model. The 90% and 95% confidence intervals were calculated for treatment comparisons. For the analysis of Tmax and TmaxPT the Wilcoxon rank sum test was used.

Safety:

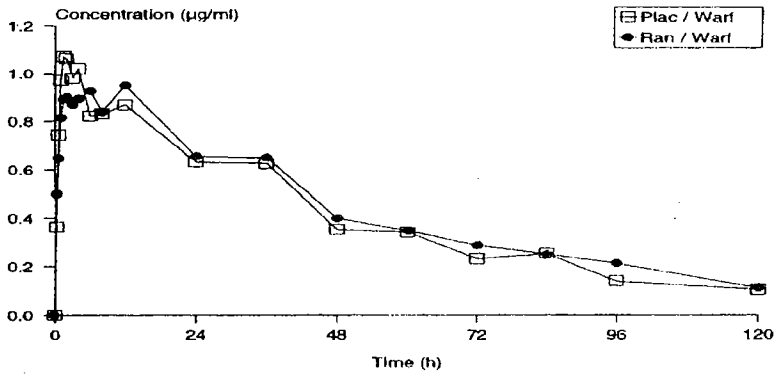
Standard 12 lead ECG recordings were performed and systolic and diastolic erect and supine blood pressure and heart rate measured at the following times:
Day 1: Pre morning dose and 1 hour after morning dose of ranolazine
Day 4: Pre morning dose and 1 hour and 9 hours after morning dose (no vital signs were measured 9 hours after the morning dose)
Days 5-10: Pre morning dose
The ECG intervals as measured by the machine were taken.

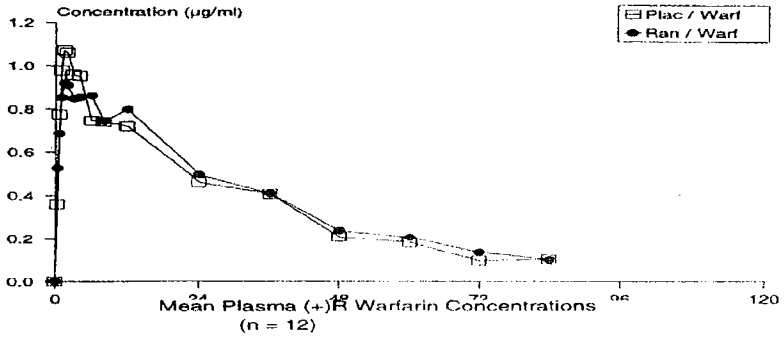
RESULTS:

Twelve subjects entered and completed the study. All subjects were males and of Caucasian origin. Their mean age was 26.5 years.

PK:

The plasma concentration profiles of (+) R- and (-) S warfarin in the presence and absence of ranolazine are shown in the figures below:





The mean pharmacokinetic parameters for (+) R and (-) S warfarin and the results of the statistical analysis of the ln transformed data are listed in the following tables:

- Mean ± SD Warfarin Pharmacokinetic Parameters (n = 12)

Parameter	(+)R Warfarin		(-)S Warfarin	
	Plac/Warf	Ran/Warf	Plac/Warf	Ran/Warf
Cmax (µg/ml)	1.41 ± 0.501	1.24 ± 0.562	1.42 ± 0.498	1.27 ± 0.606
Median Tmax (h)	2.50	3.00	1.50	1.00
AUCinf (µg.h/ml)	59.7 ± 16.9†	65.4 ± 19.5†*	37.8 ± 13.5	40.6 ± 15.4
CL/F (ml/min/kg)	0.0520 ± 0.0185†	0.0473 ± 0.0152†	0.0819 ± 0.0273	0.0775 ± 0.0260
t1/2 (h)	39.4 ± 5.57†	44.9 ± 11.4†	31.1 ± 12.5	31.8 ± 12.2

†: n = 11

Warfarin Pharmacokinetic Parameters : R enantiomer
Log-transformed Data

Treatment		Parameter			
		Cmax (R) (µg/ml)	AUCinf (R) (µg.h/ml)	CL/F (R) (ml/min/kg)	t½ (R) (h)
Ran/Warf	mean	1.1583	63.12	0.04513	43.11
	n	12	11	11	11
Plac/Warf	mean	1.3024	57.47	0.04956	38.74
	n	12	11	11	11
Ran/Warf-Plac/Warf	ratio	88.9%	109.8%*	91.0%*	111.3%
	p	0.360	0.033	0.033	0.130
	95% CI	(67.8%,116.7%)	(101.0%,119.5%)	(83.7%,99.1%)	(96.3%,128.7%)
	90% CI	(71.3%,111.0%)	(102.6%,117.6%)	(85.0%,97.5%)	(98.9%,125.2%)

Key: mean = least square mean
n = number of subjects
ratio = ratio of least square geometric means
p = probability * p<0.05, ** p<0.01, *** p<0.001

95% CI = 95% Confidence Interval for ratio of means
90% CI = 90% Confidence Interval for ratio of means
Ran/Warf = Ranolazine IR 400 mg tid/Warfarin 25 mg on Day 4
Plac/Warf = Placebo Ranolazine IR 400 mg tid/Warfarin 25 mg on Day 4
(R) = Warfarin R enantiomer

Warfarin Pharmacokinetic Parameters : S enantiomer
Log-transformed Data

Treatment		Parameter			
		Cmax (S) (µg/ml)	AUCinf (S) (µg.h/ml)	CL/F (S) (ml/min/kg)	t½ (S) (h)
Ran/Warf	mean	1.1742	37.97	0.07338	30.07
	n	12	12	12	12
Plac/Warf	mean	1.3172	35.78	0.07788	29.18
	n	12	12	12	12
Ran/Warf-Plac/Warf	ratio	89.2%	106.1%	94.2%	103.1%
	p	0.354	0.309	0.309	0.766
	95% CI	(68.5%,116.0%)	(93.8%,120.1%)	(83.3%,106.6%)	(82.7%,128.5%)
	90% CI	(72.0%,110.4%)	(96.0%,117.4%)	(85.2%,104.2%)	(86.2%,123.3%)

Key: mean = least square mean
n = number of subjects
ratio = ratio of least square geometric means
p = probability * p<0.05, ** p<0.01, *** p<0.001

95% CI = 95% Confidence Interval for ratio of means
90% CI = 90% Confidence Interval for ratio of means
Ran/Warf = Ranolazine IR 400 mg tid/Warfarin 25 mg on Day 4
Plac/Warf = Placebo Ranolazine IR 400 mg tid/Warfarin 25 mg on Day 4
(S) = Warfarin S enantiomer

The k value for (+) R warfarin could not be determined reliably for 1 subject, as plasma concentrations were not quantifiable for a sufficient length of time during the terminal phase. The AUCinf, CL/F and t1/2 were computed for this subject, but not included in the statistical analysis. Tmax for (-) S warfarin showed a sequence effect.
The P eriod 1 and complete data sets provided similar results. The arithmetic mean Cmax of (+) R warfarin was 12.1% smaller and AUCinf was 9.5% greater during co-administration of ranolazine than during placebo treatment with the complete data set. For (-) S warfarin, similarly mean Cmax was 10.6% smaller and AUCinf 7.4% greater during co-administration of ranolazine than during placebo treatment. Similar results were obtained when the geometric mean wefre used. The 90% confidence intervals for Cmax for both enantiomers were not contained in the 80% to 125% range. The Tmax values for the 2 enantiomers appeared not to be affected by the co-administration of ranolazine.

Safety:

There was a statistically significant sequence effect observed with the untransformed and ln transformed PT data and an anlysis of the period 1 data was perfomed. The results of the period 1 PT data and results of the statistical evaluation are shown in the following 2 tables:

PERIOD 1 - MEAN ± SD WARFARIN PROTHROMBIN TIME PARAMETERS AND THEIR STATISTICAL COMPARISONS (n=6)

Parameter	Plac / Warf	Ran / Warf
PTmax (sec)	19.8 ± 3.32	28.2 ± 6.65
Median TmaxPT (h)	36.0	36.0
AUC0-144hPT (sec.h)	2311 ± 226	2775 ± 271

Prothrombin Time Parameters
Log-transformed Data - Period 1

Treatment		Parameter	
		AUC0-144PT (sec.h)	PTmax (sec)
Ran/Warf	mean	2763.9	27.58
	n	6	6
Plac/Warf	mean	2302.1	19.58
	n	6	6
Ran/Warf-Plac/Warf	ratio	120.1%**	140.8%*
	p	0.009	0.016
	95% CI	(105.8%,136.3%)	(108.3%,183.2%)
	90% CI	(108.3%,133.1%)	(113.7%,174.4%)

Key: mean = least square mean
n = number of subjects
ratio = ratio of least square geometric means
p = probability * p<0.05, ** p<0.01, *** p<0.001
95% CI = 95% Confidence Interval for ratio of means
90% CI = 90% Confidence Interval for ratio of means
Ran/Warf = Ranolazine IR 400 mg tid/Warfarin 25 mg on Day 4
Plac/Warf = Placebo Ranolazine IR 400 mg tid/Warfarin 25 mg on Day 4

The arithmetic mean PTmax and AUC0-144hPT in the presence of ranolazine increased 1. 42 and 1.20 fold respectively. Similar results were obtained using the log transformed data. The 90% confidence intervals of neither parameter were contained in the 80% to 125% range.

The mean QTc intervals observed in both periods and in period 1 of the study are presented in the following 2 tables:

MEAN ECG DATA
QT_c Interval (msec)

Day	Time Post-Dose	Treatment					
		Ran/Warf			Plac/Warf		
		n	mean	se	n	mean	se
1	Pre-dose	12	400.3	5.1	12	396.8	4.2
	1 h	12	400.6	4.5	12	396.6	4.3
4	Pre-dose	12	395.7	3.7	12	387.3	4.9
	1 h	12	397.8	4.2	12	385.8	3.8
	9 h	12	393.4	3.7	12	385.3	5.5
5	Pre-dose	12	393.6	5.1	12	385.8	2.9
6	Pre-dose	12	388.7	4.4	12	389.2	3.7
7	Pre-dose	12	392.3	5.1	12	386.6	3.8
8	Pre-dose	12	394.3	4.9	12	388.3	5.0
9	Pre-dose	12	396.7	4.5	12	384.8	6.0
10	Pre-dose	12	387.0	4.5	12	391.7	4.2

Key: n = number of subjects
mean = raw (unadjusted) mean
se = standard error of the mean
Ran/Warf = Ranolazine IR 400 mg tid/Warfarin 25 mg on Day 4
Plac/Warf = Placebo Ranolazine IR 400 mg tid/Warfarin 25 mg on Day 4

MEAN ECG DATA
QT_c Interval (msec)
Period 1

Day	Time Post-Dose	Treatment					
		Ran/Warf			Plac/Warf		
		n	mean	se	n	mean	se
1	Pre-dose	6	403.3	7.3	6	388.7	6.3
	1 h	6	410.5	4.8	6	390.5	6.3
4	Pre-dose	6	396.3	6.0	6	380.2	7.7
	1 h	6	400.3	4.9	6	376.2	4.6
	9 h	6	389.5	5.5	6	372.8	6.8
5	Pre-dose	6	396.7	7.5	6	383.8	3.9
6	Pre-dose	6	395.7	6.9	6	388.7	5.9
7	Pre-dose	6	400.2	6.4	6	379.8	5.4
8	Pre-dose	6	400.8	6.5	6	382.7	8.0
9	Pre-dose	6	404.0	6.8	6	377.3	9.6
10	Pre-dose	6	395.3	6.8	6	382.0	4.5

Key: n = number of subjects
mean = raw (unadjusted) mean
se = standard error of the mean
Ran/Warf = Ranolazine IR 400 mg tid/Warfarin 25 mg on Day 4
Plac/Warf = Placebo Ranolazine IR 400 mg tid/Warfarin 25 mg on Day 4

With the complete data set the maximum observed mean QTc interval was recorded pre-dose on Day 1 with the plac/warf and the ran/warf treatments. The subsequent decrease in the QTc intervals, obeserved during the course of both treatments, was more pronounced with the

plac/warf treatment than with the ran/warf treatment. With the period 1 data the mean QTc interval measured pre-dose on Day 1 was much smaller for the plac/warf treatment than for the ran/warf treatment. This difference was maintained thorughout the treatments.

The most common AE reported was headache for 5 subjects during the ran/warf treatment and 5 during the plac/warf treatment. Nausea was reported by 3 subjects during the ran/warf treatment and in 2 subjects during the plac/warf treatment. Other events reported more frequently during the ran/warf treatment than during the plac/warf treatment included rash (2 subjects), lightheadedness/dizziness (2 subjects) and vomiting (1 subject).

CONCLUSION:

Co-administration of ranolazine 324 mg tid to a single dose of 25 mg warfarin impacts the pharmacokinetics of both enantiomers of warfarin and the prothrombin time parameters.

COMMENT:

1. Details on the characteristics of the calibration curves for the warfarin enantiomers were not provided.
2. The estimates for precision of the assay determined from the QC samples for both warfarin enatiomers were outside the ± 15% limits. Estimates for accuracy were not given.
3. The protocol stated that the protein binding of the enantiomers was to be determined. However, protein binding data were not provided.
4. CL/f was corrected for body weight on the assumption that the oral clerance depends linearly on body weight. No evidence in support of this normalization procedure was provided.
5. The present study used subtherapeutic dose levels of ranolazine and the extent of the interaction between ranolazine and warfarin at therapeutically effective dose levels of ranolazine may be greater. A study using therapeutically effective dose levels of ranolazine should have been performed.

Appears This Way
On Original

STUDY RANS0121- A STUDY TO INVESTIGATE THE POTENTIAL INTERACTION BETWEEN RANOLAZINE SR AND DILTIAZEM IN HEALTHY YOUNG MALE SUBJECTS

STUDY INVESTIGATOR AND SITE: [

]

Report No.: RANS0121
Volume: 230-232, ITEM 6

Objectives:

To explore possible pharmacokinetic and pharmacodynamic interactions between diltiazem and ranolazine SR

FORMULATIONS:

SR tablets containing 500 mg ranolazine (Lot No. CT1147SC1215B)
Matching placebo tablets (Lot No. CT1147 SC1211A)
Tablets blinded into capsules containing 60 mg diltiazem (Lot No. CT1147 PMID: 8773 Lot No. 5589) (Tildiem®, Lorex Pharmaceuticals Ltd))
Matching placebo atenolol tablets (ICI) blinded into capsules (Lot No.CT1147 PMDI: 8053 Lot No. 5588)

STUDY DESIGN:

This was a randomized, double-blind, placebo-controlled, four-way crossover study, with the subjects dosed with diltiazem or placebo on Days 1-3, then continued from Day 4 on a combination of ranolazine SR or placebo until Day 8. Diltiazem or placebo was taken orally at a dose of 60 mg tid on Days 1-7, with 2 doses taken on Day 8, ranolazine SR or placebo was taken orally at a dose of 1000 mg bid on Days 4-7, with a single dose on Day 8. During the dosing period, hemodynamic, ECG and adverse event data were recorded and blood samples taken for the analysis of ranolazine and diltiazem plasma levels.
Based on previous data and using a two-sided t-test, enrollment of 12 subjects provided 80% power of detecting 20% and 25% differences in the AUC of ranolazine or diltiazem.

ASSAY:

Ranolazine and RS-88390 (CVT 2514):
The plasma concentrations of ranolazine and RS-88390 (CVT-2514) were determined at Syntex Reasearch Laboratories. The plasma concentrations of ranolazine and the metabolite were measured using a HPLC method with fluorimetric detection. The calibration range was from 9

ng/mL to 1844 ng/mL for ranolazine and from 5 ng/mL to 1656 ng/mL for RS-88390 (CVT-2514). RS-87986 was used as internal standard. Precision (CV, %) determined from the QC samples for ranolazine was within the ± 15% limits. Recovery for ranolazine ranged between 98.0% to 118%. Precision for RS-88390 (CVT-2514) ranged between 13.5% and 19.3% and was ouside the ± 15% limits. The recovery for RS-88390 (CVT-2514) ranged between 95.5% and 100%.

Diltiazem:

The diltiazem plasma concentrations were determined at [ ] The plasma concentrations of diltiazem were measured by a HPLC method with UV detection. The calibration range for the method was from 5 ng/mL to 1000 ng/mL. Precision (CV, %) of the method determined from QC samples was within the ±20% or
±15% limits.

Blood Sample Collection:

Blood samples for the determination of ranolazine, its metabolite RS-88390 (CVT-2514) and diltiazem were collected at the following times:
Days 4 and 8: Pre morning dosing and 1, 2, 3, 4, 5, 6, 8, and 12 hours post

PK and Statistical Analysis

The parameters Cmax, Tmax and Cmin were determined for ranolazine, and RS-88390 (CVT-2514) on Days 4 and 8. AUC0-12h (Day 4) and AUC 96-108h (Day 8) were determined for ranolazine and AUCtau on both days for diltiazem. The AUC values were computed on application of the linear trapezoidal rule.

All data (except Tmax) were analyzed using mixed effects analysis of variance (ANOVA) models. Day 4 and 8 data were analyzed separately. For the PK parameters the analysis was performed on both untransformed and log transformed data. For the blood pressure, heart rate and ECG interval data, the analysis was performed on both the observed values and changes from pre-dose within Day 4 and Day 8. For these parameters, pre-dose Day 1 values were also analyzed. The fixed effects included in ANOVA were treatment, phase, time and time by treatment. Carry-over and phase by time effects were tested and removed from the final model. Following the ANOVA, all comparisons at individual time points were performed via two-sided t-tests. No adjustments were made for multiple comparisons. The 90% and 95% confidence intervals were computed. The tmax data were analyzed by the Wilcoxon signed rank test, with Day 4 and 8 measurements analyzed separately.
For the blood pressure, heart rate and ECG interval data, the occurrence of a pharmacodynamic interaction was tested by analyzing whether the effect seen with the combination was greater or less than the sum of the expected effects of each drug given alone using the following contrast between treatment means:
(dilt/ran SR - pac/ran SR - dilt/plac + plac/plac)
In the absence of a significant interaction between diltiazem and ranolazine, the main effects of the two individual treatments were examined via the following contrasts:

Main effect of ranolazine: ½ (dilt/ran SR+plac/ran SR-dilt/plac-plac/plac)
Main effect of diltiazem: ½ (dilt/ran SR+dilt/plac-plac/ran SR-plac/plac)

If a statistically significant pharmacodynamic interaction was detected, the above main effects were no longer valid due to the presence of a synergistic element. In this case the main effects were calculated using the following contrasts:

Main effect of ranolazine: (plac/ran SR versus plac/plac)

Main effect of diltiazem: (dilt/plac versus plac/plac)

At each time point the following comparisons between treatment groups were also perfomed:
1. Dilt/Ran SR versus plac/ran SR
2. Dilt/Ran SR versus dilt/plac
3. Dilt/Ran SR versus plac/plac

Safety:

Standard 12-lead ECG recordings were performed at the following times:
Days 4 and 8: Pre-morning dosing and 2, 4, 6, 8, 10 and 12 hours after the morning dosing
Days 5-7: Pre-morning dosing and 4 and 12 hours post morning dosing

Supine and erect blood pressure and heart rate were recorded at the following times:
Days 4, 5-7 and 8: Pre-morning dosing and 2, 4, 6, 8, 10 and 12 hours after the morning dose

RESULTS:

Fourteen (14) healthy male subjects were enrolled and 12 completed the study. Their mean age was 26 years. All were Caucasians. Two subjects were withdrawn after the first dose of the study as they had been inappropriately enrolled (pre-dose interval PR >200msec). Two additional subjects stopped dosing after the first dose of Phase 4 for personal reasons. Both subjects returned to the clinic to repeat Phase 4.

PK:
The mean pharmacokinetic parameters obtained for ranolazine and the results of the statistical analysis are listed in the following 3 tables:

MEAN RANOLAZINE PHARMACOKINETIC PARAMETERS AND THEIR STATISTICAL COMPARISONS

Parameter	Day 4				Day 8			
	Plac / Ran SR		Dilt / Ran SR		Plac / Ran SR		Dilt / Ran SR	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cmax (ng/ml)	1121	649	1679	534	3052	1094	5497	1851
Median Tmax (h)	4.50	-	4.00	-	3.00	-	3.00	-
Cmin (ng/ml)	285	95.1	556	295	1422	834	3074	1017
AUC (ng.h/ml)*	7758	2965	14207	4082	26550	11417	50415	17157

* = AUC0-12h for Day 4 and AUC96-108h for Day 8

Ranolazine Pharmacokinetic Parameters : Day 4
Log-Transformed Data

Treatment		Parameter		
		AUC0-12h (ng.h/ml)	Cmax (ng/ml)	Cmin (ng/ml)
Plac/Ran SR	mean	7229.1	985.9	271.4
	n	12	12	12
Dilt/Ran SR	mean	13512.3	1588.6	480.6
	n	12	12	12
Dilt/Ran SR - Plac/Ran SR	ratio	186.9%***	161.1%**	177.1%*
	p	<0.001	0.003	0.012
	95% CI	(152.3%,229.4%)	(123.6%,210.1%)	(117.6%,266.7%)
	90% CI	(158.5%,220.5%)	(130.1%,199.6%)	(127.3%,246.4%)

Key:
n = number of subjects
mean = least square geometric mean
ratio = ratio of least square geometric means
p = probability * p<0.05, ** p<0.01, *** p<0.001
95% CI = 95% Confidence Interval for mean ratio
90% CI = 90% Confidence Interval for mean ratio
Plac/Ran SR = Placebo Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid
Dilt/Ran SR = Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid

Ranolazine Pharmacokinetic Parameters : Day 8
Log-Transformed Data

Treatment		Parameter		
		AUC96-108h (ng.h/ml)	Cmax (ng/ml)	Cmin (ng/ml)
Plac/Ran SR	mean	24527.8	2884.2	1233.0
	n	12	12	12
Dilt/Ran SR	mean	47960.3	5241.2	2928.3
	n	12	12	12
Dilt/Ran SR - Plac/Ran SR	ratio	195.5%***	181.7%***	237.5%***
	p	<0.001	<0.001	<0.001
	95% CI	(164.7%,232.1%)	(152.3%,216.8%)	(179.4%,314.4%)
	90% CI	(170.3%,224.5%)	(157.6%,209.5%)	(189.4%,297.6%)

Key:
n = number of subjects
mean = least square geometric mean
ratio = ratio of least square geometric means
p = probability * p<0.05, ** p<0.01, *** p<0.001
95% CI = 95% Confidence Interval for mean ratio
90% CI = 90% Confidence Interval for mean ratio
Plac/Ran SR = Placebo Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid
Dilt/Ran SR = Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid

The arithmetic mean Cmax and AUC values of ranolazine on Day 4 in the presence of diltiazem increased 1.50 and 1.83 fold, respectively. On Day 8 the Cmax and AUC values for ranolazine in the presence of diltiazem increased 1.80 and 1.90 fold and 89.9%, respectively. Similar 1.61 and 1.87 fold increases in Cmax and AUC,respectively, of ranolazine in the presence of diltiazem were obtained on Day 4 when the geometric means were used. The corresponding increases in Cmax and AUC on Day 8 were 1.82 and 1.96 fold, respectively. None of the 90% confidence intervals of the log transformed data was contained within the 80% to 125% range. There was no difference in the median Tmax values observed for ranolazine.

The mean pharmacokinetic parameters of the metabolite RS-88390 (CVT-2514) are listed in the following tables:

DAY 4 MEAN RS-88390 PHARMACOKINETIC PARAMETERS

Treatment = Plac / Ran SR

Parameter		
Cmax (ng/ml)	505	405
Tmax (h)	5.50*	-
Cmin (ng/ml)	116	43.7
AUC0-12h (ng.h/ml)	3455	1849
AUC ratio	0.455	0.189

Treatment = Dilt / Ran SR

Parameter		
Cmax (ng/ml)	620	385
Tmax (h)	9.94*	-
Cmin (ng/ml)	153	107
AUC0-12h (ng.h/ml)	5217	2929
AUC ratio	0.372	0.169

AUC ratio = AUC0-12h(RS-88390)/AUC0-12h(Ranolazine)

* = median Tmax

DAY 8 MEAN RS-88390 PHARMACOKINETIC PARAMETERS

Treatment = Plac / Ran SR

Parameter		
Cmax (ng/ml)	811	310
Tmax (h)	4.00*	-
Cmin (ng/ml)	458	180
AUC0-12h (ng.h/ml)	7267	2529
AUC ratio	0.320	0.178

Treatment = Dilt / Ran SR

Parameter		
Cmax (ng/ml)	1216	665
Tmax (h)	4.00*	-
Cmin (ng/ml)	660	242
AUC0-12h (ng.h/ml)	10255	4538
AUC ratio	0.231	0.149

AUC ratio = AUC0-12h(RS-88390)/AUC0-12h(Ranolazine)

* = median Tmax

The arithmetic mean Cmax and AUC0-12 values for RS-88390 (CVT-2514) on Day 4 increased 1.23 and 1.50 fold, respectively, in the presence of diltiazem. The Cmax and AUC0-12 values of the ranolazine metabolite on Day 8 increased 1.50 ans 1.41 fold, respectively, in the presence of diltiazem. The mean AUC ratio of metabolite to ranolazine tended to be smaller in the presence than in the absence of diltiazem on both Day 4 and 8. The ratios on Day 8 tended to be smaller than on Day 4

The mean pharmacokinetic parameters and the results of the statistical analysis for diltiazem are provided in the following 3 tables:

MEAN DILTIAZEM PHARMACOKINETIC PARAMETERS AND THEIR STATISTICAL COMPARISONS

Parameter	Day 4				Day 8			
	Dilt / Plac		Dilt / Ran SR		Dilt / Plac		Dilt / Ran SR	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cmax (ng/ml)	121	37.4	136	41.9	114	47.0	120	36.8
Median Tmax (h)	3.00	-	2.00	-	2.00	-	2.00	-
Cmin (ng/ml)	62.5	22.3	65.4	21.3	52.6	20.5	59.4	23.1
AUCtau (ng.h/ml)	736	241	813	250	662	249	723	232

Diltiazem Pharmacokinetic Parameters : Day 4
Log-Transformed Data

Treatment	[redacted]	Parameter		
		AUCtau (ng.h/ml)	Cmax (ng/ml)	Cmin (ng/ml)
Dilt/Plac	mean	700.3	115.42	58.42
	n	12	12	12
Dilt/Ran SR	mean	772.0	129.05	61.63
	n	12	12	12
Dilt/Ran SR - Dilt/Plac	ratio	110.2%	111.8%	105.5%
	p	0.103	0.122	0.462
	95% CI	(97.6%,124.5%)	(96.3%,129.8%)	(89.9%,123.8%)
	90% CI	(99.9%,121.6%)	(99.2%,126.1%)	(92.7%,120.0%)

Key: n = number of subjects
mean = least square geometric mean
mean difference = ratio of least square geometric means
p = probability * p<0.05, ** p<0.01, *** p<0.001
95% CI = 95% Confidence Interval for mean ratio
90% CI = 90% Confidence Interval for mean ratio
Dilt/Plac = Diltiazem 60 mg tid/Placebo Ranolazine SR 1000 mg bid
Dilt/Ran SR = Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid

Diltiazem Pharmacokinetic Parameters : Day 8
Log-Transformed Data

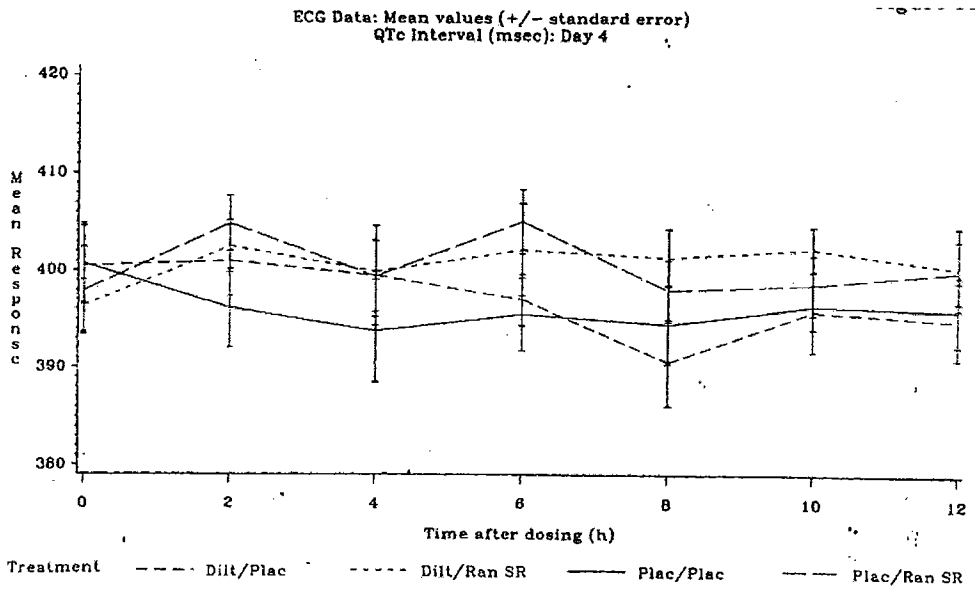
Treatment	[redacted]	Parameter		
		AUCtau (ng.h/ml)	Cmax (ng/ml)	Cmin (ng/ml)
Dilt/Plac	mean	618.6	105.85	48.65
	n	12	12	12
Dilt/Ran SR	mean	684.3	114.48	54.85
	n	12	12	12
Dilt/Ran SR - Dilt/Plac	ratio	110.6%	108.2%	112.7%
	p	0.294	0.453	0.189
	95% CI	(89.9%,136.1%)	(86.0%,136.0%)	(93.0%,136.7%)
	90% CI	(93.6%,130.7%)	(89.9%,130.1%)	(96.5%,131.7%)

Key: n = number of subjects
mean = least square geometric mean
ratio = ratio of least square geometric means
p = probability * p<0.05, ** p<0.01, *** p<0.001
95% CI = 95% Confidence Interval for mean ratio
90% CI = 90% Confidence Interval for mean ratio
Dilt/Plac = Diltiazem 60 mg tid/Placebo Ranolazine SR 1000 mg bid
Dilt/Ran SR = Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid

The arithmetic mean Cmax and AUCtau values of diltiazem on Day 4 in the presence of ranolazine increased 1.12 and 1.10 fold, respectively. The mean Cmax and AUCtau values on Day 8 in the presence of ranolazine increased 1.05 and 1.09 fold, respectively. Using the geometric means for Cmax and AUC similar 1.12 and 1.10 fold increases, respectively, were observed for diltiaazem in the presence of ranolazine on Day 4. The corresponding values on Day 8 were 1.08 and 1.11, respectively. The 90% confidence intervals of the log transformed data were only for Cmax on Day 4 contained within the 80% to 125% range, whereas the log transformed data for AUCtau on Day 4, and for Cmax and AUCtau on Day 8 were outside of the 80% to 125% range. There was no difference in the median Tmax values for diltiazem observed.

Safety:

The mean QTc intervals during a dosing ranolazine interval on Day 4 are shown in the following figure:



The mean QTc intervals measured, the changes from pre-dose and the treatment comparisons for Day 4 are listed in the following 3 tables:

QT_c Interval (msec)
Treatment Comparisons : Changes from Pre-dose : Day 4

Comparison		Time (h) 2	4	6	8	10	12
Dilt/Ran SR - Plac/Ran SR	mean difference	-0.8	2.1	-1.3	5.0	5.3	1.9
	sed	6.4	6.4	6.4	6.4	6.4	6.4
	p	0.907	0.747	0.836	0.439	0.409	0.768
Dilt/Ran SR - Dilt/Plac	mean difference	5.7	4.6	9.3	15.0*	10.7	9.6
	sed	6.4	6.4	6.4	6.4	6.4	6.4
	p	0.380	0.478	0.149	0.021	0.099	0.138
Dilt/Ran SR - Plac/Plac	mean difference	10.8	10.6	11.1	11.3	10.4	8.8
	sed	6.4	6.4	6.4	6.4	6.4	6.4
	p	0.094	0.102	0.087	0.080	0.107	0.172
Ranolazine Main Effect	mean difference	8.8	8.5	10.9*	10.7*	7.9	6.3
	sed	4.6	4.6	4.6	4.6	4.6	4.6
	p	0.060	0.152	0.018	0.020	0.085	0.072
Diltiazem Main Effect	mean difference	2.2	4.0	0.2	0.7	2.5	0.6
	sed	4.6	4.6	4.6	4.6	4.6	4.6
	p	0.628	0.376	0.964	0.884	0.577	0.898
Interaction	mean difference	-5.9	-3.9	-3.1	8.7	5.6	2.7
	sed	9.1	9.1	9.1	9.1	9.1	9.1
	p	0.517	0.668	0.735	0.343	0.541	0.770

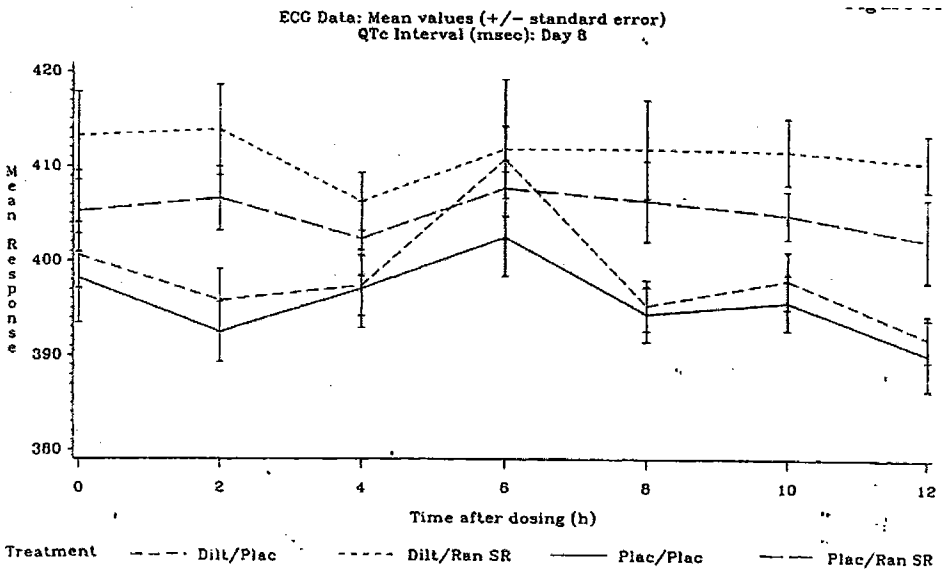
Key:
mean difference = least square mean difference
sed = standard error of least square mean difference
p = probability * p<0.05, ** p<0.01, *** p<0.001
Plac/Plac = Placebo Diltiazem 60 mg tid/Placebo Ranolazine SR 1000 mg bid
Plac/Ran SR = Placebo Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid
Dilt/Plac = Diltiazem 60 mg tid/Placebo Ranolazine SR 1000 mg bid
Dilt/Ran SR = Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid

QT_c Interval (msec)
Treatment Comparisons : Changes from Pre-dose : Day 4

Comparison		Time (h) 2	4	6	8	10	12
Dilt/Ran SR - Plac/Ran SR	mean difference	-0.8	2.1	-1.3	5.0	5.3	1.9
	sed	6.4	6.4	6.4	6.4	6.4	6.4
	p	0.907	0.747	0.836	0.439	0.409	0.766
Dilt/Ran SR - Dilt/Plac	mean difference	5.7	4.6	9.3	15.0*	10.7	9.6
	sed	6.4	6.4	6.4	6.4	6.4	6.4
	p	0.380	0.478	0.149	0.021	0.099	0.138
Dilt/Ran SR - Plac/Plac	mean difference	10.8	10.6	11.1	11.3	10.4	8.8
	sed	6.4	6.4	6.4	6.4	6.4	6.4
	p	0.094	0.102	0.087	0.080	0.107	0.172
Ranolazine Main Effect	mean difference	8.6	6.5	10.9*	10.7*	7.9	8.3
	sed	4.6	4.6	4.6	4.6	4.6	4.6
	p	0.060	0.152	0.018	0.020	0.085	0.072
Diltiazem Main Effect	mean difference	2.2	4.0	0.2	0.7	2.5	0.6
	sed	4.6	4.6	4.6	4.6	4.6	4.6
	p	0.628	0.376	0.964	0.884	0.577	0.898
Interaction	mean difference	-5.9	-3.9	-3.1	8.7	5.6	2.7
	sed	9.1	9.1	9.1	9.1	9.1	9.1
	p	0.517	0.668	0.735	0.343	0.541	0.770

Key: mean difference = least square mean difference
sed = standard error of least square mean difference
p = probability * p<0.05, ** p<0.01, *** p<0.001
Plac/Plac = Placebo Diltiazem 60 mg tid/Placebo Ranolazine SR 1000 mg bid
Plac/Ran SR = Placebo Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid
Dilt/Plac = Diltiazem 60 mg tid/Placebo Ranolazine SR 1000 mg bid
Dilt/Ran SR = Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid

The mean QTc intervals during a ranolazine dose interval on Day 8 are depicted in the following figure:



The mean QTc intervals measured, the changes from pre-dose and the treatment comparisons for Day 8 are presented in the following 3 tables:

Mean QT_c Interval (msec)
Changes from Pre-dose : Day 8

Comparison		Time (h) 2	4	6	8	10	12
Plac/Plac	mean	-5.7	-1.1	4.4	-3.8	-2.5	-8.0
	se	4.2	4.2	4.2	4.2	4.2	4.2
	n	12	12	12	12	12	12
Plac/Ran SR	mean	1.4	-2.8	2.5	1.2	-0.3	-3.0
	se	4.2	4.2	4.2	4.2	4.2	4.2
	n	12	12	12	12	12	12
Dilt/Plac	mean	-4.8	-3.2	10.3	-5.3	-2.6	-8.7
	se	4.2	4.2	4.2	4.2	4.2	4.2
	n	12	12	12	12	12	12
Dilt/Ran SR	mean	0.7	-6.9	-1.3	-1.3	-1.6	-2.8
	se	4.2	4.2	4.2	4.2	4.2	4.2
	n	12	12	12	12	12	12

Key: n = number of subjects
mean = least square mean
se = standard error of least square mean
Plac/Plac = Placebo Diltiazem 60 mg tid/Placebo Ranolazine SR 1000 mg bid
Plac/Ran SR = Placebo Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid
Dilt/Plac = Diltiazem 60 mg tid/Placebo Ranolazine SR 1000 mg bid
Dilt/Ran SR = Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid

QT_c Interval (msec)
Treatment Comparisons : Changes from Pre-dose : Day 8

Comparison		Time (h) 2	4	6	8	10	12
Dilt/Ran SR - Plac/Ran SR	mean difference	-0.8	-4.1	-3.8	-2.5	-1.3	0.2
	sed	5.9	5.9	5.9	5.9	5.9	5.9
	p	0.898	0.487	0.514	0.670	0.831	0.977
Dilt/Ran SR - Dilt/Plac	mean difference	5.4	-3.8	-11.6*	3.9	1.0	5.8
	sed	5.9	5.9	5.9	5.9	5.9	5.9
	p	0.356	0.523	0.049	0.505	0.865	0.321
Dilt/Ran SR - Plac/Plac	mean difference	6.3	-5.8	-5.8	2.4	0.9	5.2
	sed	5.9	5.9	5.9	5.9	5.9	5.9
	p	0.281	0.321	0.328	0.680	0.876	0.378
Ranolazine Main Effect	mean difference	6.3	-2.8	-6.8	4.4	1.6	5.4
	sed	4.1	4.1	4.1	4.1	4.1	4.1
	p	0.133	0.508	0.105	0.288	0.703	0.192
Diltiazem Main Effect	mean difference	0.1	-3.1	1.0	-2.0	-0.7	-0.3
	sed	4.1	4.1	4.1	4.1	4.1	4.1
	p	0.984	0.458	0.810	0.630	0.872	0.952
Interaction	mean difference	-1.7	-2.0	-9.7	-1.0	-1.2	0.8
	sed	8.3	8.3	8.3	8.3	8.3	8.3
	p	0.841	0.810	0.245	0.904	0.888	0.920

Key: mean difference = least square mean difference
sed = standard error of least square mean difference
p = probability * p<0.05, ** p<0.01, *** p<0.001
Plac/Plac = Placebo Diltiazem 60 mg tid/Placebo Ranolazine SR 1000 mg bid
Plac/Ran SR = Placebo Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid
Dilt/Plac = Diltiazem 60 mg tid/Placebo Ranolazine SR 1000 mg bid
Dilt/Ran SR = Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid

QT_c Interval (msec)
Treatment Comparisons : Day 8

Comparison		Time (h) Pre-dose	2	4	6	8	10	12
Dilt/Ran SR - Plac/Ran SR	mean difference	8.0	7.3	3.9	4.2	5.5	6.8	8.2
	sed	4.4	4.4	4.4	4.4	4.4	4.4	4.4
	p	0.073	0.104	0.378	0.349	0.216	0.130	0.067
Dilt/Ran SR - Dilt/Plac	mean difference	12.7**	18.1***	8.9*	1.1	16.6***	13.7**	18.5***
	sed	4.4	4.4	4.4	4.4	4.4	4.4	4.4
	p	0.005	<0.001	0.046	0.807	<0.001	0.002	<0.001
Dilt/Ran SR - Plac/Plac	mean difference	15.1***	21.4***	9.3*	9.3*	17.5***	16.0***	20.3***
	sed	4.4	4.4	4.4	4.4	4.4	4.4	4.4
	p	<0.001	<0.001	0.038	0.036	<0.001	<0.001	<0.001
Ranolazine Main Effect	mean difference	9.9**	16.1***	7.1*	3.1	14.3***	11.5***	15.3***
	sed	3.1	3.1	3.1	3.1	3.1	3.1	3.1
	p	0.002	<0.001	0.024	0.320	<0.001	<0.001	<0.001
Diltiazem Main Effect	mean difference	5.2	5.3	2.1	6.2*	3.2	4.5	5.0
	sed	3.1	3.1	3.1	3.1	3.1	3.1	3.1
	p	0.098	0.093	0.499	0.049	0.308	0.149	0.115
Interaction	mean difference	5.6	3.9	3.6	-4.1	4.6	4.4	6.4
	sed	6.3	6.3	6.3	6.3	6.3	6.3	6.3
	p	0.375	0.533	0.569	0.516	0.466	0.482	0.308

Key: mean difference = least square mean difference
sed = standard error of least square mean difference
p = probability * p<0.05, ** p<0.01, *** p<0.001
Plac/Plac = Placebo Diltiazem 60 mg tid/Placebo Ranolazine SR 1000 mg bid
Plac/Ran SR = Placebo Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid
Dilt/Plac = Diltiazem 60 mg tid/Placebo Ranolazine SR 1000 mg bid
Dilt/Ran SR = Diltiazem 60 mg tid/Ranolazine SR 1000 mg bid

There was a statisticaly significant difference in the pre-dose Day 1 QTc interval when dilt/ran SR was compared with dilt/plac. Neither with the observed values nor with the change from baseline values was there evidence of a statistically significant pharmacodynamic interaction between ranolazine and diltiazem on Days 4 or 8. On Day 4 at 8 hours post dose there was a statistically significant difference between the dilt/ran SR and dilt/plac treatments in terms of the observed and change from baseline values. This was attributable to ranolazine and the increase in apparent QTc was in the range of 7.2 msec to 10.7 msec. On Day 8, in contrast to Day 4, there was a consistant pattern of prolonged apparent QTc intervals. There were statistically significant differences for the observed values pre-dose, 2, 4, 8, 10 and 12 hours after administration when dilt/ran SR was compared with dilt/plac. They were attributable to ranolazine and the estimated increase in apparent QTc ranged between 7.1 msec to 16.1msec. Similarly, statistically significant differences for the observed values were found at pre-dose, 2, 4, 6, 8, 10, and 12 hours post dose when the treatments dilt/ran SR and plac/plac were compared.
Changes in the T-wave morphology were observed in 8 subjects on the dilt/ran SR treatment. Three (3) of these subjects showed the same changes also during the ran/plac treatment. One subject displayed T-wave alterations also during the plac/plac treatment.

Statistically significant prolongations of the PR interval sustained throughout the ranolazine dosing interval and mostly attributable to diltiazem were seen on Days 4 and 8.

A statistically significant interaction between ranolazine and diltiazem affecting the erect diastolic blood pressure was seen on Day 4 at 4 hours after drug administration.

Headache was the most frequently reported AE: 3 subjects on placebo, 2 subjects on diltiazem alone, 2 subjects on ranolazine SR and 5 subjects on the combination treatment.
Nausea occurred in 1 subject on placebo, in 1 subject on diltiazem alone, and in 2 subjects on ranolazine alone. Nausea and vomitus occurred in 1 subject receiving the combination treatment.
One subject experienced lightheadedness during placebo treatment, 3 during treatment with ranolazine alone and 1 during combination treatment.
There was no clear relationship between the time of dosing and the occurrence of these episodes.

CONCLUSIONS:

The co-administration of diltiazem 60 mg tid to ranolazine 1000 mg bid impacts the pharmacokinetics of ranolazine clinically significantly. The impact of diltiazem co-administration on ranolazine is greater than on RS-88390 (CVT-2514). The increase in arithmetic mean Cmax and AUC observed in this study and in another study that used the same doses of ranolazine and diltiazem are comparable (CVT 3012). Ranolazine affects the pharmacokinetics of diltiazem statistically demonstrably, but the extent of the interaction is small. The ECG, blood pressure and heart rate data do not provide evidence for an important and consistent pharmacodynamic (synergistic) interaction between diltiazem and ranolazine. There is evidence for QTc prolongation by ranolazine that is more pronounced on Day 8 than on Day 4. The PR prolongation by diltiazem is expected.

COMMENTS:

1. The calibration curve characteristics for diltiazem, ranolazine and RS-88390 (CVT-2514) and estimates for the respective accuracies were not provided. The precision for RS-88390 (CVT-2514) was outside of the ±15% range.
2. Data on the crossvalidation of the HPLC method with UV detection used in the present study to measure ranolazine and the HPLC/MS/MS method used in other studies was not provided.
3. The formula for correcting QT for heart rate and a justification for its use was not provided.
4. The 90% confidence intervals derived from the log transformed data ought to be used to conclude default presence or absence of an interaction between diltiazem and ranolazine.
5. All the subjects enrolled were healthy male subjects. Higher than 60 mg tid doses of diltiazem are used. There may be limitations to the extrapolation of the data to the female and male target population.
6. A comparison of the results of the present study with those of the other study investigating the interaction between diltiazem and ranolazine at the same dose levels is presented in the following table:

Study	Subjects	Diltiazem Dose, mg	Regimen	Product	Ranolaz. Dose, mg	Regimen	Day	xCmax	xAUC

RAN0121	M, HV	60	tid	Tildiem	1000	bid	4	1.50	1.83
							8	1.80	1.90
CVT 3012	M, HV	180	qd	Cardizem	1000	bid	4	1.90	2.16
							8	1.50	1.52

M=Male, HV= Healthy volunteer, xCmax, = fold increase in Cmax of ranolazine in the presence of diltiazem, xAUC= fold increase in AUC of ranolazine in the presence of diltiazem

In the presence of Cardizem the inhibition of ranolazine's metabolism appears to decrease with time whereas in the presence of Tildiem the inhibition of ranolazine appears to be more time independent. The plasma concentrations of diltiazem were not measured in both studies so that the possible impact of differences in the time profiles of diltiazem associated with the immediate release and controlled relase formulations of diltiazem cannot be assessed.

Appears This Way
On Original

STUDY RAN 0111 (CL 6875) - A STUDY TO INVESTIGATE THE POTENTIAL PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTIONS BETWEEN RANOLAZINE AND DIGOXIN IN HEALTHY YOUNG MEN

STUDY INVESTIGATORAND SITE: [

]

Reporty No.: RAN0111 (CL 6875)
Volume No.: 220, 221, ITEM 6

OBJECTIVES:

To determine whether there is a pharmacokinetic or pharmacodynamic interaction when ranolazine and digoxin are co-administered.

FORMULATIONS:

IR caspules containing 400 mg ranolazine hydrochloride (342 mg base)(Lot No. CT1117 SC987H)
Matching placebos (Lot No. CT1117 SC272K)
Tablets containing 0.250 mg digoxin (Lanoxin®, Wellcome) (Lot No. CT 1117 11793/3746)

STUDY DESIGN:

This was a randomized, two-way crossover study with open administration of digoxin at a dose of 0.25 mg qd and double blind, placebo-controlled administration of ranolazine IR at a dose of 342 mg tid. Both drugs ae given for seven days with a single dose of each on Day 8. It was expected that steady state levels of ranolazine and digoxin would be reached by Day 3 and 7, respectively. There was a washout period of at least 13 days between phases.

ASSAY:

The plasma concentrations of digoxin were determined at [
]J A[ ]J immunoassay was used.
The LLOQ was 0.19 nmol/L. The precision (CV, %) of the method determined from the QC samples was within the ± 15% limits.

Blood Sample Collection:
Blood samples for the determination of the plasma digoxin levels were obtained on the following times:
Days 4-7: 6 hours after the digoxin dose

Day 8: Pre-dose, 20 and 40 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after the digoxin dose

PK and Statistical Analysis:

Cmax, tmax, C174 and AUC168-192h and Clpo were determined after the final dose of digoxin and ranolazine/placebo on Day 8. AUC168-192h was obtained on application of the trapezoidal rule and Clpo was computed from D/AUC168-192h. Statistical comparisons were made for Cmax, tmax, AUC168-192h, C174h and Clpo between treatments. In addition, the treatment differences of the 6 hour post-dose plasma digoxin levels on Days 4-7 were statistically evaluated. With the exception of tmax the pharmacokinetic parameters of digoxin were analyzed using a mixed effect analysis of variance (ANOVA) model with fixed effects of sequence, phase and treatment, and random effects of subject (within sequence) and the resisual. Carryover was tested for by testing the sequence effect against the subject (within sequence) effect. Phase and treatment effects were tested against the residual. The analysis was performed using the untransformed and log transformed data. All treatment comparisons were performed via two-sided t-tests using estimates of variability from the ANOVA model. Confidence intervals (90% and 95%) were calculated for the treatment comparisons. No adjustments were made for multiple comparisons.
The tmax data were analyzed using the Wilcoxon rank sum test and non-parametric 90% and 95% confidence intervals were calculated for the median difference between treatments.

Safety:

Standard 12 lead ECG recordings were performed at the following times:
Days 1-7: Pre-dose, and 1 and 4 hours post-dose
Day 8: pre-dose, and 2, 3, 4, 6, 8, 12 and 24 hours after administration of digoxin.
The ECG intervals as measured by the machine were used.

Supine and erect systolic and diastolic blood pressure and heart rate were determined at the following times:
Days 1-8: Pre-dose and 1 and 4 hours after the digoxin dose.

For both the PR and the QTc intervals, Day 1 pre-dose treatment means were compared between treatments using a mixed effects ANOVA model. The Day 8 data on the intervals were analyzed by a mixed effects ANOVA model. All treatment comparisons at individual time points were performed via two-sided t-tests using estimates of variability form the ANOVA model. Confidence intervals (95% and 90%) for differences between treatments means were calculated with no adjustments for multiple comparisons.

RESULTS:

Eight male subjects entered and completed the study and their data were evaluable for analysis. All were of Caucasian origin. The mean age of the subjects was 27.6 years.

PK:

The mean values of the pharmacokinetic parameters of digoxin and the statistical evaluation are presented in the following 2 tables:

MEAN ± SD DAY 8 DIGOXIN PHARMACOKINETIC PARAMETERS

Parameter	Treatment		Dig/Ran - Dig/Plac	
	Dig/Plac	Dig/Ran	p value	90 % CI
C_{max} (nmol/l)	1.65 ± 0.466	3.79 ± 1.47	<0.01	1.16, 3.12
t_{max} (h)	1.50*	0.667*	<0.05	-1.834, -0.334
$AUC_{168-192h}$ (nmol.h/l)	16.3 ± 3.60	22.6 ± 3.65	<0.01	3.44, 9.01
Cl_{po} (ml/min/kg)	4.44 ± 1.02	3.13 ± 0.478	<0.01	-1.951, -0.656
C_{174h} (nmol/l)	0.800 ± 0.193	0.938 ± 0.207	0.162	-0.03, 0.31

* = median t_{max}

To convert plasma levels to ng/ml, multiply nmol/l value by 0.781

Digoxin Pharmacokinetic Parameters : Day 8
Log-transformed Data

Treatment		Parameter			
		C_{max} (nmol/L)	$AUC_{168-192h}$ (nmol.h/L)	Oral Clearance (ml/min/kg)	C_{174h} (nmol/L)
Dig/Ran	mean	3.40	22.29	3.102	0.92
	n	8	8	8	8
Dig/Plac	mean	1.59	15.98	4.325	0.78
	n	8	8	8	8
Dig/Ran / Dig/Plac	ratio	213.9%*	139.4%**	71.7%**	117.6%
	p	0.012	0.006	0.006	0.172
	95% CI	(126.9%,360.8%)	(115.0%,169.0%)	(59.1%,87.0%)	(91.0%,152.0%)
	90% CI	(141.3%,324.0%)	(119.7%,162.5%)	(61.5%,83.6%)	(96.0%,144.2%)

Key: mean = least square mean
n = number of subjects
ratio = ratio of least square geometric means
p = probability * p<0.05, ** p<0.01, *** p<0.001
95% CI = 95% Confidence Interval for ratio of means
90% CI = 90% Confidence Interval for ratio of means
Dig/Ran = Digoxin 0.25 mg qd/Ranolazine IR 400 mg tid
Dig/Plac = Digoxin 0.25 mg qd/Placebo Ranolazine IR 400 mg tid

The arithmetic mean Cmax and AUC168-192h values of digoxin increased 2.30 and 1.39 fold, respectively, in the presence of ranolazine. Using the geometric means similar results were obtained. Cmax and AUC increased 2.14 and 1.39 fold, respectively, in the presence of ranolazine. For both parameters the 90% confidence intervals for the log transformed data were not contained in the 80% to 125% range. The median tmax value of digoxin was statistically significantly smaller in the presence than in the absence of ranolazine.

The mean digoxin levels measured 6 hours after administration on Days 4-8 are listed in the following table:

MEAN 6 H POST-DOSE PLASMA DIGOXIN LEVELS

Day	Mean ± SD Digoxin Plasma Level (nmol/l)		Dig/Ran - Dig/Plac	
	Dig/Plac	Dig/Ran	p value	90 % CI
4	0.625 ± 0.149	0.700 ± 0.151	0.107	0.00, 0.15
5	0.600 ± 0.107	0.638 ± 0.245	0.723	-0.16, 0.23
6	0.625 ± 0.116	0.763 ± 0.130	0.059	0.02, 0.25
7	0.713 ± 0.083	0.913 ± 0.155	<0.01	0.11, 0.29
8	0.800 ± 0.193	0.938 ± 0.207	0.162	-0.03, 0.31

To convert plasma levels to ng/ml, multiply nmol/l value by 0.781

Only the Day 7 value of digoxin was statistically significantly greater during treatment with ranolazine than during placebo treatment.

Safety:

The mean QTc values, the statistical evaluation of the pre-dose QTc intervals on Day 1 and the treatment comparisons of the mean QTc values are presented in the following 3 tables:

MEAN ECG DATA
QT_c Interval (msec)

Day	Time Post-Dose	Treatment					
		Dig/Ran			Dig/Plac		
		n	mean	se	n	mean	se
1	Pre-dose	8	391.4	6.5	8	401.8	6.7
	1 h	8	397.9	6.3	8	399.5	8.1
	4 h	8	395.5	3.9	8	395.1	6.0
2	Pre-dose	8	388.1	8.1	8	397.4	7.8
	1 h	8	390.9	6.7	8	393.1	6.3
	4 h	8	403.8	3.5	8	393.6	2.5
3	Pre-dose	8	396.4	7.5	8	395.3	4.7
	1 h	8	402.5	3.4	8	391.9	7.0
	4 h	8	396.8	4.0	8	390.0	5.9
4	Pre-dose	8	391.1	4.8	8	386.0	8.0
	1 h	8	392.6	3.5	8	393.3	5.2
	4 h	8	394.9	5.0	8	390.0	5.4
5	Pre-dose	8	400.6	6.5	8	384.9	6.2
	1 h	8	392.0	6.9	8	392.5	4.8
	4 h	8	403.0	8.3	8	393.0	3.4
6	Pre-dose	8	395.4	5.4	8	394.0	7.2
	1 h	8	394.5	4.4	8	393.9	5.7
	4 h	8	394.6	3.9	8	386.4	6.9
7	Pre-dose	8	393.6	4.1	8	384.9	4.0
	1 h	8	393.0	5.5	8	391.3	6.9
	4 h	8	399.0	3.6	8	388.4	4.8
8	Pre-dose	8	395.3	4.0	8	392.1	4.0
	1 h	8	388.6	5.1	8	388.5	4.5
	2 h	8	393.6	5.0	8	387.5	5.6
	4 h	8	390.9	5.0	8	393.3	4.3
	6 h	8	399.6	4.0	8	398.6	4.3
	8 h	8	398.4	4.2	8	386.3	5.1
	12 h	8	395.4	6.5	8	394.9	6.7
	24 h	8	395.8	6.8	8	387.9	7.1

Key: n = number of subjects
mean = raw (unadjusted) mean
se = standard error of the mean
Dig/Ran = Digoxin 0.25 mg qd/Ranolazine IR 400 mg tid
Dig/Plac = Digoxin 0.25 mg qd/Placebo Ranolazine IR 400 mg tid

QT_c Interval (msec)
Mean Values: Pre-dose Day 1

Treatment		
Dig/Ran	mean	391.4
	se	6.7
	n	8
Dig/Plac	mean	401.8
	se	6.7
	n	8
Dig/Ran - Dig/Plac	mean difference	-10.4
	sed	4.6
	p	0.064
	95% CI	(-21.6,0.8)

Key:
mean = least square mean
se = standard error of least square mean
n = number of subjects
mean difference = least square mean difference
sed = standard error of least square mean difference
p = probability * = p<0.05, ** = p<0.01, *** = p<0.001
95% CI = 95% Confidence Interval for mean difference
Dig/Ran = Digoxin 0.25 mg qd/Ranolazine IR 400 mg tid
Dig/Plac = Digoxin 0.25 mg qd/Placebo Ranolazine IR 400 mg tid

QT_c Interval (msec)
Mean Values and Treatment Comparisons : Day 8

Treatment		Time							
		Pre-dose	1 h	2 h	4 h	6 h	8 h	12 h	24 h
Dig/Ran	mean	395.3	388.6	393.6	390.9	399.6	398.4	395.4	395.8
	se	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1
	n	8	8	8	8	8	8	8	8
Dig/Plac	mean	392.1	388.5	387.5	393.3	398.6	386.3	394.9	387.9
	se	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1
	n	8	8	8	8	8	8	8	8
Dig/Ran - Dig/Plac	mean difference	3.1	0.1	6.1	-2.4	1.0	12.1	0.5	7.9
	sed	6.3	6.3	6.3	6.3	6.3	6.3	6.3	6.3
	p	0.622	0.984	0.335	0.708	0.875	0.058	0.937	0.216
	95% CI	(-9.4,15.7)	(-12.4,12.7)	(-6.4,18.7)	(-14.9,10.2)	(-11.6,13.6)	(-0.4,24.7)	(-12.1,13.1)	(-4.7,20.4)

Key:
mean = least square mean
se = standard error of least square mean
n = number of subjects
mean difference = least square mean difference
sed = standard error of least square mean difference
p = probability * p<0.05, ** p<0.01, *** p<0.001
95% CI = 95% Confidence Interval for mean difference
Dig/Ran = Digoxin 0.25 mg qd/Ranolazine IR 400 mg tid
Dig/Plac = Digoxin 0.25 mg qd/Placebo Ranolazine IR 400 mg tid

The mean QTc intervals were longer when ranolazine was co-administered with digoxin, even though the pre-dose Day 1 mean QT interval was shorter with dig/ran than with dig/plac. However, there were no statistical significant differences between the treatments on Day 8.

Headache was the most frequent AE reported by 1 subject after dig/plac and 6 subjects after dig/ran. Lightheadedness or dizziness, usually upon standing for the erect blood pressure measurements, was reported by 1 subject after dig/plac and by 2 subjects during dig/ran. These events occurred on mutiple occasions, mostly 1 hour after ranolazine administration and limited the recordings of the erect blood pressure.

CONCLUSIONS:

Ranolazine interacts significantly with the pharmacokinetics of digoxin resulting in a greater increase in Cmax than in AUC168-192. Digoxin is known to be a substrate of P-glycoprotein. In vitro data with human Caco2 cells (CVT 303.010-N, p.95) suggest that ranolazine can inhibit the baso-apical transport of digoxin. The observed interaction between ranolazine and digoxin observed in the present study confirms the findings obtained in 2 other studies with healthy volunteers (CVT 3011) and male and female patients with congestive heart failure (CVT 3021).

COMMENTS:

1. The characteristics of the calibration curve and estimates for the accuracy of the digoxin assay were not provided. Data documenting the absence of an interference from ranolazine were not given.
2. Baseline QTc interval determinations should have been performed over a 24 hour period.
3. The QT intervals should have been evaluated manually by a blinded cardiologist. A justification for the heart rate correction formula used for the QT intervals should have been provided.
4. The percent increase in arithmetic mean Cmax and AUC obtained in the three interaction studies conducted with digoxin and ranolazine were as follows:
5. The results of the 3 digoxin interaction studies are listed in following table:

Study	Digoxin Dose, mg	Regimen	Product	Ranolaz. Dose, mg	Regimen	Subjects	xCmax	xAUC
CVT 3021	0.125	qd	Lanoxin	SR 750	bid	M/F CHF	1.68	1.88
CVT 3011	0.125	qd	Lanoxin	SR 1000	bid	M, HV	1.46	1.60
RAN0111	0.250	qd	Lanoxin	IR 342	tid	M, HV	2.30	1.33

CHF= Congestive heart failure, HV= healthy volunteers, M=male, F= female, xCmax and xAUC= Fold increase in Cmax and AUC of digoxin in presence of ranolazine

The 3 studies studies indicate an interaction between digoxin and ranolazine. The ratio of the dose of ranolazine to digoxin appears not to impact the extent of the interaction. CHF may increase the effect of ranolazine on digoxin. The greater increase in dCmax in study RAN0111 may be caused by the more rapid release of ranolazine from the IR formulation.

DISSOLUTION SPECIFICATIONS FOR RANOLAZINE

Objective

1) To assess the acceptability of the dissolution conditions,
2) To assess the acceptability of the dissolution specifications proposed by the sponsor.
3) To assess the acceptability of biowaiver request for the in vivo testing of the 375 mg strength tablets. The sponsor tested the in vivo bioequivalence of only the 500 mg tablets (commercial to clinical) in the study CVT 301-15.

Formulation – Scale Up Batches

Ranolazine SR tablet, 375 mg
Lot Number: 1K2757A

Treatment B: Ranolazine SR tablet, 500 mg
Lot Number: 1K2754A

Dissolution pH

The sponsor tested the solubility of ranolazine at various pH values.

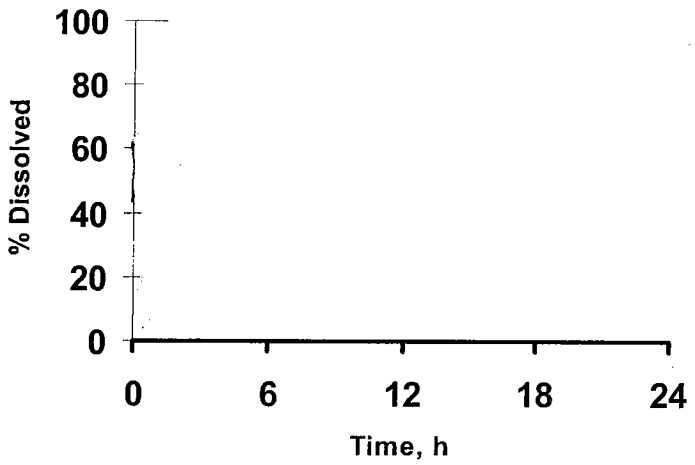
The sponsor has selected 0.1N HCl

Dissolution media

Paddle Speed

Both [ ] rpm paddle speeds provide similar dissolution profiles. The sponsor proposed to use — rpm.

Figure 2. Mean percent dissolved in citrate and 0.1N HCl buffers at [ ] rpm. 500 mg SR ranolazine tablets (batch# 1K2754A) were used.



Dissolution specifications

The dissolution specifications proposed by the sponsor are shown in Table 1.

Table 1. Dissolution specifications as proposed by the sponsor.

Time	% of Label Strength (LS) Dissolved		
	Level 1 (L1) (n = 6)	Level 2 (L2) (n = 6)	Level 3 (L3) (n = 12)
0.5 h 4.0 h 12.0 h 24.0 h	NMT [NLT]	NMT [NLT]	NMT [NLT]
	All individual values within L1 criteria (6 tablets)	Mean (6 L1 + 6 L2 tablets) is within L1 criteria; all individual values within L2 criteria	Mean (12 L1 + 12 L2 + 12 L3 tablets) is within L1 criteria; NMT 2 tablets are outside L2 individual criteria; all individual values within L3 criteria

The dissolution results for different formulations used in different clinical studies are shown in Table 2.

Table 2. Mean percent dissolved for different formulations used in different clinical studies and the proposed acceptance riteria.

Lot (Supply Chain)	Phase 3 or BE Study	No. of L1 or L2 Dissolution Results Available	Mean Dissolution Result (% of LS)			
			0.5 h	4.0 h	12.0 h	24.0 h
791751 (Syntex)	CVT 3031[a] CVT 3013[b]					
791771 (Syntex)	CVT 3031[a] CVT 301-15[b]					
8E2729A — DSM)	CVT 3033[c] CVT 301-15[b]					
8H2748A — DSM)	CVT 3033[c]					
9G2714A — DSM)	CVT 3033[c]					
8H2749A — DSM)	CVT 3013[b]					
1K2754A[d] — DSM)	CVT 301-15[b]					
Weighted Mean[e] (Number of L1 or L2 Dissolution Results)	NA					
Mean of 7 Lots	NA					
Proposed Acceptance Criteria	NA		NMT [			NLT]

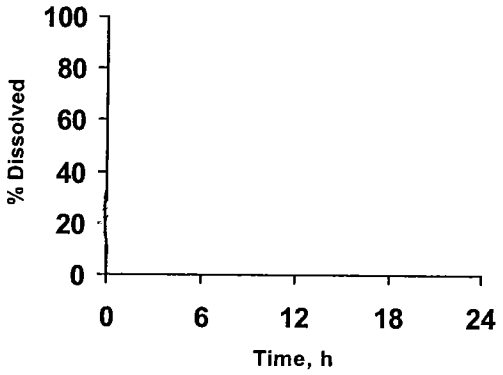
[a] Phase 3 study

[b] BE study

[c] Phase 3 study

[d] Primary stability lot. Representative of proposed commercial product.

[e] Using data for — lots [ ] including those lots that were not used in clinical/bioavailability studies, the mean dissolution results for 0.5, 4.0, 12.0, and 24.0 h time points were [ ], respectively.



The sponsor proposed acceptance criteria are not suitable and alternative criteria are suggested by the reviewer. The reasoning is provided below in Table 3.

Table 3. Sponsor and FDA suggested dissolution acceptance criteria.

Sponsor Criteria	FDA Criteria	Reasoning
0.5 h: NMT [redacted]	0.5 h: [redacted]	[redacted] of the drug is released in 0.5 h. Hence zero release is not acceptable. Further, the acceptable width of the criteria should be [redacted]
4.0 h: [redacted]	4.0 h: [redacted]	Sponsor proposed criteria acceptable
12.0 h: [redacted]	12.0 h: [redacted]	Sponsor proposed criteria acceptable
24.0 h: NLT [redacted]	20.0 h: NLT [redacted]	Guidance[a] recommends that the last time point should be such that about 80% of the drug is released.

[a] Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations

Biowaiver for the 375 mg strength tablets

1. 500 mg and 375 mg tablets are compositionally similar, as shown in the Table 4.
Table 4. Composition of the 375 mg and 500 mg tablets.

Ingredient		375 mg (mg/tablet)	500 mg (mg/tablet)	Percent Composition
Core Tablet				
Ranolazine		375.0	500.0	
Methacrylic Acid Copolymer Type C, NF				
Microcrystalline Cellulose, NF				
Hydroxypropyl Methylcellulose	USP			
Sodium Hydroxide, NF				
Magnesium Stearate, NF				
Tablet Core Weight (mg)		500.0	666.7	—
Film Coating				
Light Blue				
Orange				
Carnauba Wax, NF				
Film-Coated Tablet Weight (mg)				

[a] Removed during processing

2. The dissolution profiles of the 375 mg tablets are shown in Figure 4 along with the dissolution profiles of the 500 mg tablet in the proposed media (0.1N HCl). The 375 mg tablets were found to have similar dissolution profiles as the 500 mg in all the media tested, as shown in Table 5.

Figure 4. Dissolution profiles of the 375 mg tablets in 3 media. The dissolution profile of the 500 mg tablet in the proposed media is also shown for comparison.

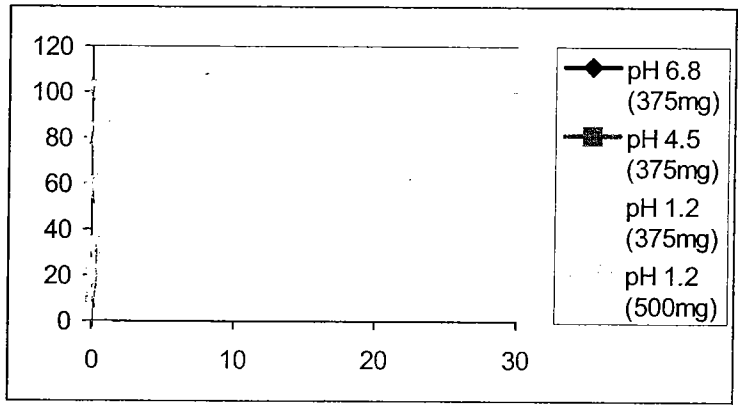


Table 5. Comparison of the 375 mg and 500 mg tablet dissolution profiles in four media.

Test Tablet (375 mg)	Reference Tablet		f_2 Values[b]			
Lot Number	**Strength**	**Lot Number**	**Water**	**pH 6.8**	**pH 4.5**	**pH 1.2**
1K2757A	500 mg	1K2754A	54.25	60.08	71.62	61.94
		8E2729A	50.32	84.67	90.02	82.32
	375 mg	8E2728A	64.84	83.05	84.48	71.97

[a] Dissolution profiles were obtained using twelve tablets in each medium. A 9-point dissolution profile was obtained in pH 1.2, 4.5, and 6.8 media. With water as the dissolution medium, 7-data points defined the dissolution curve. Mean dissolution profiles for the tablet lots in the different media are provided in Section 6.6.5 (see Table 6.6-6 and Table 6.6-7).

[b] Dissolution curves are not dissimilar if $50 < f_2 < 100$.

RECOMMENDATION:

The following dissolution specifications are recommended by the Office of Clinical Pharmacology and Biopharmaceutics:

1. The FDA suggested dissolution acceptance criteria, as shown below, are recommended.

Condition	FDA Recommendation
Dissolution Medium	0.1N HCl
Paddle Speed	— rpm
Specifications	0.5 h: [redacted]
	4.0 h:
	12.0 h:
	20.0 h: NLT [redacted]

2. The requested biowaiver for the 375 mg strength is granted based on the compositional and dissolution profile similarities.

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PHARMACOMETRICS REVIEWS

Effectiveness and Safety (Other than QT)

NDA :	**21-526**
Compound:	**Ranolazine**
Submission Dates:	**12/27/02** **04/15/03** **06/25/03** **07/01/03**
Sponsor:	**CV Therapeutics**
Pharmacometrics Reviewer:	**B. Nhi Nguyen, Pharm.D.**
Pharmacometrics Team Leader:	**Joga Gobburu, Ph.D.**

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- **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

Lmax	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

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- **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.

- **Executive Summary**

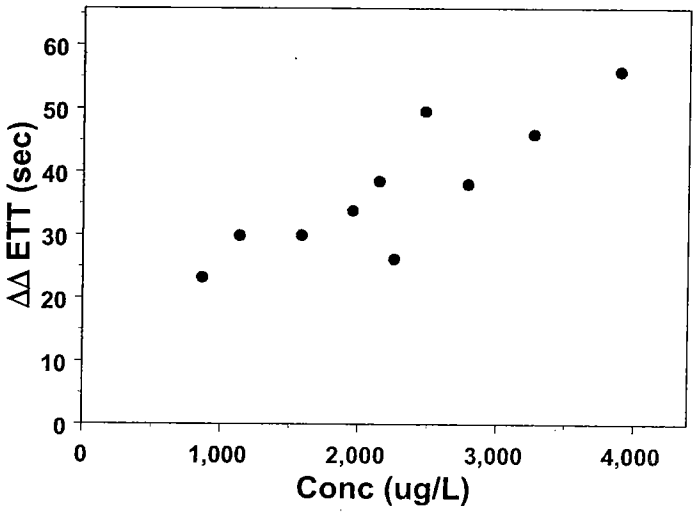
There is a significant nonlinear relationship between ranolazine plasma concentrations and effectiveness. Females have less proportional (effect relative to placebo) benefit from ranolazine than males; ~ 70 % and 60 % less proportional benefit from ranolazine SR 500 mg q 12 h and 1000 mg q 12 h, respectively. 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.

- **Question Based Review – Effectiveness**

1. **Is there a ranolazine concentration dependent change in ETT duration from placebo (ΔΔETT)?**

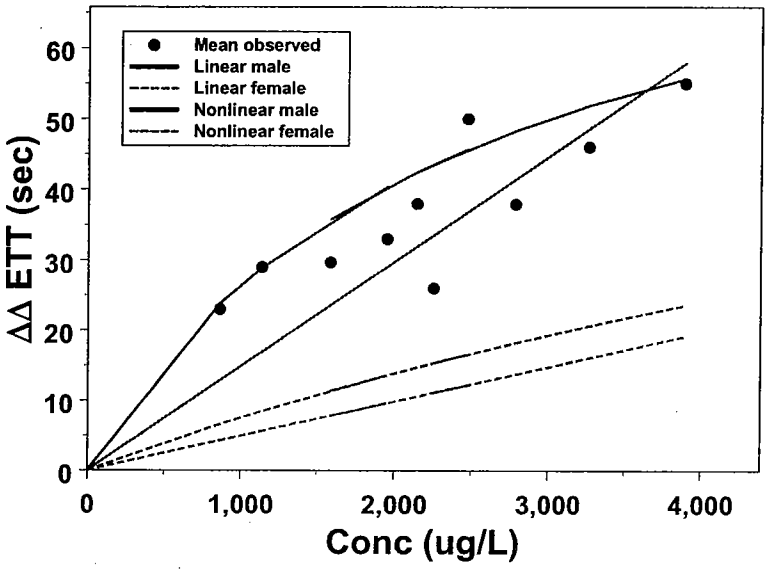
Figure 1 shows the relationship between observed mean peak and trough concentrations of the doses used in the two pivotal trials CVT 3031 and CVT 3033 and the observed mean ΔΔETT in seconds. (See 0 for mean concentrations by dose.) Figure 1 suggests that there is a concentration effect relationship.

Figure 1. Observed mean peak and trough concentration vs. observed mean ΔΔETT 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 ΔΔETT 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 ΔΔETT duration, especially at lower concentrations, and was significantly better than the linear model. The linear model underpredicted the observed mean drug effect (ΔΔETT) 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 ΔΔETT of males, as one would expect, are higher than the naïve average of observed ΔΔETT. Thus, combining the gender data would result in a model predicted line closer to the observed mean ΔΔETT.

Figure 2. Reviewer's model predicted and observed mean ΔΔETT



The reviewer's final model predicted ΔΔETT 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 ΔΔETT 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 ΔΔETT (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 (52, page 339).

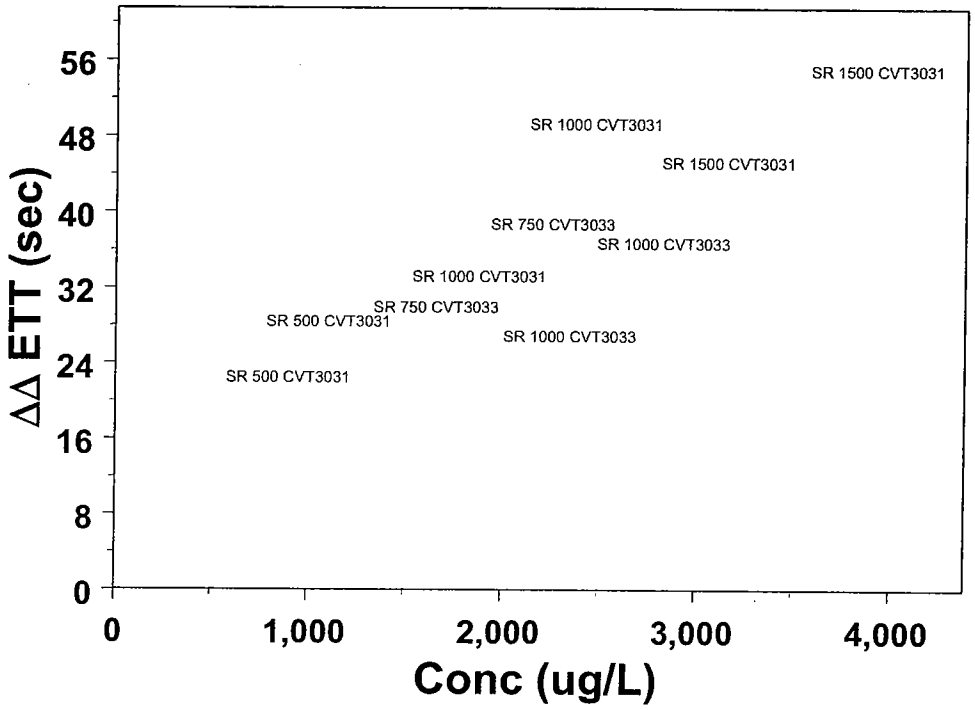
Table 4. Peak and trough concentrations in CVT 3031 and CVT 3033

	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 ΔΔETT 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 ΔΔETT 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 ΔΔETT in CVT 3031 and CVT 3033 – data shown by dose and study



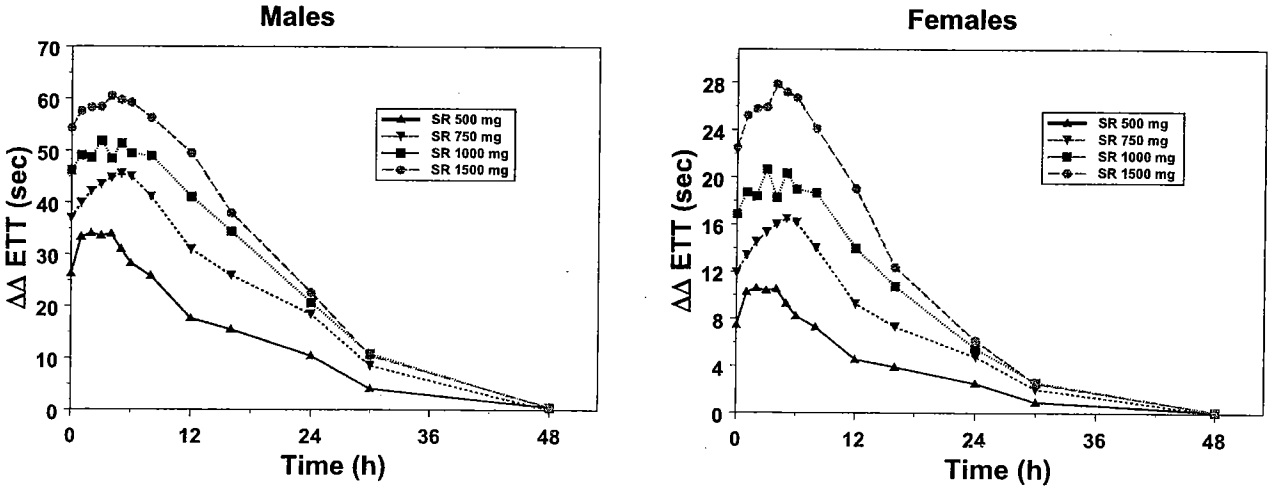
2. What is the time course of effectiveness of ranolazine?

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



3. <u>Is there a gender difference in baseline walking time?</u>

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.

4. <u>Is there a gender difference in effectiveness?</u>

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,

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

where TV_{BSL} is the typical baseline ETT (min) and TV_{LMAX} 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,

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

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.)

5. <u>Do patients with CHF benefit more from ranolazine?</u>

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, ± 6.6 %). Patients with CHF have ~25 % less maximal learning capacity than patients without CHF, or 2.39 minutes (SE, ± 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,

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

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

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

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.

6. <u>Do concomitant medications significantly affect the effectiveness of ranolazine?</u>

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.

7. <u>Is there a carry-over effect on the effectiveness in study CVT 3031?</u>

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.

8. <u>Does Russian center 710 in study CVT 3033 have more influence on the effectiveness than the other centers?</u>

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**
1st Quartile	1,118.00	636.23
Median	1,765.00	1,460.30
Mean	1,837.00	1,777.10
3rd 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.

9. 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 2, 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 ΔΔETT. Note that the predictions of ΔΔETT (Figure 5) for the q 12 hour simulation are similar to predicted ΔΔETT 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 ΔΔETT of at least 12 seconds (Tiazac 120 mg dose trough ΔΔETT 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. ΔΔETT from 500 mg BID regimens in males (left) and females (right) – Note the different y-axes range

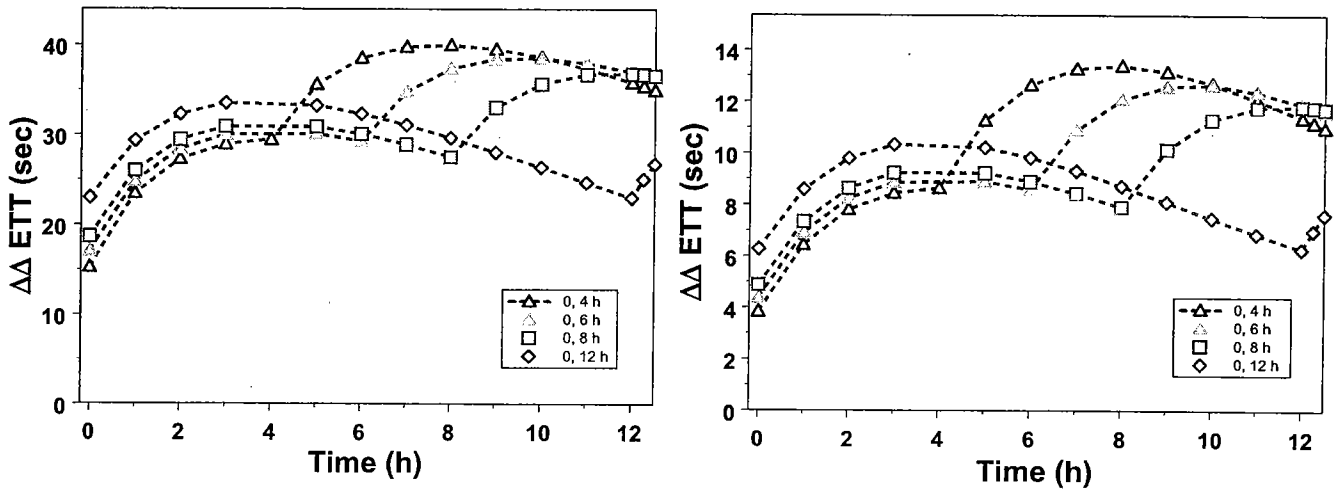
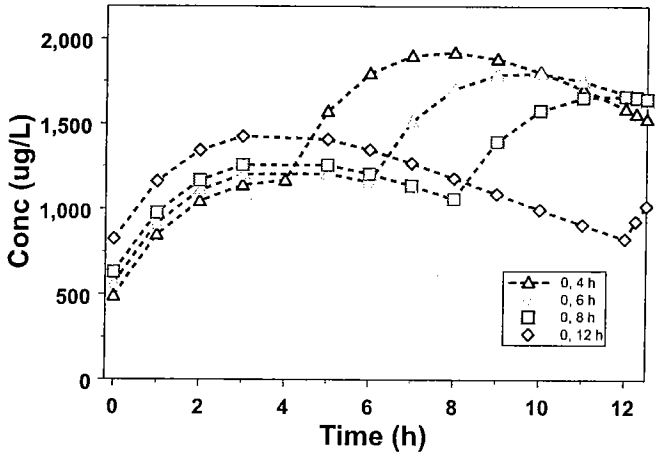


Figure 6 shows the concentration over time. The concentrations required for effectiveness with each dosing schedule should be considered with respect to safety also. Dosing at 0 and 4 hours does not seem to provide added benefit at 12 hours, compared to dosing at 0 and 6 hours or 0 and 8 hours, however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



- **Question Based Review – Safety Other than QT**

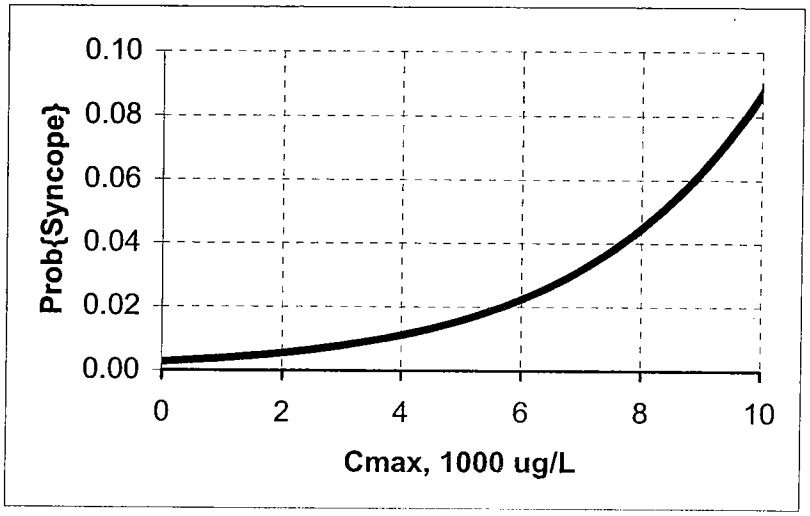
Data from 25 parallel studies (2,431 patients) were used in the safety analysis. These studies contain the longest exposure (12 weeks) and concentrations as high as 12,172 ug/L. The mean maximum concentration was 1,960 ug/L. Cmax was used as a measure of exposure. It should

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

10. 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.

11. 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.

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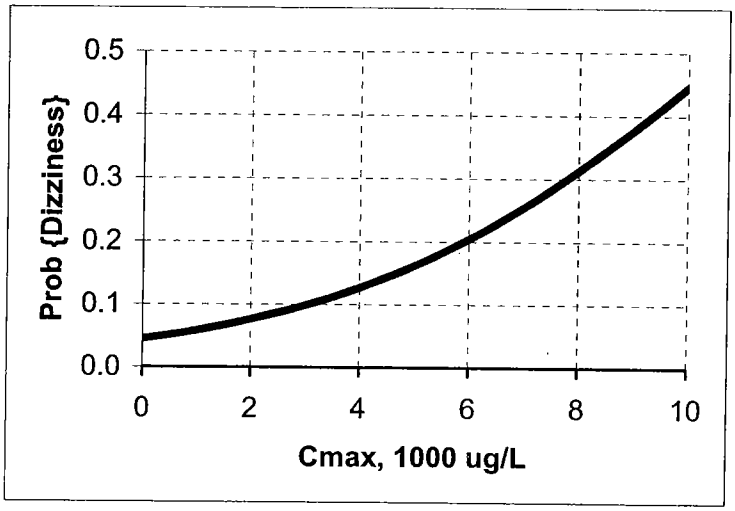
12. Is dizziness concentration dependent?

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.

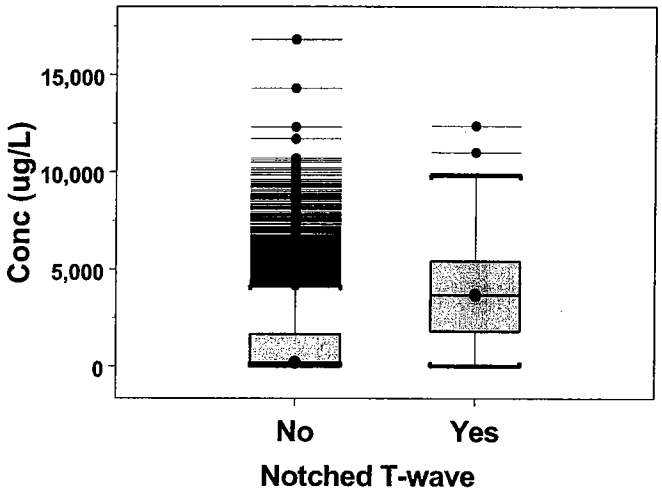
13. Are notched T-waves concentration dependent?

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

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



- **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.

- **Sponsor's Methods - Effectiveness**

14. <u>Design of CVT 00204 – Concentration - Effectiveness Analysis</u>

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.

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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 Stratified by background antianginals • diltiazem 180 mg qd • atenolol 50 mg qd or • amlodipine 5 mg qd Antianginal started at least 5 days prior to ranolazine or placebo.
Treatment duration	7-10 days each	1 wk each	1 wk each	12 wks

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

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

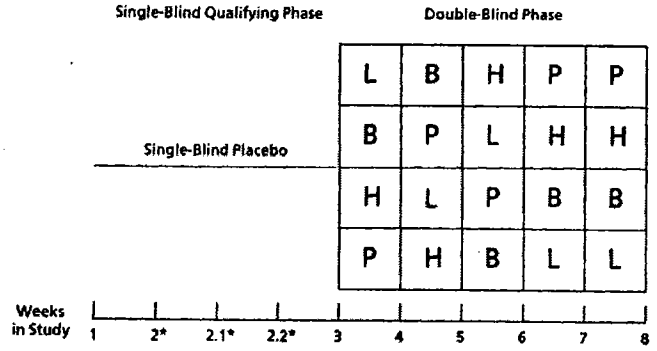
	RAN 080	RAN 1514	CVT 3031 Pivotal monotherapy trial	CVT 3033 Pivotal combination therapy trial
Initial phase	Single-blind placebo phase (7 – 10 days) during which beta-blocker therapy was withdrawn Followed by qualifying baseline ETT	Single-blind, placebo qualifying phase (2-7 wks) First patients were exercised on current antianginals. Antianginals were discontinued one at a time for a max total of 3 with a nitrate being the first to be withdrawn. ETTs were performed after each discontinuation. Specific criteria required for inclusion.	single-blind, placebo qualifying phase (1 wk) included two qualifying ETTs	single-blind, placebo qualifying phase (1-2 wks)
ETT assessments on Treatment (Tx)	Peak at end of each tx period for a total of 3 ETTs	Trough & peak with each visit for a total of 10 ETTs	Trough & peak at end of each one week dosing period for a possible total of eight ETTs per patient	Trough: Wk 2,6,12 and wk 12 day 2 Peak: Wk 2, 12
Actual time of peak ETT assessment	not specified in protocol	8 AM to 11AM	11 AM to 4 PM	11 AM to 4 PM

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: US, 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.

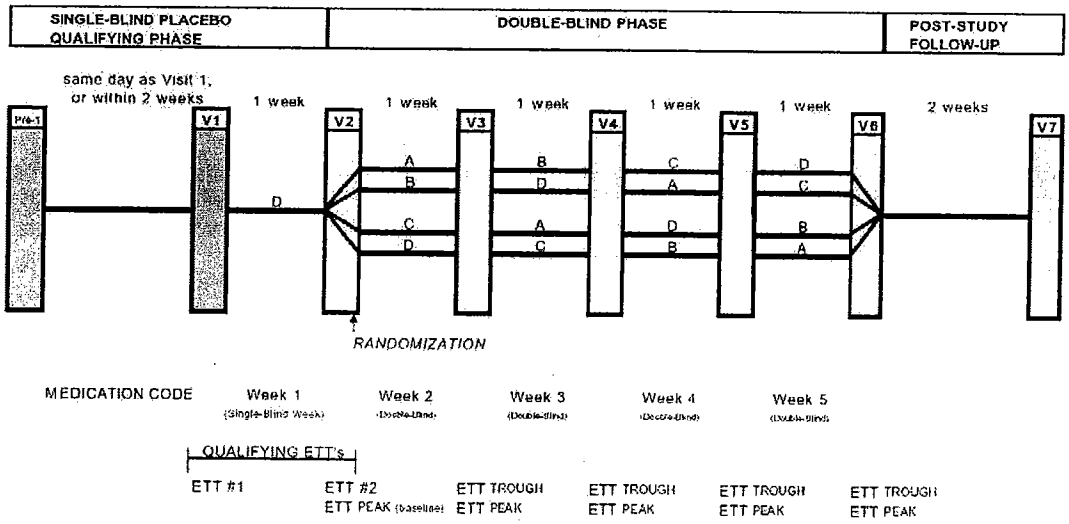
Figure 10. Study procedures RAN 1514



Note: P= Placebo
B= Ranolazine 400 mg bid
L= Ranolazine 267 mg tid
H= Ranolazine 400 mg tid

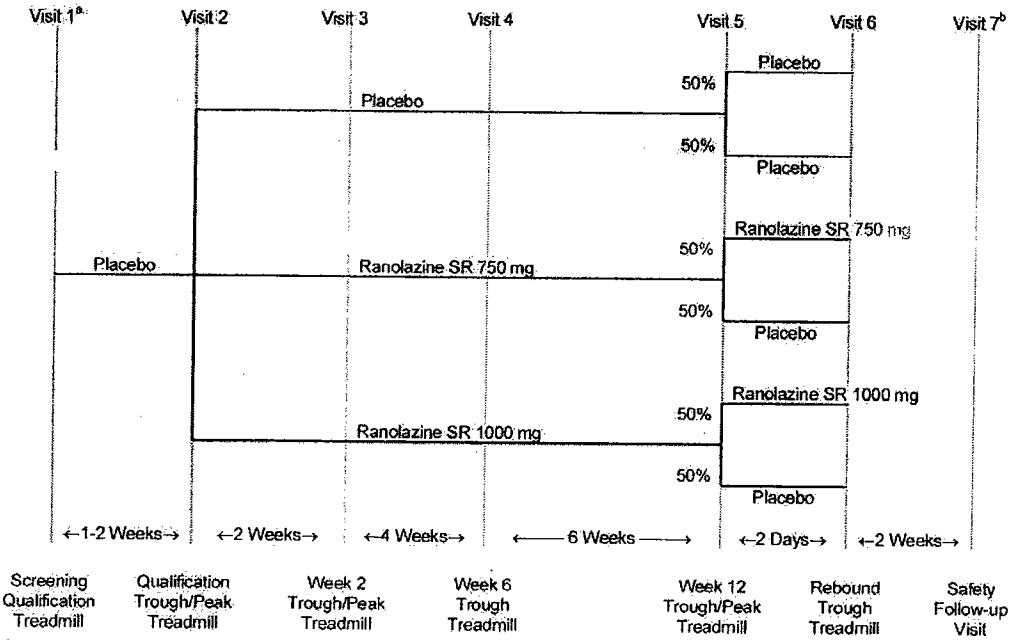
* Single-blind placebo could be given two additional weeks in order to qualify for entry. Evaluations at weekly visits during the double-blind phase included: exercise treadmill tests and hemodynamic data at trough and peak, weekly diary data, ECG at rest, laboratory tests, compliance, concomitant medications,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



[a] An optional pre-screening visit could be performed at which all the screening procedures could be performed except vital signs, ECG and exercise treadmill test measurements.
[b] Visit 7 was not necessary for patients who enrolled in the long-term, open-label safety study, CVT 3034.

15. 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

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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 %)	324 (23 %)
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

16. 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.)

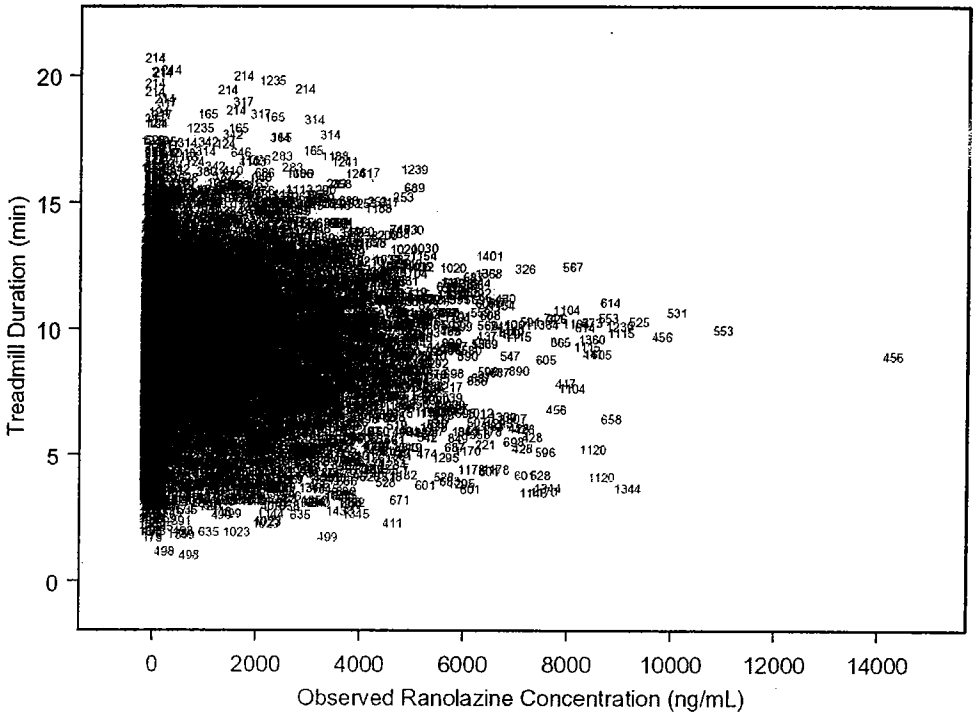
17. Pharmacodynamics

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 52.)

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



18. Study RAN 080

19. 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 ± 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.

20. 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).

21. Study RAN 1514

22. 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 reason's cited in Reviewer's Comments, section 52, 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.

23. 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.

24. Study CVT 3031

25. 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 52, 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)

26. 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.

27. Study CVT 3033

28. 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 52, page 339).

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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)

29. 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.

30. 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.

31. Models

32. Pharmacokinetics

33. 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.

34. Pharmacodynamics

35. 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.

36. 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:

$$TVBSL = \mu_{BSL(RAN080,CVT3031,CVT3033)} \text{ or } \mu_{BSL(RAN1514)} \quad \text{(Eq 1)}$$

where
TVBSL is the typical value of the baseline treadmill duration,
$\mu_{BSL(RAN080,CVT3031,CVT3033}$ is the mean baseline ETT duration if the patient is in study RAN 080, CVT 3031 or CVT 3033 and
$\mu_{BSL(RAN1514)}$ 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:

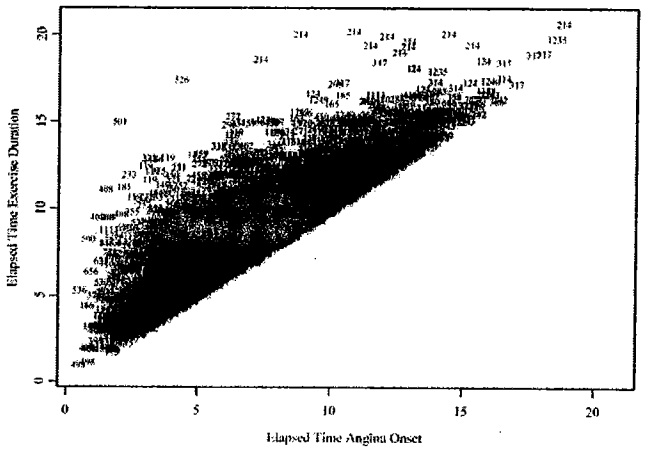
$$TVBSL = (\mu_{BSL(RAN080,CVT3031,CVT3033)} \text{ or } \mu_{BSL(RAN1514)}) + \Delta\mu_{BSL(female)} + \Delta\mu_{BSL(age-64\,years)} \quad \text{(Eq 2)}$$

where
$\Delta\mu_{BSL(female)}$ is the mean difference from males in baseline treadmill duration for females. This value is zero if the patient is male.
$\Delta\mu_{BSL(age-64\,years)}$ 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



37. 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.

$$Peff = \frac{(TVLmax \bullet time)}{(time + TVL_{50})} \quad \text{(Eq 3)}$$

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
TVL_{50} 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.

$$TVL_{50} = \mu_{L_{50}RAN1514} \; or \; \mu_{L_{50}CVT3031} \; or \; \mu_{L_{50}CVT3033} \quad \text{(Eq 4)}$$

where
$\mu_{L_{50}RAN1514}$ is the mean L_{50} 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 Lmax in minutes,

$\Delta\mu_{L\max CHF}$ is the mean difference in Lmax in minutes for patients with CHF. This value collapses to zero if the patient does not have CHF.

38. Concentration effect model

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

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

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 ug/L

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

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

where

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

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

39. 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 (Ω^2_{Lmax}), time to reach half the maximal treadmill learning ($\Omega^2_{L_{50}}$), 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.

40. Model Selection

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

41. 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.

42. 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.

43. 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.

44. 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).

- **Sponsor's Results**

45. Sponsor's Final Model - Linear

46. 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 those 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.

47. 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.

48. 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.

49. 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

	Sponsor's final model		**Sponsor's final model ran by the Agency**	
Compiler	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)	
$Lmax_{RAN\ 1514,CVT\ 3031,CVT\ 3033}$ (minutes)	2.89 (5.2)	91.7 (6.7)	2.91 (4.4)	88.7 (6.6)
$\Delta Lmax_{CHF}$ (minutes)	-0.91 (23.9)		-0.91 (22.6)	
$L_{50\ RAN\ 1514}$ (weeks)	0.84 (21.7)	185.7 (35.0)	0.81 (15.2)	66.7 (29.6)
$L_{50\ CVT\ 3031}$ (weeks)	2.75 (7.4)		2.70 (7.5)	
$L_{50\ CVT\ 3033}$ (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) (σ^2) (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 L_{50} 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
L_{50} = time to reach ½ of maximal learning
DE= drug effect

50. 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

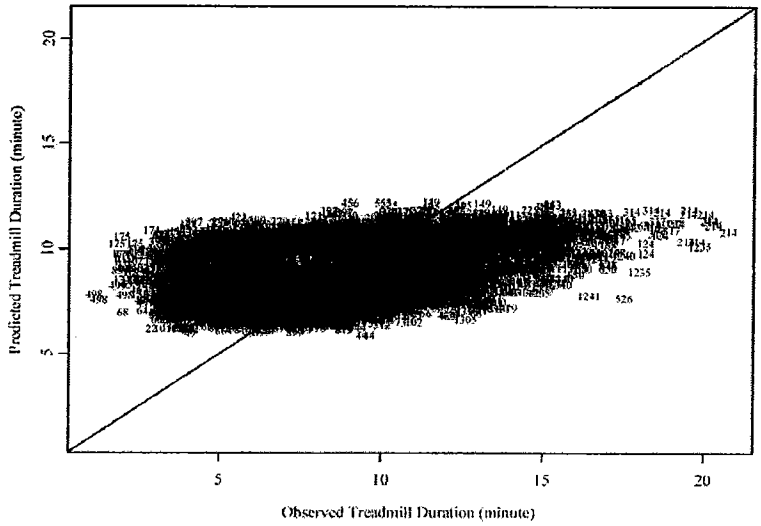
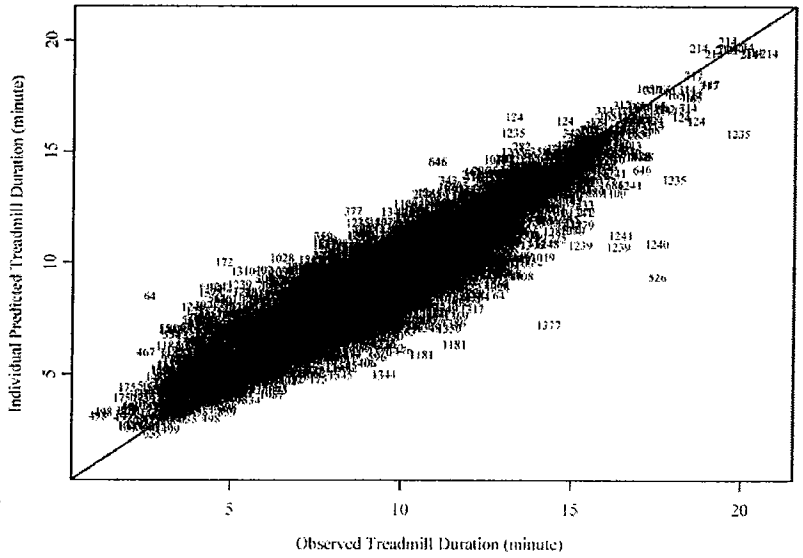


Figure 16. Observed treadmill duration vs. individual predicted treadmill duration



51. 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.

- **Reviewer's Comments of Sponsor's Analysis**

52. <u>Data</u>

- 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 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.

53. 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.

54. The significance of the results

55. 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,

$$\frac{Drug\ Eff}{Pbo\ ETT\ duration} = \frac{Drug\ Eff}{TV_{BSL} + TV_{LMAX}} = \frac{0.106\ \text{min}/1000ug/L}{6.08\ \text{min} + 2.89\ \text{min}} = 1.18\%\ per\ 1000ug/L$$

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

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

$$\frac{Drug\ Eff}{Pbo\ ETT\ duration} = \frac{Drug\ Eff}{TV_{BSL} + TV_{LMAX}} = \frac{0.278\ \text{min}/1000ug/L}{6.85\ \text{min} + 2.89\ \text{min}} = 2.85\%\ per\ 1000ug/L$$

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.

56. 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,

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

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

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

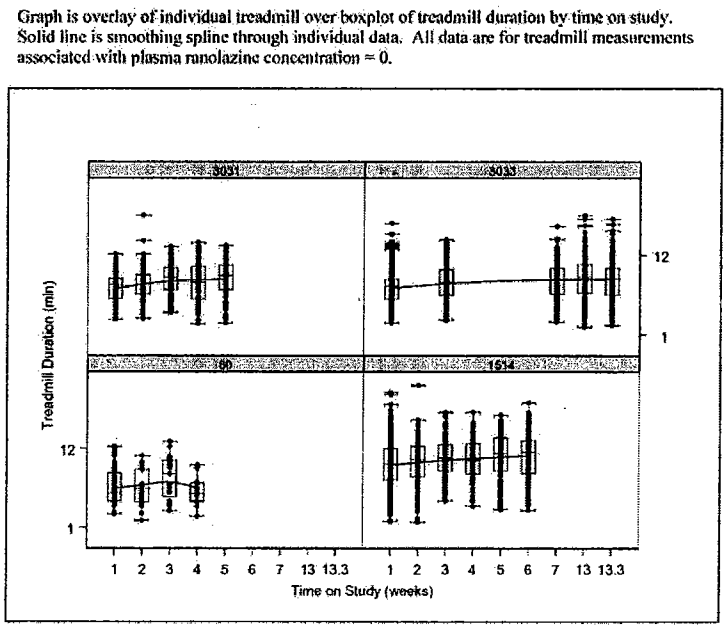
Therefore, a patient with CHF will walk 57.5 seconds (6.85 minutes • 0.14 per 1000 ug/L•60 sec/min) more from baseline, and a patient without CHF will walk 37 seconds more from baseline. Thus, while the maximal learning capacity is smaller in patients with CHF, patients with CHF benefit more from ranolazine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

57. <u>The validity of the results</u>

58. Learning Effect

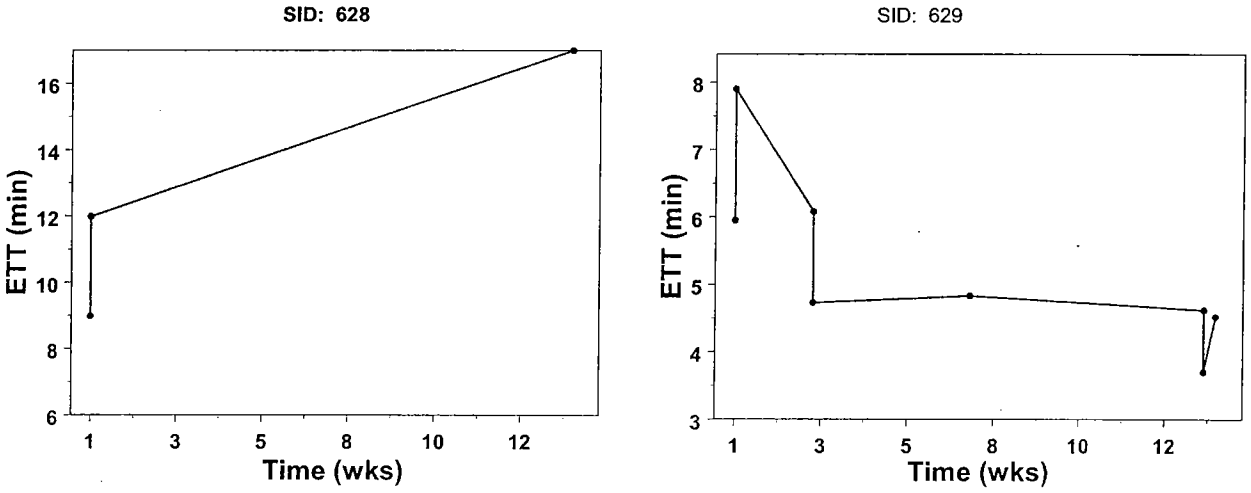
Because learning can occur after repeated exercise treadmill testing, the sponsor chose to use the observed duration of treadmill exercise rather than change from baseline in the model. Figure 17 helps explain why an Emax model was chosen to describe the learning effect. For studies RAN 1514, CVT 3031 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.

59. 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).

60. 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 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.

- 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.

- **Reviewer's Analysis of Effectiveness**

61. Models

62. 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)	
$Lmax_{RAN\ 1514,CVT\ 3031,CVT\ 3033}$ (minutes)	2.91 (4.4)	88.7 (6.6)	2.92 (5.2)	90.8 (6.8)
$\Delta Lmax_{CHF}$ (minutes)	-0.91 (22.6)		-0.90 (25.8)	
Slope of learning in RAN 080	N/A	N/A	0.098 (62.7)	
$L_{50\ RAN\ 1514}$ (weeks)	0.81 (15.2)	66.7 (29.6)	0.83 (21.2)	66.3 (34.2)
$L_{50\ CVT\ 3031}$ (weeks)	2.70 (7.5)		2.72 (7.5)	
$L_{50\ CVT\ 3033}$ (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) (σ^2) (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
Lmax = maximal learning
L_{50} = time to reach ½ of maximal learning
DE= drug effect

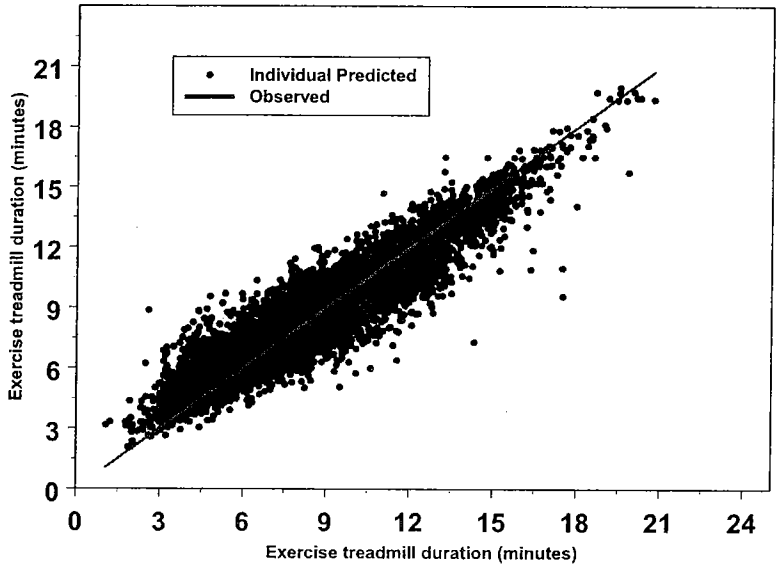
After it was discovered that the data set was incorrect, the analysis was reran with the correct number of observations (10,709). The slope of the concentration effect remained fairly similar.

63. 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 Lmax 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	
Objective function value	19,040.24	
No. observations	10,709	
	Mean (SE %)	**BSV, % CV (SE %)**
$BSL_{RAN\ 080,CVT\ 3031,CVT\ 3033}$ (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)	
$Lmax_{RAN\ 1514,CVT\ 3031,CVT\ 3033}$ (minutes)	3.26 (6.1)	105.8 (8.9)
$\Delta Lmax_{CHF}$ (minutes)	-0.663 (28.2)	
Slope of learning in RAN 080 (minutes/week)	0.196 (33.1)	N/A
$L_{50\ RAN\ 1514}$ (weeks)	4.60 (37.8)	71.8 (17.1)
$L_{50\ CVT\ 3031}$ (weeks)	1.43 (28.2)	
$L_{50\ CVT\ 3033}$ (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_{LMX}		-0.556
BSV_{BSL} and BSV_{L50}		0.262
BSV_{L50}nd BSV_{LMX}		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
L_{50} = time to reach ½ of maximal learning
DE= drug effect

64. Interpretation of reviewer's linear effectiveness model

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

male taking ranolazine SR 500 mg BID has a predicted ΔΔ ETT at trough of 12.8 ± 10.6 seconds (mean ± 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 ± 709 ug/L is the mean ± SD trough concentration of ranolazine SR 500 mg BID.

However, the reported ΔΔETT for the SR 500 mg BID dose at trough was 23.8 seconds.

Table 19 shows the predicted ΔΔ 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 ΔΔ 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 ΔΔETT (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 (52, page 339). The peak and trough data used in the reviewer's population PK/PD analysis were used to generate the ΔΔ ETT. The ΔΔ 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

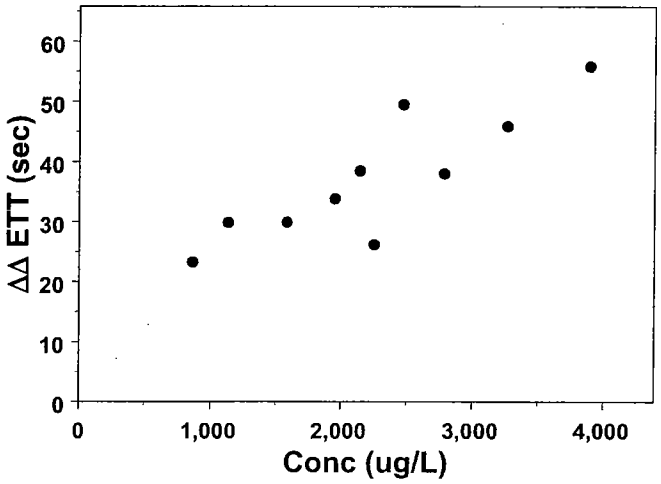
	SR 500 mg	**SR 750 mg**	**SR 1000 mg**	**SR 1000 mg**	**SR 1500 mg**
	CVT 3031	**CVT 3033**	**CVT 3031**	**CVT 3033**	**CVT 3031**
Trough (ug/L)	861 ± 709	1591 ± 1079	1904 ± 1347	2245 ± 1536	3261 ± 1915
Peak (ug/L)	1146 ± 729	2148 ± 1234	2455 ± 1508	2769 ± 1525	3857 ± 1991

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.

65. Reviewer's final model - nonlinear effectiveness model

Figure 20 shows the mean concentration, ΔΔETT 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. ΔΔETT 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 (ΔΔETT – ln(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 (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 (ΔOFV +11) and when the Emax was fixed to 2 minutes, the OFV increased to 18932.96 (ΔOFV +4.791). Thus, 1.5 was chosen as the value to fix Emax. The EC_{50} 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)
$\Delta Lmax_{CHF}$ (minutes)	-0.805 (23.5)	
Slope of learning in RAN 080 (minutes/week)	0.167 (44.7)	
$L_{50\ RAN\ 1514}$ (weeks)	0.636 (20.4)	67.3 (36.1)
$L_{50\ CVT\ 3031}$ (weeks)	1.70 (11.2)	
$L_{50\ CVT\ 3033}$ (weeks)	1.14 (12.8)	
Emax (minutes)	1.5 fixed	78.6 (24.7)
$EC_{50\ male}$ (mg/L)	2.4 (17.6)	113 (29.3)
$\Delta EC_{50\ female}$ (mg/L)	8.58 (41.3)	
Residual error (additive) (σ^2) (minutes)	SD=1.10 (3.8)	
		correlations
BSV_{BSL} and BSV_{LMAX}		-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
L_{50} = time to reach ½ of maximal learning

Emax = 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)

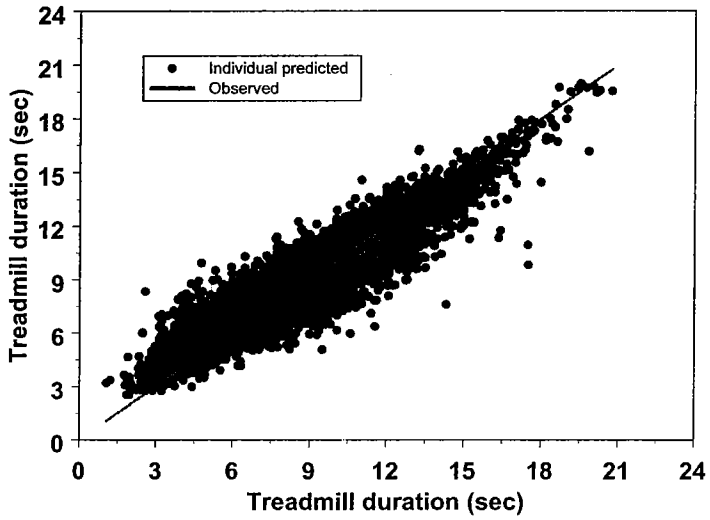
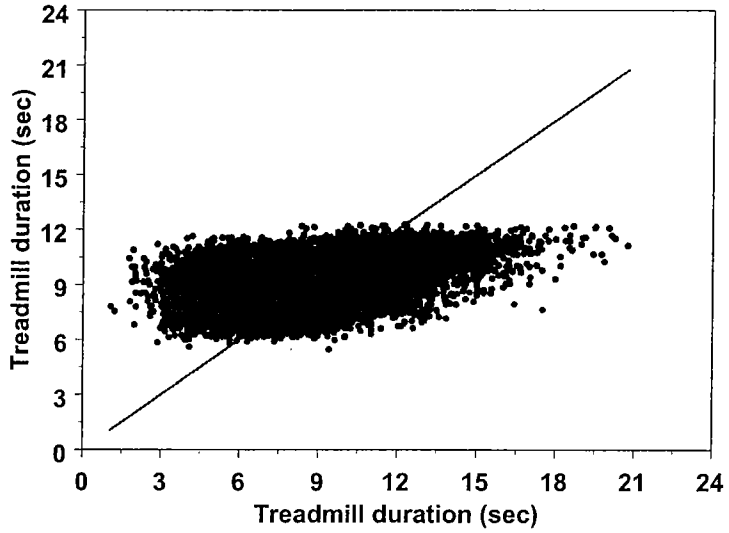


Figure 22. Goodness of fit of the population predicted concentrations of reviewer's final model (nonlinear)



66. 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 (ΔOFV +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 (ΔOFV +15) indicating that patients with CHF have significantly different maximal learning capacity than patients without heart failure. Therefore, both covariates were important.

67. 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.

68. 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 EC_{50}. The most important aspect is the ΔΔETT. It is recommended that only ΔΔETT be interpreted and no extrapolations of ΔΔETT 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.

69. 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.

70. 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.

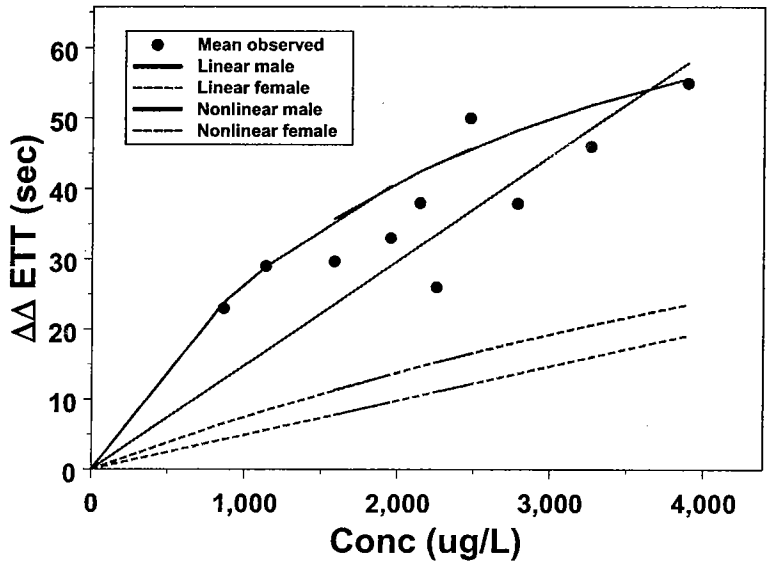
71. Drug effect

The predicted ΔΔETT 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 ΔΔETT duration and was significantly better than the linear model (Figure 23). The linear model underpredicted the observed mean drug effect (ΔΔETT) 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 ΔΔETT of males, as one would expect, are higher than the naïve average of observed ΔΔETT. Thus, combining the gender data into one mean would result in a model predicted line closer to the observed mean ΔΔETT.

Table 22. Reviewer's final model predicted peak and trough mean ΔΔETT (seconds)

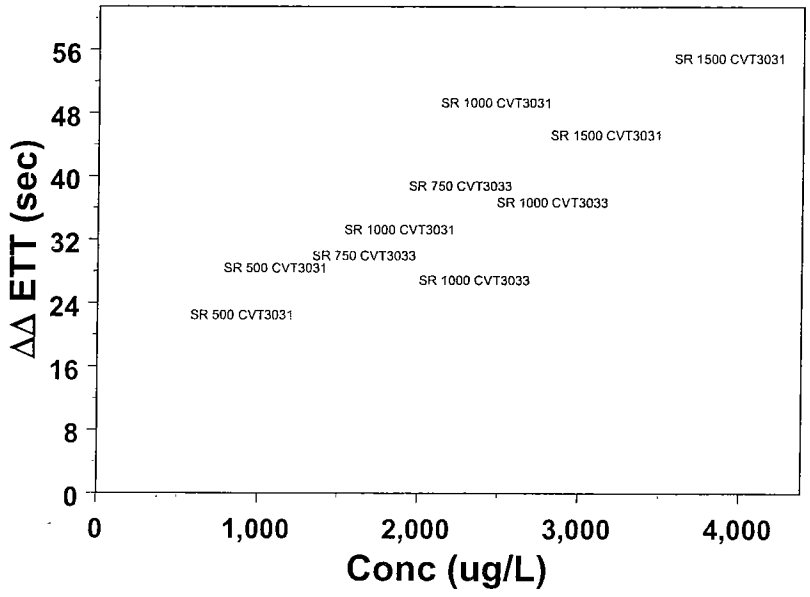
	Males		Females	
	Trough	**Peak**	**Trough**	**Peak**
500 mg SR q 12h – CVT 3031	23.8	28.9	6.6	8.4
750 mg SR q 12h – CVT 3033	35.8	42.5	11.4	14.7
1000 mg SR q 12h – CVT 3031	40.4	45.7	13.6	16.5
1000 mg SR q 12h – CVT 3033	43.6	48.3	15.3	18.2
1500 mg SR q 12h – CVT 3031	51.9	55.7	20.6	23.5

Figure 23. Reviewer's model predicted and observed mean ΔΔETT



The observed mean ΔΔETT 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 ΔΔETT 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 ΔΔETT in CVT 3031 and CVT 3033 – data shown by dose and study



72. 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 (EC_{50}) 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,

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

where TV_{BSL} is the typical baseline ETT value and TV_{LMAX} 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,

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

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.

73. 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, ± 6.6 %). Patients with CHF have ~25 % less maximal learning capacity than patients without CHF, or 2.39 minutes (SE, ± 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,

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

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

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

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.

74. <u>Test for carryover effect</u>

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. 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

75. 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
1st Quartile	1,118.00	636.23
Median	1,765.00	1,460.30
Mean	1,837.00	1,777.10
3rd 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 (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 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.

- **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 Cmax data. Cmax 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.

76. 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
```

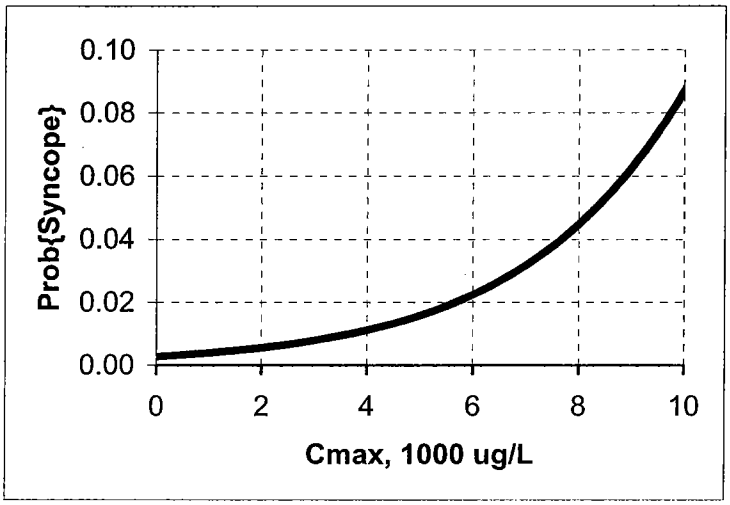
There was a significant concentration dependent effect on syncope (Table 28).

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.

77. 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.

78. 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).

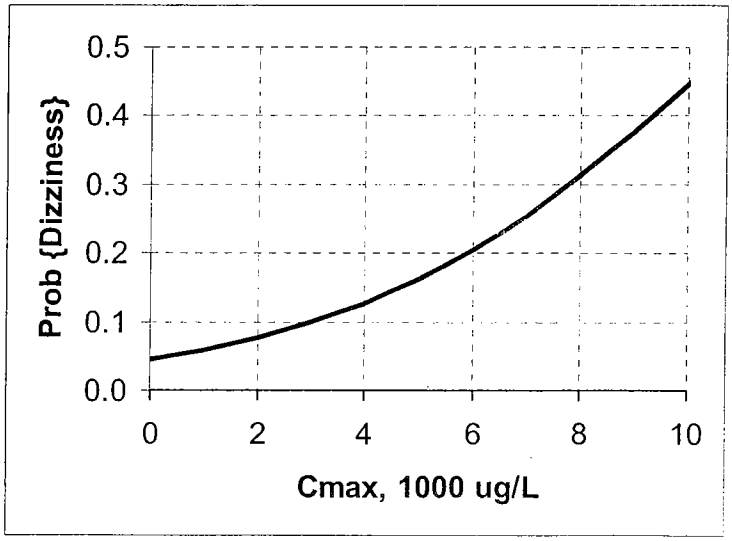


Table 29. Maximum likelihood estimates significant for dizziness

	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.

79. 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

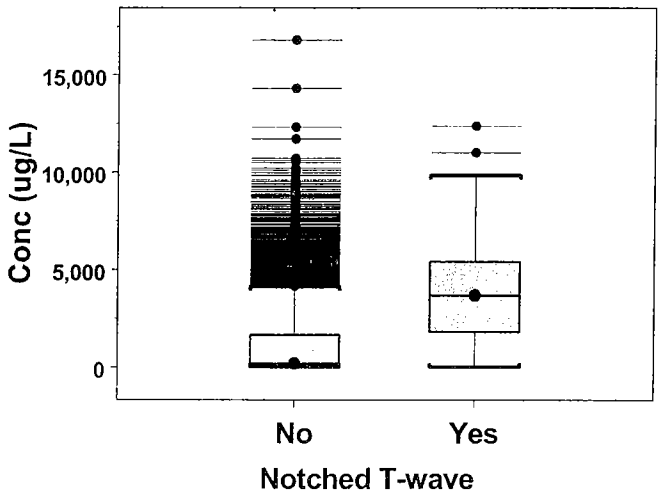


Figure 27. Concentration of notched and no notched T-waves

- **Appendix 1: NONMEM Control Streams**

80. 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


$PROB RUN# 220

$INPUT 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 ATE=DROP
  DIL=DROP AML=DROP CAL=DROP NIT=DROP EXE VER=DROP PLA CDUR

$DATA 104.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

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)
DR1=(CONC/1000)*DRSL
DR1E=DR1

 F   =  SDRE+DR1E
 Y   = F + ERR(1)
 IPRE = F

;INITIAL ESTIMATES

$THETA
 (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

$OMEGA
 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

$SIGMA
 1         ;[A]

$EST  MAXEVAL=9999 SIGD=3 PRINT=10 METHOD=1 NOABORT
    MSFO=220.MSF
$COV
$TABLE FILE=220.TAB ID ETA1 ETA2 CONC DUR ANG SCHD PER BDUR TM
STDY
     FORM SEX RACE AGE WT DR1E 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
```

81. Sponsor's Final Model

```
Run 340
;Model Desc: FINAL MODEL - base~sex+age, emax~chf, drsl~sex, using all data with
$cov
;Project Name: cvt2
;Project ID: NO PROJECT DESCRIPTION


$PROB RUN# 340

$INPUT 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]

$EST  MAXEVAL=9999 SIGD=4 PRINT=10 METHOD=1
    MSFO=340.MSF
$COV
$TABLE FILE=340.TAB ID BASE EMAX EC50 DRSL CONC TM STDY
     FORM SEX AGE WT DR1E SDR SDRE BASE CNMD IPRE NOPRINT
ONEHEADER
```

```
;$TABLE ID ETA1 ETA3 ETA4 ETA5 BASE EMAX EC50 DRSL
;NOPRINT ONEHEADER FILE=PATAB300
;$TABLE ID PRED DV WRES IPRE NOPRINT ONEHEADER FILE=SDTAB300
;$TABLE ID AGE WT NOPRINT ONEHEADER FILE=COTAB300
;$TABLE ID SEX DBT CHF CNMD FORM DSG NOPRINT ONEHEADER
FILE=CATAB300
```

82. Reviewer's Final Model

```
$PROB RUN# BASEMODEL DELMX_S_S80_TD.CTL

$INPUT 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 ATE=DROP
  DIL=DROP AML=DROP CAL=DROP NIT=DROP EXE VER=DROP PLA CDUR

$DATA c:\data\nhi\fda\nda\ranolazine\reviewer\pd\data\nopbocpdose.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

$OMEGA BLOCK(2)
 2            ;1WBSL
 0.5 2        ;2WLMX

$OMEGA  1       ;3WL50
$OMEGA  0.2     ;4Wemax
$OMEGA  0.2     ;5Wec50

$SIGMA  1

$EST MAXEVAL=9999 SIGD=3 PRINT=10 NOABORT
 METH=1; FOCE

$COV

$TABLE ID ETBSL ETLMX ETL50 ETEM ETEC BSL LMX L50 EMAX EC50 STDY
TM
     CONCMG DV Y NOPRINT ONEHEADER FILE=pemax2.fit
```

- **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 dm
         diltiazem verapamil ran
         metformin  ketoconazole coumadin
         /selection=backward slstay=0.05;
TITLE 'syncope';
run;
```

- **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: Hillcross Pharmaceuticals	CT00 SC058AQ (GF289)
placebo	manufacturer: ICI plc, England manufacturer: SRS	49182/91 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
madnesium stearate
size 0 brillant 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, methylacrylate copolymer (Type C), hydroxylpropyl methyl cellulose, megnesium stearate, sodium hydroxide, titanium dioxide, polysorbate 80, polyethylene glycol, carnuaba wax and FD&C Blue No.2

The placebo tablet contained lactose monohydrate, microcrystalline cellulose, titanium dioxidem polysorbate 80, polyethylene glycol, carnauba wax, and FD&C Blue No. 2.

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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,

Δ QTc = Drug or Placebo Effect – Baseline QTc.
$\Delta\Delta$ QTc = Drug Effect– Placebo Effect – 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:

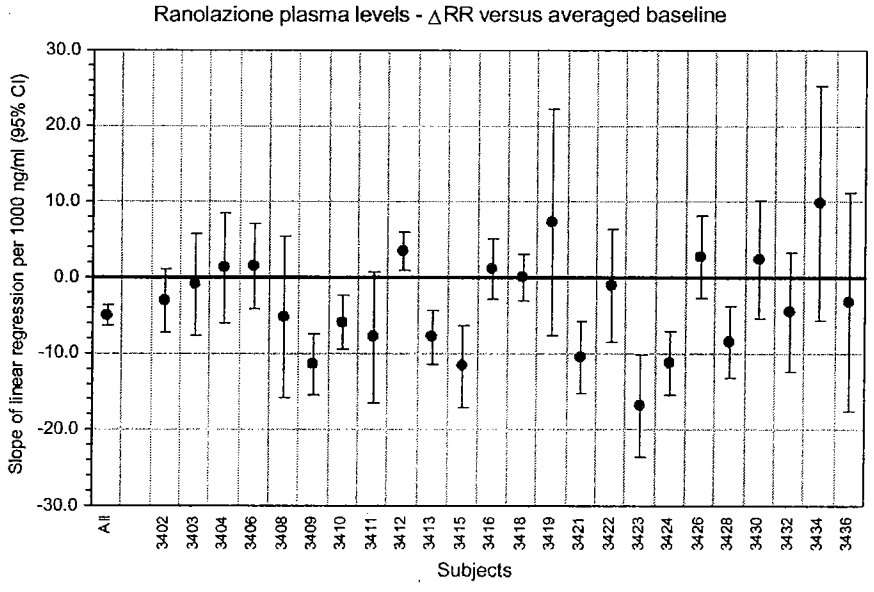

Figure 1. Relationship of averaged and individual changes in RR interval to ranolazine plasma levels in patients on active treatment (Study CVT 3111).

(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 Δ QTc has been probably attained. Upon cessation of the infusion at 72 h the Δ QTc decreases and is comparable to the placebo. The time course of ranolazine and its metabolites is shown in Figure 3 and 4.

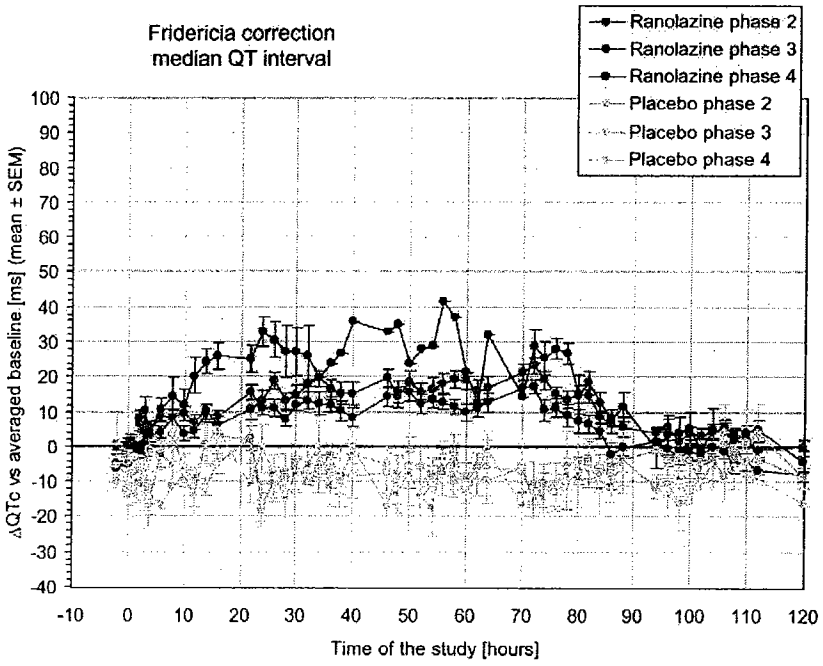

Figure 2. Development of changes in the Fridericia corrected QTc interval during different phases of the study.

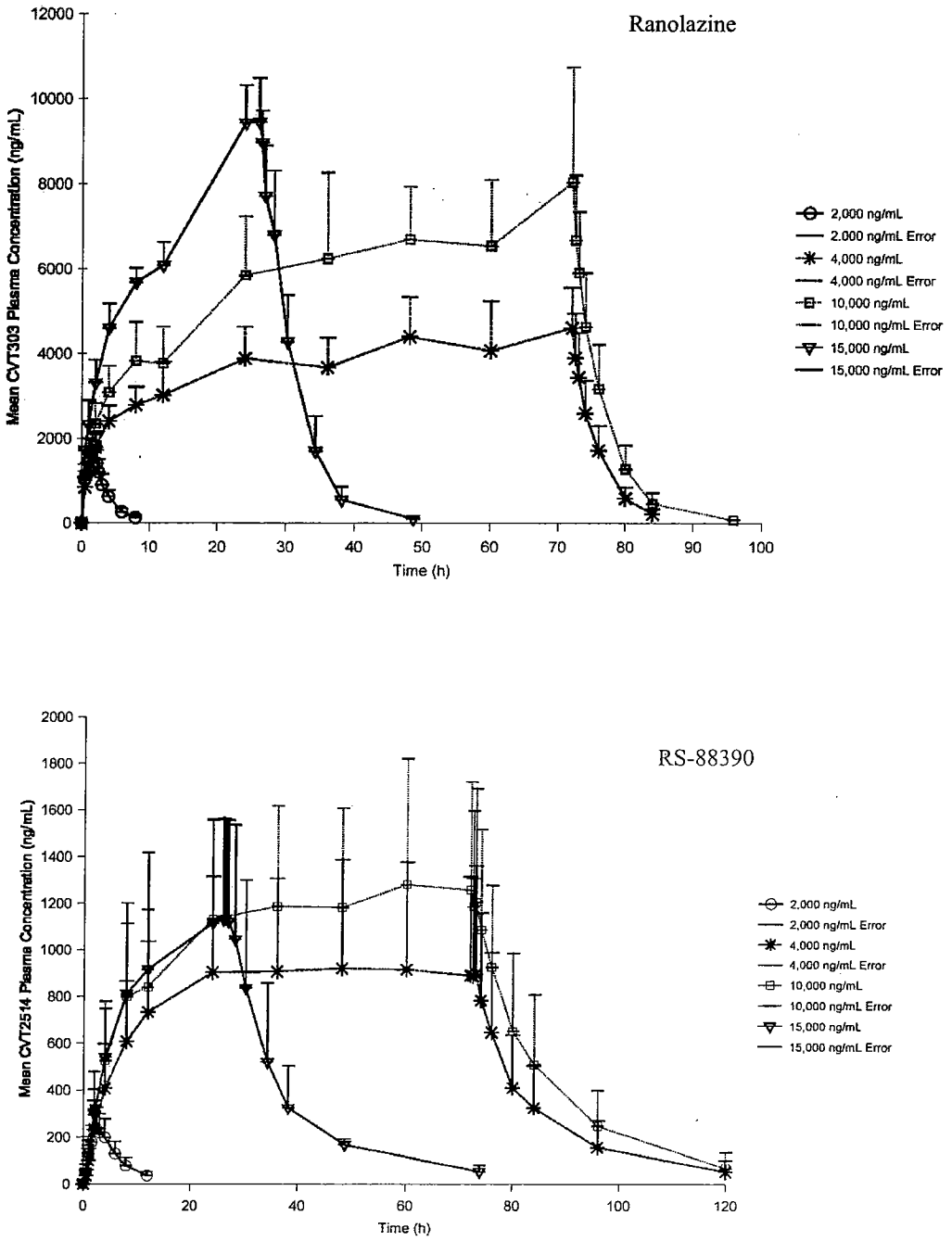

Figure 3. Plasma Concentration of Ranolazine and its metabolites after infusion of Ranolazine to target treatment.

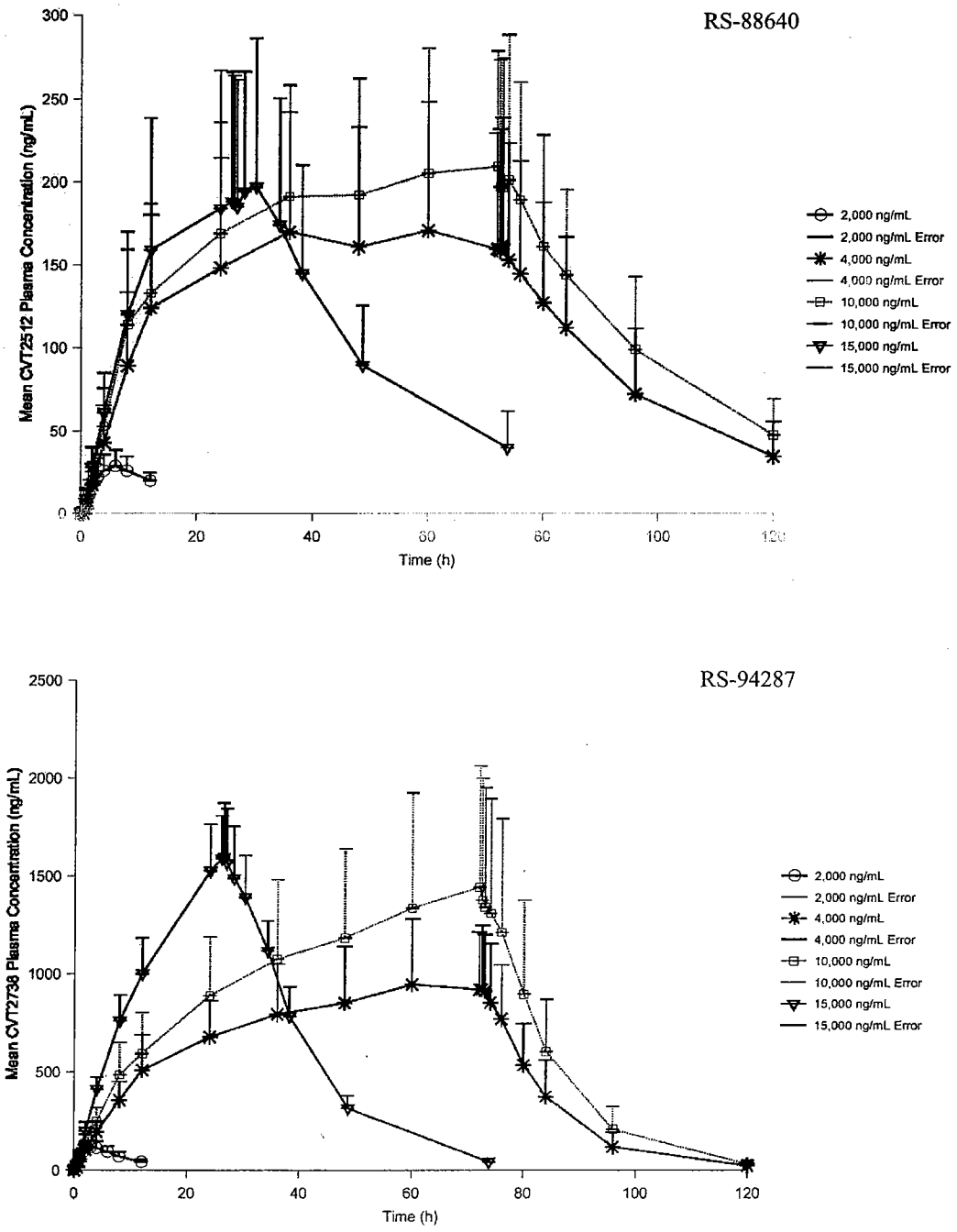

Figure 4. Plasma Concentration of Ranolazine and its metabolites after infusion of Ranolazine to target treatment.

3. Intrinsic Factors Affecting Ranolazine QTc prolongation

(a) What is the mean ΔΔ QTc - time course at different doses in a typical subject?

The linear model predicted mean of ΔΔ 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-ΔQTc relationship (2.56 msec per 1000 ng/mL) to calculate ΔΔ QTc. The model was used to predict the ΔΔ QTc because (a) Time course of ΔQTc 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 ΔQTc-concentration relationship.

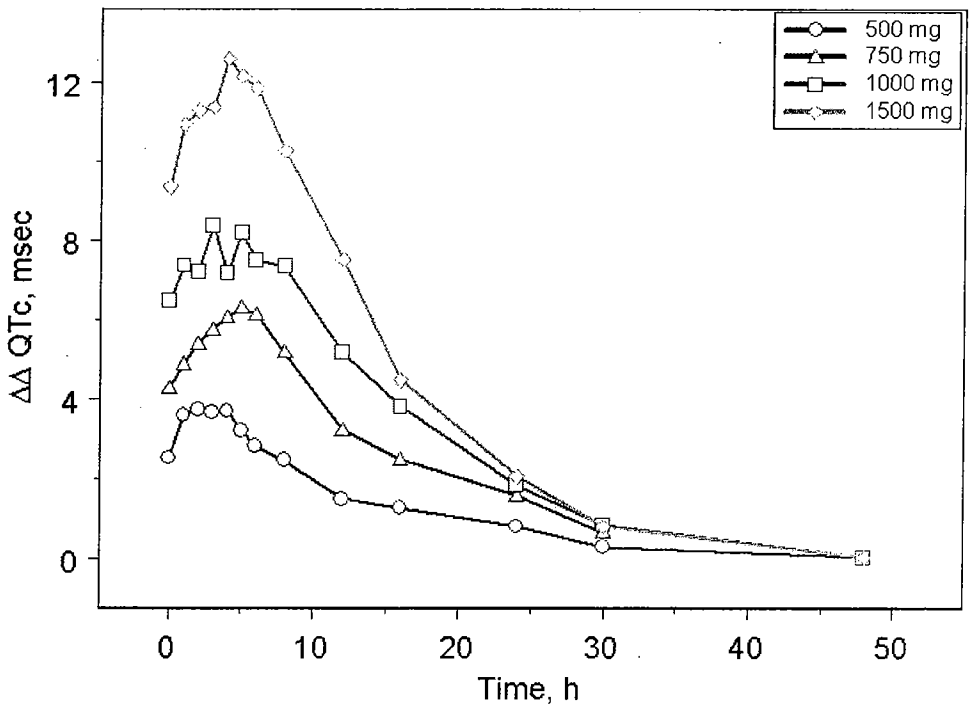

Figure 5. ΔΔ QTc at various dose levels at steady state in a typical subject.

(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 ΔΔ 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 Cmax 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 Cmax values after 375 mg dose was obtained from control group in Study CVT301-10

(Ketoconazole Interaction Study). The mean Cmax values after 500 and 1000 mg dose were obtained from Study CVT 3031. The Cmax value after 750 mg dose was calculated by multiplying the concentrations after 500 mg dose by a factor of 1.68.

The Cmax values after 375, 500, 750 and 1000 mg were multiplied by the factor corresponding to the increase in Cmax value observed in drug interaction studies. Simulations were performed using the calculated Cmax values in various scenarios (drug interactions, hepatic, renal impairment) using SAS® to determine the percentage of patients with ΔΔ QTc intervals of 0-5, 5-10 and =>10 msec. The results are shown in Table 1 and 2. Since the mean difference in Cmax 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.

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Table 1. Calculated ΔΔ QTc, msec for different ranolazine dose levels and drug interactions in a typical patient.

	Dose*	Cmax	ΔΔ QTc (msec)				
		Mean (SD)	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	3669185)	9.5	36	64	33	31
	375+240	1394(829)	3.6	79	21	17	4
	500+240	2142286)	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);

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Table 2. Calculated ΔΔ QTc, msec for different ranolazine dose levels in renal or hepatically impaired patients.

	Dose	Cmax	ΔΔ QTc (msec)				
		Mean (SD)	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 ΔΔ 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 1 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. *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.*
RAN0114	An ascending multiple dose study to assess the pharmacokinetics and tolerability of Ranolazine SR in healthy male volunteers. *Each subject received 500, 750 and 1000 mg ranolazine SR bid.*
RAN0117	An ascending multiple dosing study to assess the safety, tolerability and pharmacokinetics of Ranolazine SR administered three times daily in healthy male subjects. *Each subject received 500, 750 and 1000 mg ranolazine SR tid.*
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 ofranolazine 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-bind, 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-bind, 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}, $AUC_{0-\infty}$, $\%AUC_{extrapolated}$, $t_{½,z}$, 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

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 electrocarodiographically in healthy volunteers.

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).

$$QT_{ij} = \alpha_i * RR_{ij}^{\beta i} \qquad (1)$$

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 (Emax) relationship between concentration and QTc prolongation.
The linear relationship is shown below:

$$QT_{ij} = \alpha_i * RR_{ij}^{\beta i} + C_{ij} * Slope_i \qquad (2)$$

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 ($AUC_{metabolite}/AUC_{ranolazine}$) 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)	AUC0-∞ (ng·h/mL)	t½,z (h)	CL (L/h)	Vss (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)	AUC0-∞ (ng·h/mL)	t½,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)	Cinitial (ng/mL)	AUC0-∞ (ng·h/mL)	t½,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)	Cinitial (ng/mL)	AUC0-∞ (ng·h/mL)	t½,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).

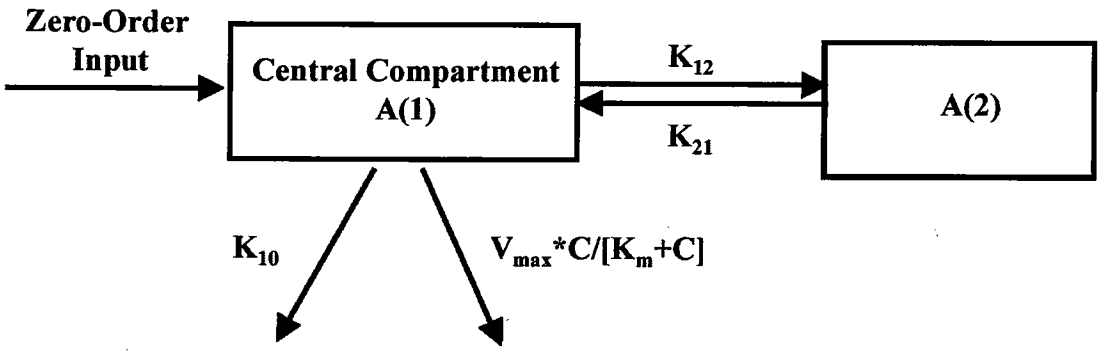


Figure 6. Non-linear Pharmacokinetic Model for Ranolazine (Intravenous Infusion).

The pharmacokinetic parameters used to characterize the model were: central compartment volume of distribution (Vc), maximum velocity (Vmax) and Michaelis-Menten constant (Km) for the saturable metabolic pathway, first-order elimination rate constant (K10) for the linear metabolic pathway and K12 and K21 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)[§]
Vmax (mg/h)	55.4 [25.2-85.6]	27.8
Km (ng/mL)	1660 [580-2740]	33.2
V (L)	44.5 [40.4-48.6]	4.7
K10 (h^{-1})	0.307 [0.220-0.393]	14.4
K12 (h^{-1})	1.04 [0.79-1.29]	12.1
K21 (h^{-1})	0.558 [0.506-0.670]	7.1
Inter-patient variability in Vmax (%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 K10 (%CV)	15.4 [6.5-20.8]	41.9
Inter-patient variability in K12 (%CV)	16.2 [8.2-21.3]	37.7
Inter-patient variability in K21 (%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. Infuence 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)
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:

$$TVV = 110 \bullet \left(\frac{Age,years}{51}\right)^{0.635} \bullet \left(\frac{Weight,kg}{78}\right)^{0.936}$$

$$TVCL = 22.4 \bullet \left(\frac{Age,years}{51}\right)^{-0.326} \bullet \left(\frac{Weight,kg}{78}\right)^{1.07}$$

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, σ2prop Phase II = proportional component of the residual error model associated with Phase II studies, σ2prop Phase I = proportional component of the residual error model associated with Phase I studies σ2add = additive component of the residual error model, NE = Not Estimated.		

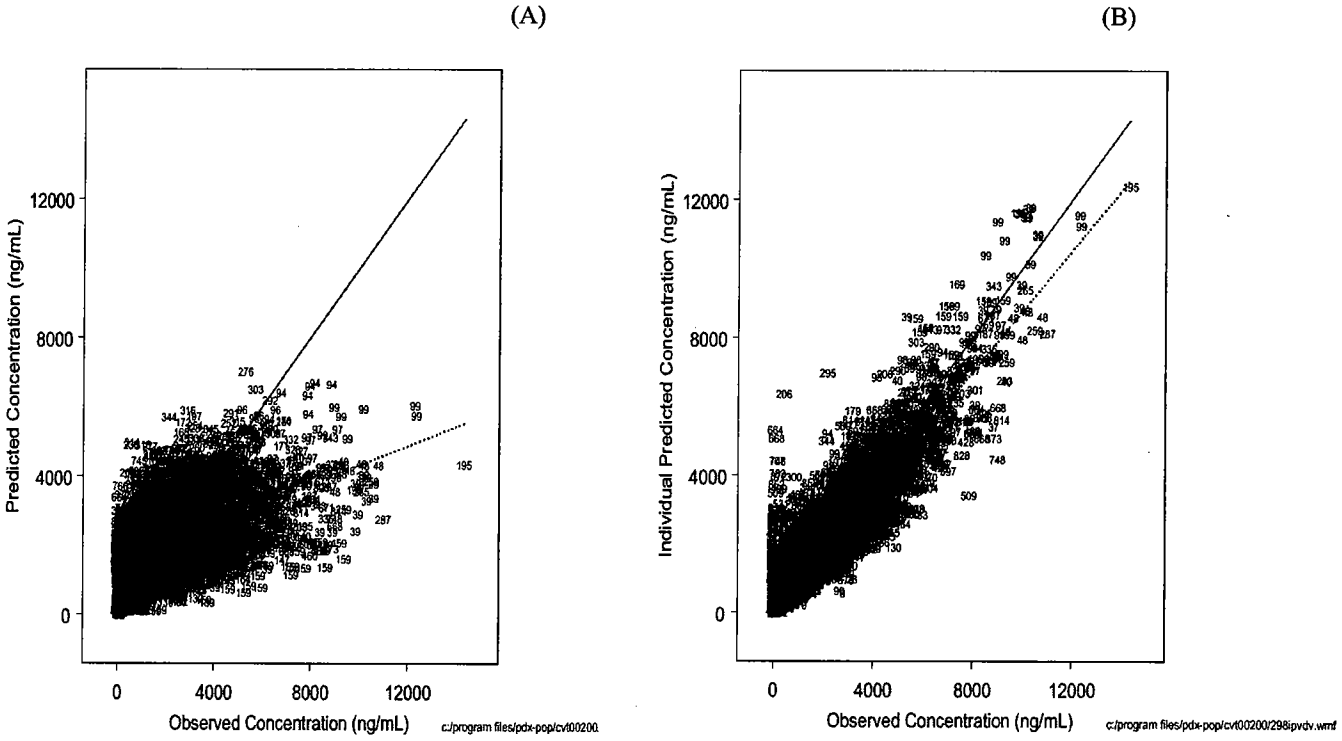


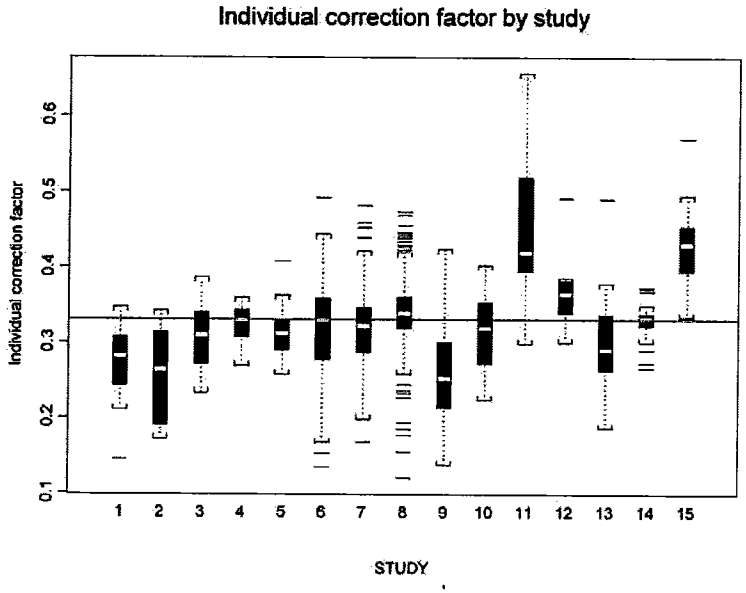
Figure 7 (A) Population mean (B) Individual prediction versus observed Plasma Ranolazine Concentration (ng/mL) after oral administration of ranolazine.

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).



1	CVT 301-10	6	CVT 3021	11	RAN0117
2	CVT 301-13	7	CVT 3031	12	RAN0201
3	CVT 3012	8	CVT 3033	13	RAN069
4	CVT 3015	9	CVT 3111	14	RAN2302
5	CVT 3017	10	RAN0114	15	RAN0121

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.

ΔQTc-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).

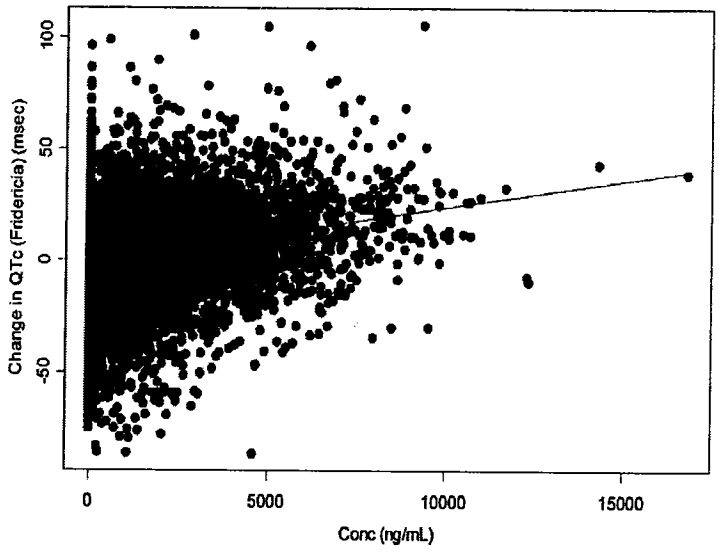


Figure 9. Observed change from baseline of QTc interval (Fridericia's Correction) versus Ranolazine Concentration.

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	266
	SR	1440
	IV	31
	IR	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=(Baseline QTc-418)/24.5
COV4=(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^2_{add}	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, σ2add = 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.

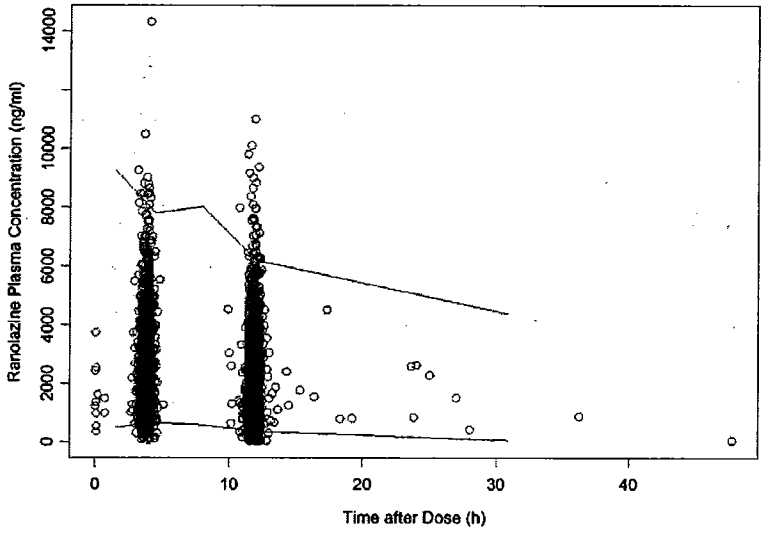


Figure 10. Evaluation of the Final Population Pharmacokinetic Model. Observations were grouped according to time taken after dose to reflect sampling scheme in studies CVT 3031 and CVT 3033.

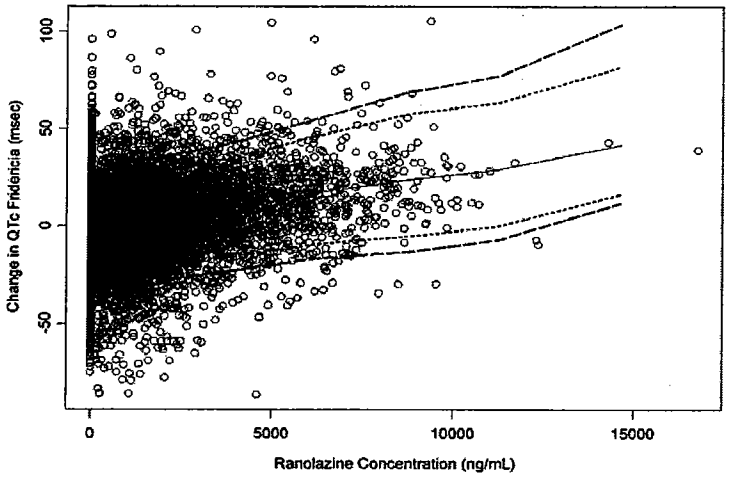


Figure 11. Pharmacodynamic Model Evaluation (The solid line represents the 50th percentile, the short dashed lines represent the 20th and 80th percentile, and the long dashed lines represent the 10th and 90th percentile.

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).

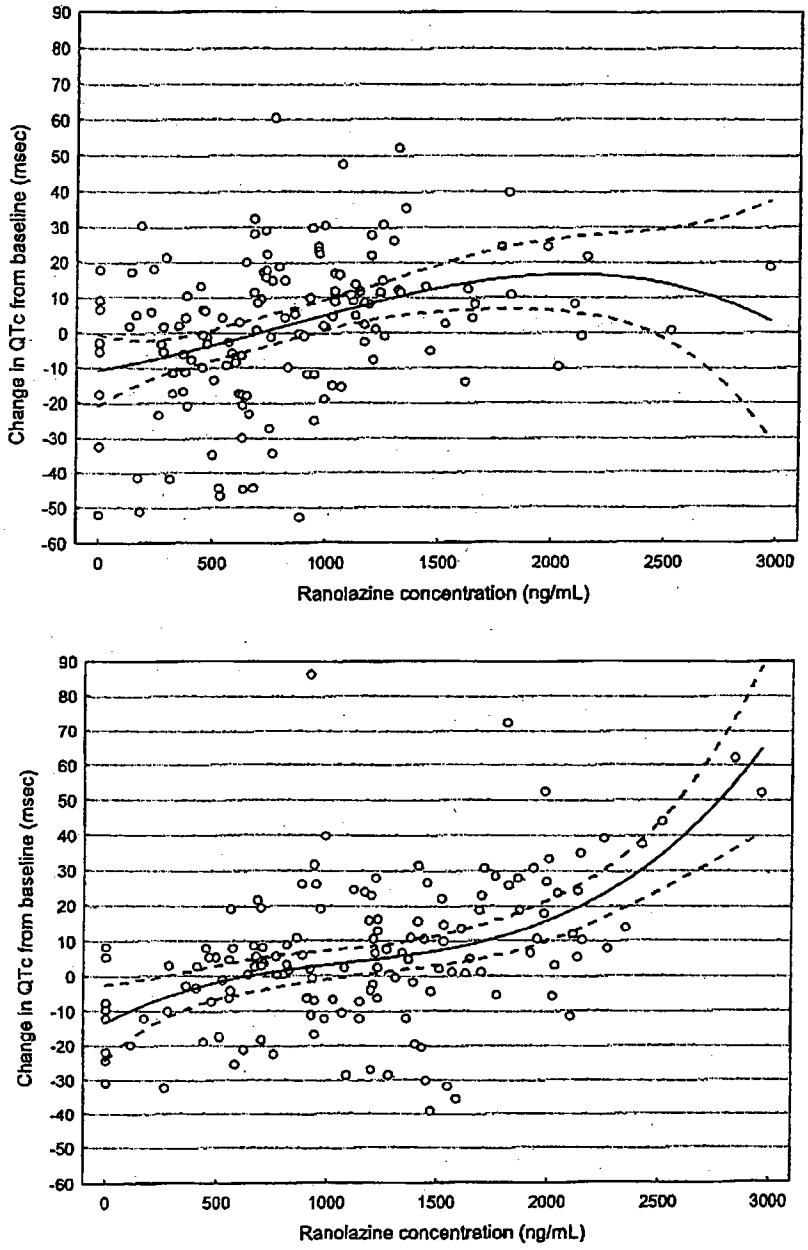


Figure 12. Concentration-Response Relationship for Change in QTc from baseline in subjects with (A) Mild and (B) Moderate hepatic impairment.

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: $C_{max(Observed)}$=1440 ng/mL, $C_{max(Predicted)}$=892 ng/mL; $C_{trough\ (Observed)}$=988 ng/mL, $C_{trough(Predicted)}$=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 ΔQTc 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
$\Delta QTc_{placebo} = X-Y$

Model for Placebo Group: $\Delta QTc_{placebo} = Intercept$

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 10^{th} and 90^{th} 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 ranoalzine, 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 ΔQTc (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 jth QT interval of the ith patient, similarly α_i is the corrected QT and RR is the RR interval and βi is the exponent coefficient of the ith 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 techiniques 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 ΔQTc-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.

$$\Delta QTc = INT + SLP \bullet CONC$$

Model 3: Includes the effect of placebo (PLBEFF).

$$\Delta QTc = INT + SLP \bullet CONC + PLBEFF \bullet ON$$

Where ON is a binary variable for placebo effect (0 if time=0, 1if time > 0).

Model 4: Expands Model 3 by including the concept of threshold concentrations.

$$\Delta QTc = INT + SLP \bullet (THRESHOLD - CONC) + PLBEFF \bullet ON$$

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.

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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:

$$TVINT_1 \left(\frac{Age}{Median}\right)^{\theta_2}$$

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Male Female	1407 420
Race Caucasian Black Asian Hispanic Others	 1714 52 17 26 18
Disease Condition	
Diabetes Yes No	 403 1424
Congestive Heart Failure Yes No	 447 1380
NYHA Classification 0 1 2 3 4	 1380 133 236 76 2
Hepatic Impairment **NO** Mild Moderate	 1811 8 8

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.

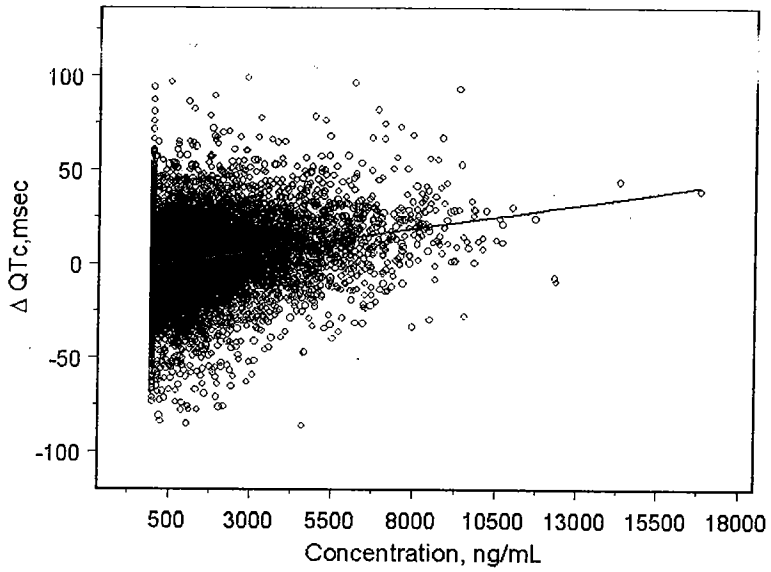

Figure 13. Δ QTc vs Ranolazine Concentrations

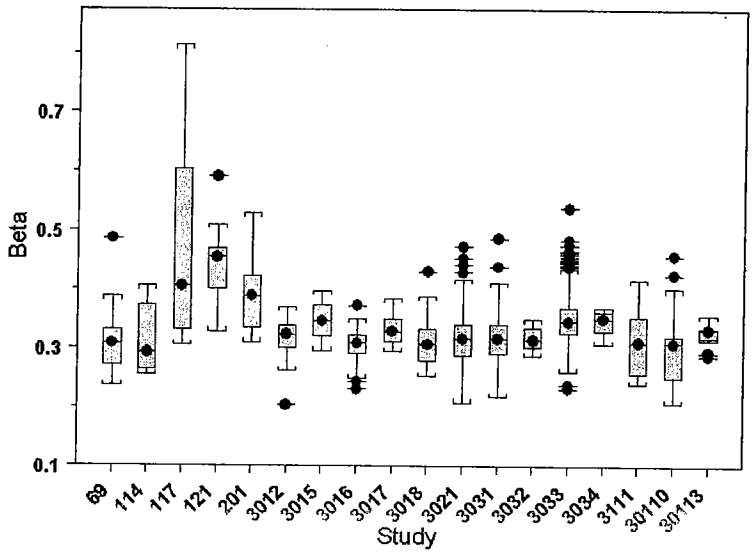

Figure 14. Individual Correction Factor (β) by Study

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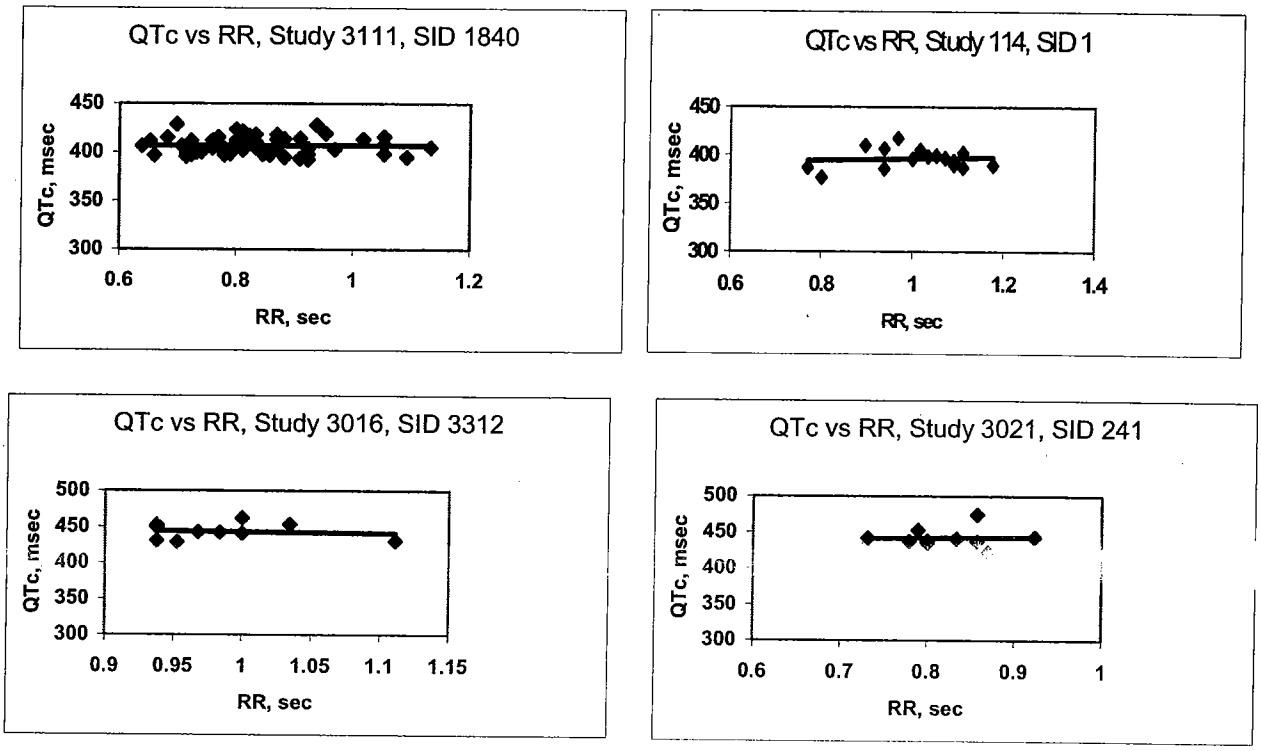

Figure 15. QTc vs RR in representative subjects using individual correction method (SID is a unique ID associated with a patient in the database).

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.

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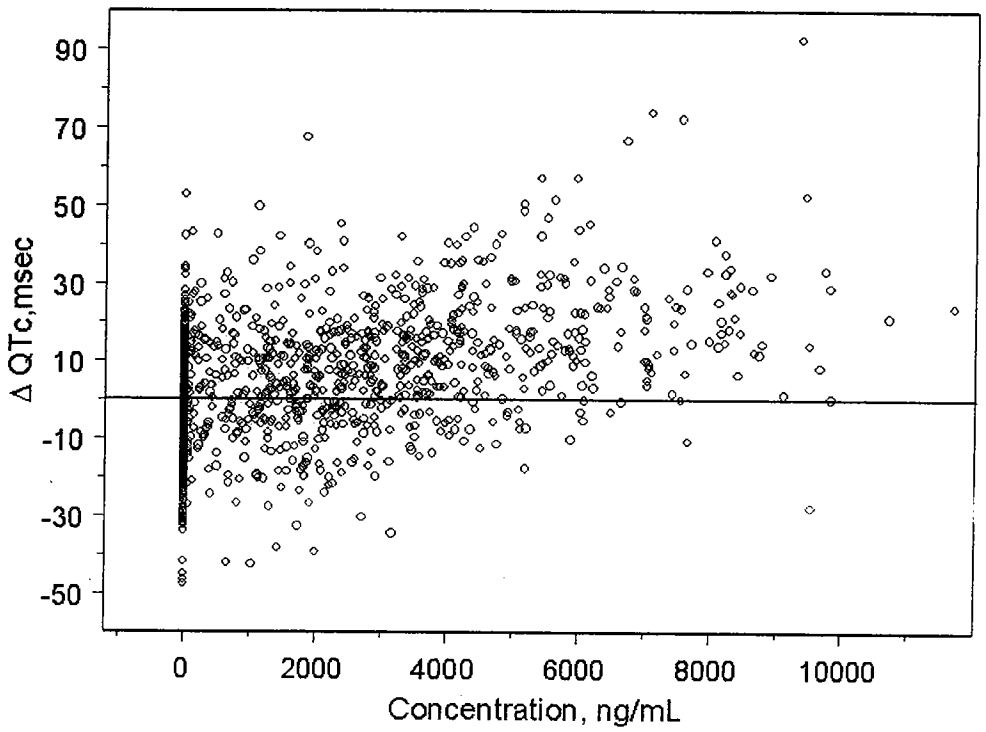

Figure 16. ΔQTc vs Concentration in intravenous infusion study (CVT3111) (One concentration of 18000 ng/mL was removed for clarity).

Initial analysis of the data using the threshold model was faced with diffficulties 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 ΔQTc 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	ΔOBJ*	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

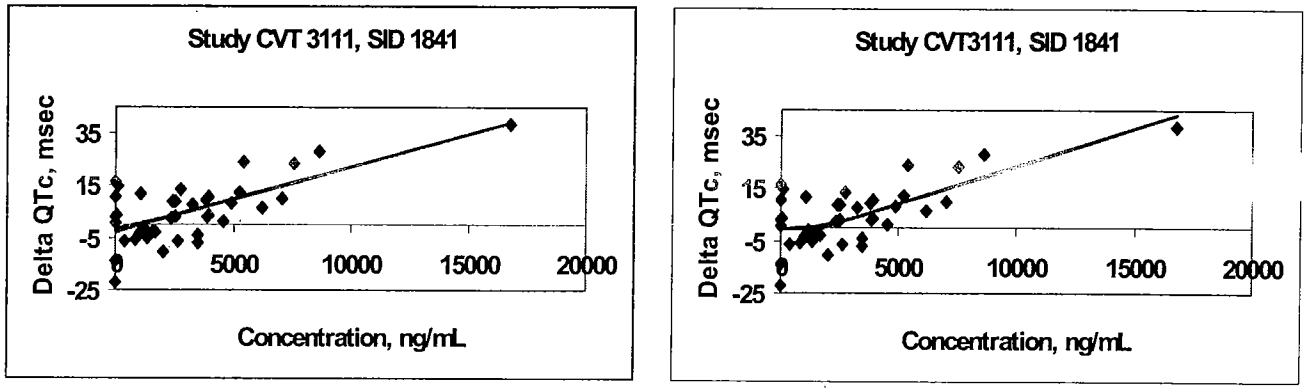

Figure 17. ΔQTc vs Concentration (A) Linear Model (B) Threshold Concentration Model (Observed data (♦) with the individual prediction line is shown; SID is a unique ID associated with a patient in the database)

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.

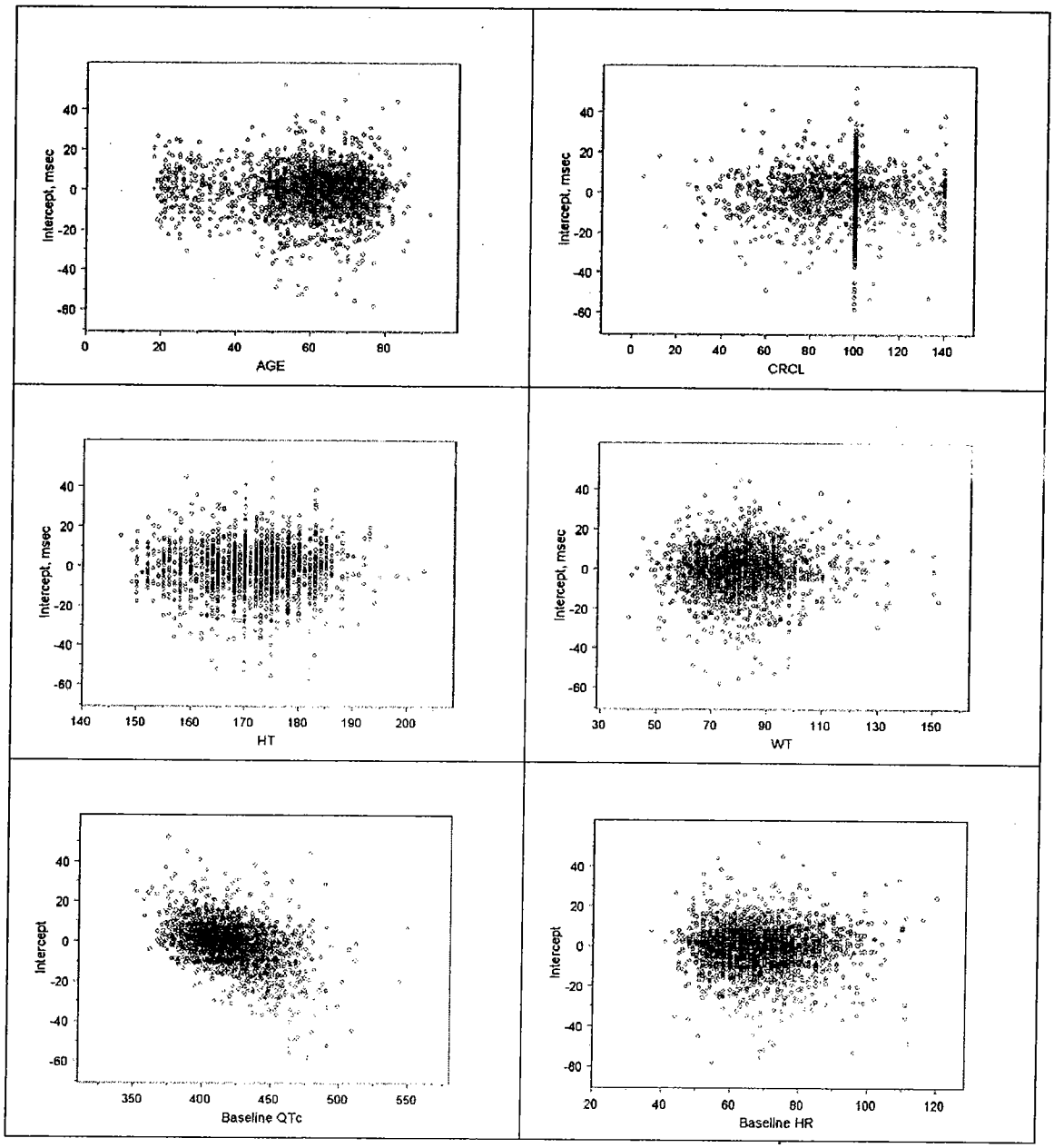

Figure 18 (A). Diagnostic Plots of Intercept versus Covariates (Age, Creatinine Clearance (CrCL), Weight (WT), Height (HT))

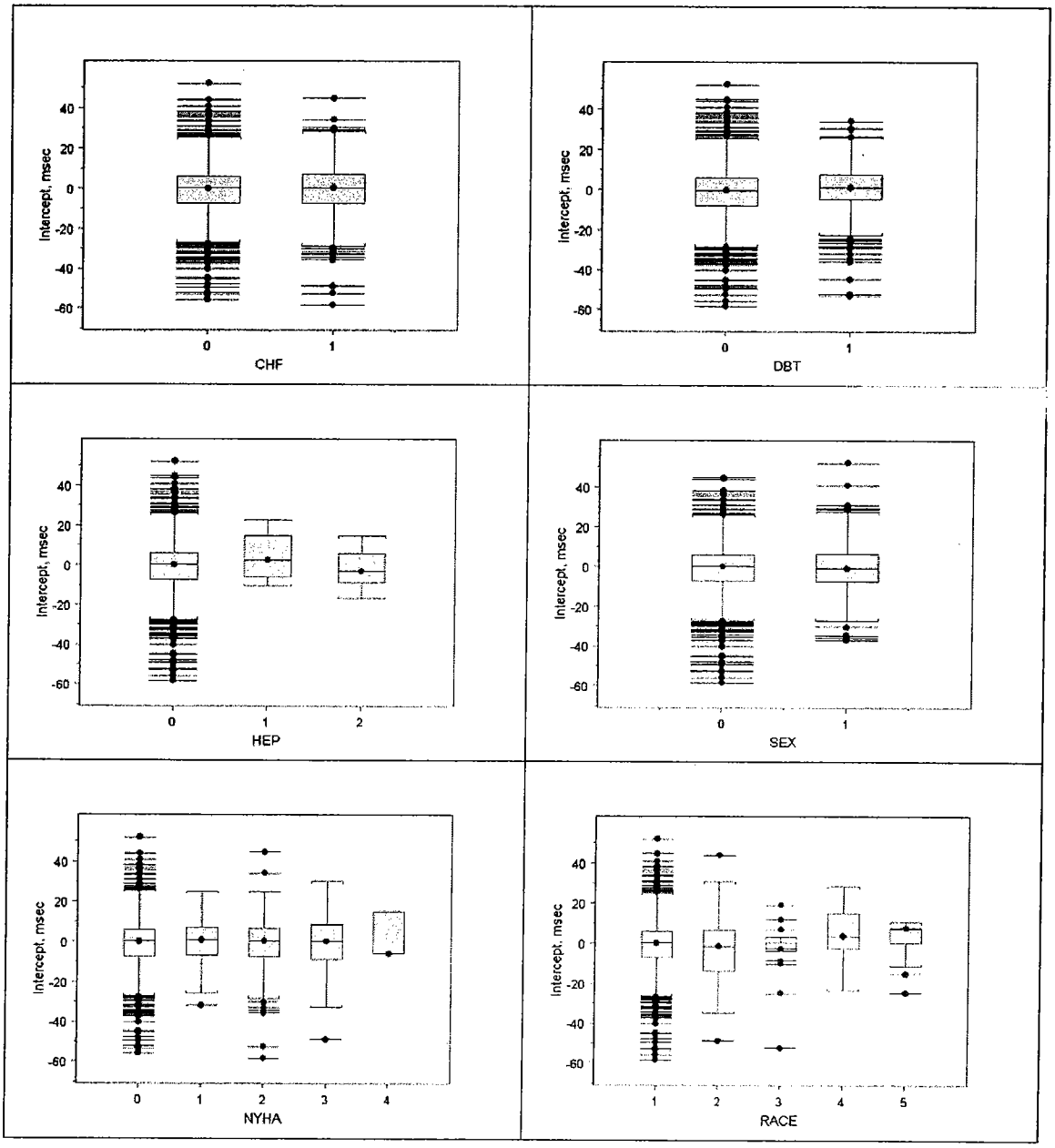

Figure 18 (B). Diagnostic Plots of Intercept versus Categorical Covariates (CHF, DBT, Hep, NYHA, RACE, SEX)

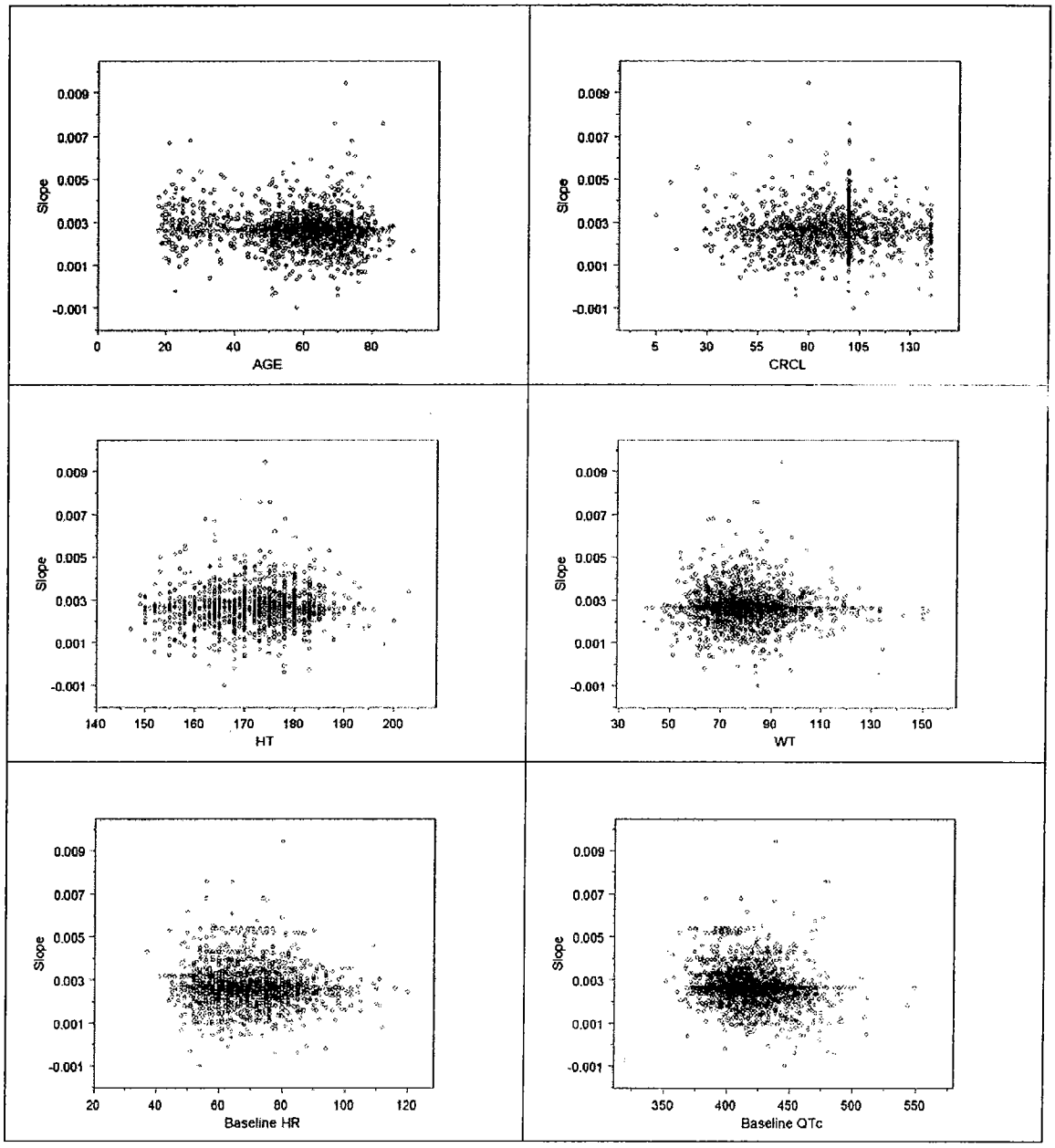

Figure 19 (A). Diagnostic Plots of Slope versus Covariates (Age, Creatinine Clearance (CrCL), Weight (WT), Height (HT))

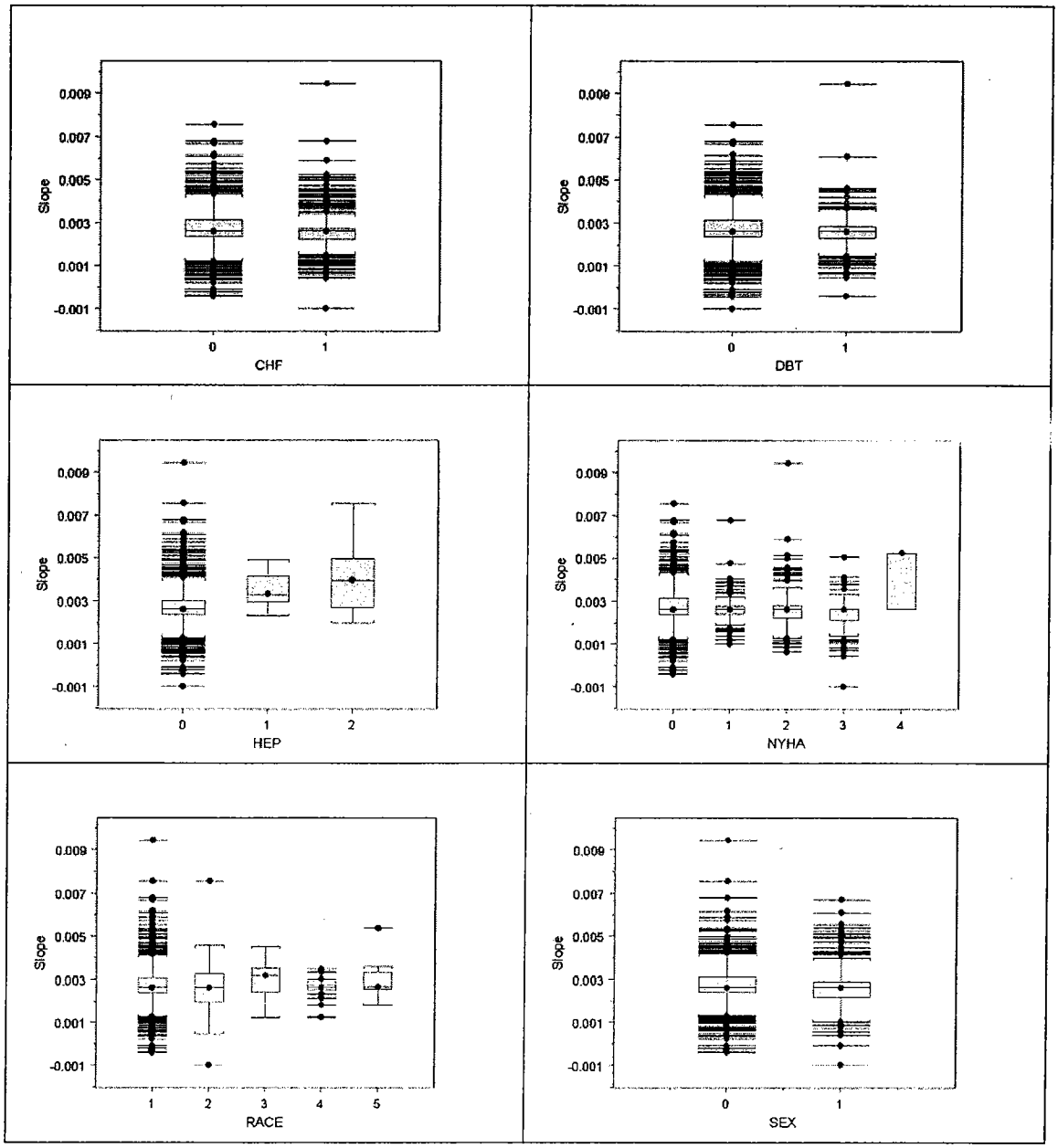

Figure 19 (B). Diagnostic Plots of Slope versus Categorical Covariates (CHF, DBT, Hep, NYHA, RACE, SEX)

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

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. Inspite 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:

$$\Delta QTc = -1.27 - 1.46 \bullet PlaceboEffect + Slope \bullet Concentration$$

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-ΔQTc Relationship.

Parameter	Base Model		Final Model	
OBJF	107605		107579	
No. of Parameters	7		10	
Parameter	Mean	SE[a] (%CV)	Mean	SE[a] (% CV)
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 Mild Moderate			0.0026 [0.0024, 0.0028] 0.0071[b] [0.0039, 0.010]	3.9 16.3
$\omega_{Intercept}$ (SD, msec)	13.03	5.9	13.03	5.9
ω_{Slope} (SD, msec/ng/mL)	0.0018	23.2	0.0017	23.6
$\omega_{Placebo}$ (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.

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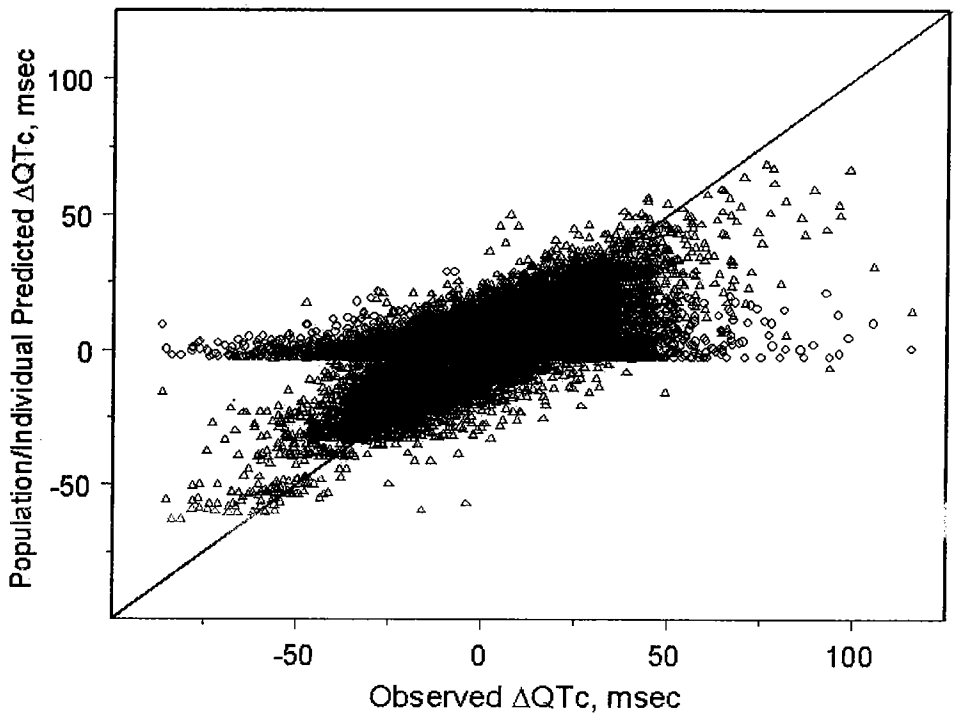

Figure 20. Population (O), Individual Predicted (Δ) vs Observed ΔQTc (Final Covariate Model using Simple Linear Equation).

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Appendix III

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

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) -				
Healthy Volunteers-				
single dose:	X	24	5	
multiple dose:	X	10	6	
Patients-				
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	

Filability and QBR comments

	"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

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/s/

Peter Hinderling
10/11/2005 09:21:30 AM
BIOPHARMACEUTICS

Patrick Marroum
10/11/2005 10:11:35 AM
BIOPHARMACEUTICS