CENTER FOR DRUG EVALUATION AND RESEARCH

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

Division of Clinical Pharmacology I

NDA 21526 S-004/ (b) (4)
(b) (4)

Type: NDA Supplement
Priority: Standard
Submission Dates: September 27, 2007, December 11, 2008
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Brand Name: Ranexa
Generic Name: Ranolazine
Dosage Strength: 500 mg and 1000 mg ER tablets
Sponsor: CV Therapeutics
Indications: Chronic Stable Angina
Reviewing Divisions: Division of Cardiovascular and Renal Products, HFD-110
Division of Metabolic and Endocrine Products, HFD-510
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1. EXECUTIVER SUMMARY

The NDA Supplement contained 12 new reports in the Clinical Pharmacology domain: 7 reports including a POPPK analysis reported the results of 6 in vivo studies in humans, 1 report summarized the results from an in vitro study with human liver tissue and 4 reports were assay related. The 7 Clinical Pharmacology reports reported the results from a PK-PD study (CVT-3114) using ranolazine infusions in patients with long QT-3 syndrome, LQT-3; an interaction study (CVT-3119) with diltiazem 180 mg bid co-administered with 500 mg or 1000 mg ranolazine bid in subjects with poor metabolizer (PM) or extensive metabolizer (EM) genotype and phenotype; an ascending dose study with PK information in angina patients (CVT-3023) receiving oral doses of 750 mg, 1500 mg and 2250 mg ranolazine bid; two long term safety studies with measurements of trough plasma concentrations of ranolazine after administration of 750 mg and 1000 mg ranolazine bid (CVT-3032) or 500 mg bid, 750 mg bid and 1000 mg bid ranolazine (CVT-3034); and from an efficacy study

CVT-3036 in non-ST elevation (NSTEMI) acute coronary syndrome patients receiving ranolazine initially by intravenous administration followed by oral treatments with ranolazine 375 mg bid, 500 mg bid, 750 mg bid or 1000 mg bid. The POPPK report using sparse sampling information compared the ranolazine levels obtained during the intravenous and oral treatment phases of study CVT-3036.

The 8 reports of the 7 in vivo studies and 1 in vitro study were reviewed. The 4 assay related reports which did not contain relevant new information were not reviewed.

Salient Clinical Pharmacology Findings

Mechanism of Action

The open-label study CVT-3114 in patients with the long QT syndrome (LTQ-3 and ΔKPQ mutation) and continuous influx of sodium through the late (sustained) sodium channel (I_{Na}) showed that ranolazine at therapeutic concentrations decreases QTcF by 25 ms. The finding indicates that ranolazine not only inhibits the rapid inward potassium channel, I_{Kr}, but also I_{Na}, and the inhibition of the latter is greater than that of the former in the patients with LTQ-3.

Pharmacokinetics

The open-label ascending dose study CVT-3023 showed that the tolerability of ranolazine defined by pre-specified endpoints is dose dependent. The incidence of somnolence, confusion/disorientation, symptomatic hypotension, dizziness, nausea, or vomitus increase with dose: 8% with the 750 m bid regimen, 46% with the 1500 mg bid regimen and 75% with the 2250 mg bid regimen. The number of subjects terminated from the study because of an adverse event increases also with dose: 0% with the 750 mg bid regimen, 8% with the 1500 mg bid regimen and 33% with the 2250 mg bid regimen

Two long term open-labeled safety studies with administration of ranolazine 500 mg bid, 750 mg bid or 1000 mg bid in angina patients (CVT-3032 and CVT-3034) and one long term efficacy and safety study with administration of ranolazine 750 mg bid or 1000 mg bid in NSTEMI acute coronary syndrome patients (CVT-3036) measured trough concentrations of ranolazine. In these studies co-administration of calcium antagonists including diltiazem or verapamil was not excluded. In studies CVT-3032 13% and 16% of the subjects received diltiazem and 1.4% and 1.0% verapamil concomitantly with ranolazine. In study CVT-3036 diltiazem and verapamil co-administration occurred in < 2% of the subjects.

The trough plasma concentrations measured in patients with angina in CVT-3032 and CVT-3034 and in patients with NSTEMI acute coronary syndrome in CVT-3036 are shown below:

Comparison of Median Trough and Individual Maximum Trough Plasma Concentrations of Ranolazine in Studies CVT 3032, CVT 3034 and CVT-3036

Study	n Subjects	Dose mg,bid	Plasma Concentration of Ranolazine	
			Median Trough Range	Individual Maximum Trough Range
3032	4-41	750	833-1705	2510- 5925
	16-82	1000	1350- 2000	4230- 10800
3034	7-122	500	800-1290	1930-6340
	11-239	750	1370-2190	4230- 8620
	11-202	1000	1840-2810	4780-9580
3036	92-101	1000*	1510-2030	8410, 8410

*4 subjects received 750 mg bid

The ranges of the median trough concentrations of ranolazine with the 500 and 750 mg bid regimens or the 750 mg and 1000 mg bid regimens are overlapping. Also, the range of the individual maximum trough values in CVT-3032 and CVT-3034 is 2 to 3 fold underlining the marked variability of the plasma concentrations of ranolazine. The trough values of up to 10 000 ng/mL in studies CVT-3032 and CVT-3034 with the angina patients exceed the threshold value of 6000 ng/mL for intolerability determined in CVT-3023.

The large majority of NSTEMI patients in the placebo controlled Phase 3 efficacy and safety study CVT-3036 received a multiple dose regimen of ranolazine 1000 mg bid or placebo that was initiated by intravenous infusion to accelerate attainment of steady-state levels of ranolazine. Less than 2% of the patients had severe renal impairment or were on diltiazem or verapamil and ranolazine. A population PK simulation exercise showed that exposure to ranolazine during the intravenous and oral phases of the regimen is similar (see Pharmacometrics Report p. 85**).**

The open-label study CVT-3114 in healthy subjects genotyped and phenotyped for CYP2D6 polymorphism showed that the exposure to ranolazine at steady-state is significantly greater in PMs than in EMs after 500 mg ranolazine bid. The increased exposure in PMs is associated with an increase in the incidence of adverse events. After 1000 mg ranolazine bid the exposure to ranolazine is not different between PMs and EMs, indicating that the contribution of the CYP 2D6 pathway to the CYP3A dominated metabolic elimination of ranolazine is negligible at the higher dose level.

Co-administration of ranolazine 500 mg bid and diltiazem 180 mg bid increases the exposure to ranolazine by a factor of about 2 in agreement with the results of previous studies. The incidence of adverse events with the co-administration regimen of ranolazine 500 mg bid and

diltiazem 180 mg bid appeared to be greater than with ranolazine 500 mg bid alone. Co-administration of ranolazine 1000 mg bid and diltiazem 180 mg is not tolerated by the healthy subjects.

An in vitro study, CVT-303.049N, using human liver microsomes showed that ranolazine at therapeutically effective concentrations does not relevantly inhibit CYP2C8.

Salient Clinical Findings

The efficacy and safety study CVT-3036 in patients with NSTEMI acute coronary syndrome using the composite of time to first occurrence of cardiovascular death, MI, or recurrent ischemia shows that ranolazine is not superior to placebo (standard care) [relative risk ranolazine: placebo= 0.919 (95% confidence interval 0.83, 1.02), p=0.11]. Additional safety related findings were that a) incidence and frequency of symptomatic documented arrhythmias (documented by any form of ECG and resulting in prolongation of hospitalization or being medically important) are not statistically different between ranolazine and placebo; and b) the number of clinically significant arrhythmias during 7-day Holter monitoring in the ranolazine treated patients is lower than in placebo treated patients. These results suggest that ranolazine up to 1000 mg bid despite its QT/QTc prolonging effect does not exhibit pro-arrhythmic activity.

Deficiencies

There are no deficiencies. However, there are issues related to the revised label proposed by the sponsor.

<u>Contraindications</u>

In the present label contraindications for ranolazine include 1) administration of ranolazine to patients with pre-existing QT/QTc prolongation 2) co-administration of ranolazine and QT/QTCc prolonging drugs 3) co-administration of ranolazine with strong and moderate CYP3A inhibitors including diltiazem 4) administration of ranolazine to patients with liver impairment Child-Pugh Class A (mild), B (moderate) and C (severe). (b) (4) .

The double-blind, placebo controlled efficacy and safety study CVT-3036 in patients with NSTEMI acute coronary syndrome showed that ranolazine 1000 mg bid is not pro-arrythmic, despite its QT/QTc prolonging effect. However, in study CVT-3036 subjects with pre-existing QT/QTc prolongation, with clinically significant liver disease or on QT/QTc prolonging drugs were excluded. Pertinent other new information was not contained in the submission. (b) (4)

Strong and Moderate CYP3A Inhibitors including Diltiazem

The short term ascending dose tolerability study CVT-3023 in angina patients showed that ranolazine is tolerated in doses up to 1500 mg bid alone. However, study CVT-3031 (MARISA) in the original NDA submission showed an increase in adverse events at dose levels of Ranexa 1500 mg bid, and the present label states that doses in excess of 1000 mg Ranexa twice daily should not be administered. In agreement with previous studies, study CVT-3119 showed that co-administration of ranolazine 500 mg bid and diltiazem 180 mg bid increases the plasma concentration of ranolazine about 2 fold. Study CVT-3119 also indicated that in PMs of CYP 2D6 the exposure to ranolazine 500 mg bid is only slightly greater than in EMs. In the open label, long term safety study CVT-3034 16% of the subjects received diltiazem in addition to ranolazine with no overt tolerability problems. In the double-blind and placebo controlled efficacy and safety study CVT 3036 patients on strong CYP3A inhibitors or moderate CYP3A inhibitors other than diltiazem or verapamil were excluded from participating in the study. However, co-administration of ranolazine with diltiazem or verapamil, although permitted, occurred in less than 5% of the subjects.

The results from studies CVT-3036 showing an absence of a pro-arrhythmic liability of Ranexa, and from CVT-3031, CVT-3023, CVT-3119 and CVT-3034 and the present label providing quantitative tolerability information, suggest that co-administration of 500 mg ranolazine and 180 mg diltiazem bid is tolerated by a substantial portion of angina patients. Close supervision with ECG monitoring of angina patients in the initial phase of co-administration treatments of Ranexa with diltiazem is recommended. Co-administration of ranolazine in doses greater than 500 mg bid and diltiazem greater than 180 mg remains contraindicated. Co-administration of ranolazine with strong CYP 3A inhibitors or moderate CYP3A inhibitors other than diltiazem remains contraindicated as well. In conclusion, the evidence provided by the sponsor does not justify a removal of contraindication 4, i.e. co-administration of Ranexa with strong and moderate CYP3A inhibitors. However, after ranolazine has been shown not to be pro-arrhythmic, co-administration of the moderate CYP3A inhibitor diltiazem can be justified, because its quantitative impact on the exposure to ranolazine is known from clinical studies. Also known is that Ranexa, a CYP 3A inhibitor, does not affect the pharmacokinetics of diltiazem, a substrate of CYP 3A, when co-administered. Verapamil 120 mg three times a day increases the plasma levels of ranolazine about 2 fold similar to diltiazem. However, the sponsor has not evaluated the possible impact of ranolazine, a CYP3A inhibitor, on the exposure to verapamil, a CYP3A substrate. Thus, the use of Ranexa in patients on verapamil should be avoided. The impact of other moderate CYP3A inhibitors on the exposure to ranolazine is unknown and thus co-administration of Ranexa with moderate CYP-3A inhibitors other than diltiazem remains contraindicated.

Renal Impairment

(b) (4)

1. 1. RECOMMENDATION

From a Clinical Pharmacology view point the submission is acceptable.

2. LABEL

(b) (4)

22 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

3. INDIVIDUAL STUDY REPORTS

3.1. Technical Report CVT 303.049N: In Vitro Evaluation of Ranolazine as an Inhibitor of CYP2C8

Investigator and Study Site

(b) (4)

Objectives

To evaluate the ability of ranolazine to directly inhibit CYP2C8 with the aim to of ascertaining the potential of ranolazine to inhibit the metabolism of other drugs that are substrates of CYP2C8.

Materials and Methods

The study was designed to determine the inhibitory constant (IC50) of ranolazine for direct inhibition of CYP2C8**.** The CYP2C8 activity was measured by determining the 6α-hydroxylation of paclitaxel, a known substrate of CYP2C8. Human liver microsomes from sixteen donated livers were pooled. In initial experiments Km and Vmax of paclitaxel were determined to select

the concentrations of the marker substrate and the incubation conditions. The results are shown in the below table:

Appendix 2: Characterization of the test system

CYP activities in a pool of sixteen individuals

		Pool of sixteen	
		Observed Vmax[a]	Observed Km[a]
Enzyme	CYP Reaction	(pmol/mg protein/min)	(μM)
CYP2C8	Paclitaxel 6α-hydroxylation	570 ± 40	11 ± 2

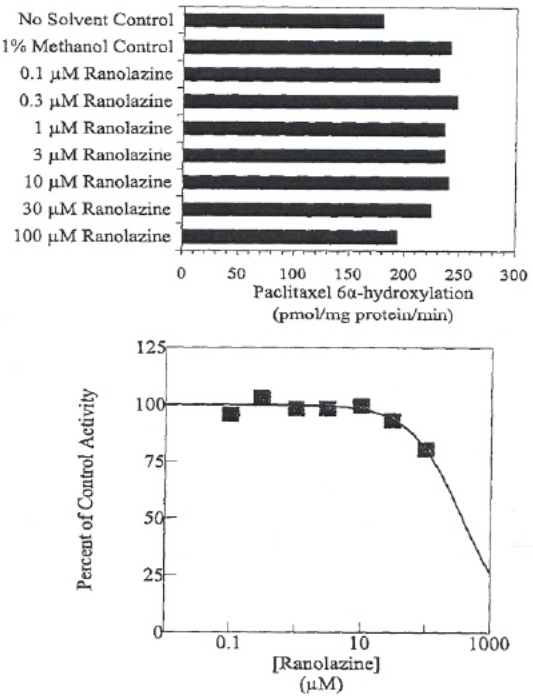
[a] The kinetic constants for the pool of human liver microsomes used for this study were determined in (b) (4) Constants are shown ± standard error (where constants are rounded to two significant figures, and standard errors are rounded to the same degree of accuracy as the constant). They were calculated using the GraFit software, which utilized rates of product formation (triplicate data, with some exceptions) at 13 substrate concentrations. A standard error of 0 indicates the standard error of less than 1% of the mean.

The incubations were conducted at approximately 37° C on 400 μL incubation mixtures (target pH 7.4) containing high purity water, potassium phosphate buffer (50 mM), $MgCl_2$ (3 mM), EDTA (1mM), an NADPH generating system [NADP (1 mM), glucose-6-phosphate dehydrogenase (1 unit/mL)] and marker substrate. Because of a possible binding of ranolazine to protein or lipids, the experiments were designed to keep the microsomal protein concentration low (0.05 mg/mL) and the incubation time short (5min). Under these conditions the rate of reaction was measured under initial rate conditions; i.e. the product formation increased with increased protein concentration and incubation time, such that the percent metabolism of the marker substrate did not exceed 20%. Preliminary experiments conducted at half and twice the normal protein concentration and half and twice the normal incubation period demonstrated linearity of the metabolic rate with protein concentration and incubation time. The incubation concentration of paclitaxel corresponded to the Km value (10 μM). The target concentrations of ranolazine were 0.1, 0.3, 1, 3, 10, 30 and 100 μM. 1% Methanol (4 μL) was used as solvent for ranolazine. Quercetin 20 μM in methanol (0.1% v/v), a known CYP2C8 inhibitor, was used as a positive control. Quercetin inhibited the metabolism of paclitaxel by 90%. Controls were run without solvent and with 1% methanol.
The concentrations of 6α- hydroxy-paclitaxel were measured by a validated HPLC/MS/MS method using (b) (4) as internal standard.

RESULTS

Ranolazine at the highest concentrations tested (100 μM) inhibited the metabolism of paclitaxel by less than 20% (IC50 > 100 μM) as shown in the below figure:

Figure 1: Inhibition of CYP2C8 (paclitaxel 6α-hydroxylation) by Ranolazine: IC50 determination



Parameter	Value	Std. Error
IC50 (µM)	> 100 µM	NA
Slope Factor	NA	NA

Conclusions

Ranolazine at a concentration of 100 µM (44 µg/mL) inhibits CYP2C8 by 20 %. Total (bound+ unbound) trough concentrations of the drug in plasma up to 7 µg/mL have been observed in clinical trials after oral administration of ranolazine. Corresponding peak plasma concentrations were not measured, but can be estimated to be less than 2 fold greater than the trough concentrations Thus, at therapeutic concentrations ranolazine is not expected to impact substrates of CY2C8 in vivo.

Comments

Estimating IC50 based on data with a maximum inhibition of 20 % is not appropriate.

3.2 Report of Study CVT 3114:"An Open Label, Exploratory Study of Ranolazine IV in Subjects with Long QT-3 with the SCN5A ΔPQ Mutation"

Clinical Site and Investigator: (b) (4)

Objectives

Primary: to evaluate the effect of ranolazine to shorten the QTc interval in subjects with long QT-3 syndrome (LQT-3) who have QTc prolongation secondary to the ΔKPQ deletion in the SCN5A sodium channel gene.

Secondary: to evaluate the safety of ranolazine

Study Rationale

The long QT syndrome (LTQS) is a familial genetic disorder characterized by prolonged ventricular repolarization on the ECG and a propensity to syncope, polymorphic ventricular tachycardia (TdP) and sudden death. One of the seven LQTS genes, SN5A, encodes for the cardiac sodium channel; a deletion of the ΔKPQ region within this gene leads to persistent sodium entry into myocardial cells, which results in marked prolongation of ventricular repolarization, manifesting as a prolonged QT interval.

The sponsor claims, based on preclinical data, that ranolazine is a selective inhibitor of the late (sustained) sodium current and has only minimal blocking effect on the peak sodium current during phase 0 of the action potential. If the preclinical data are predictive ranolazine in patients with LQT-3 with the SCN5A ΔPQ mutation should reduce the prolongation of the cardiac repolarization and shorten the QTc interval. Since a persistent sodium current can lead to calcium overload and impairment of cardiac relaxation, the sponsor expects that ranolazine improves LV relaxation.

Investigational Drugs and Formulations

Ranolazine injection formulated at 25 mg/mL and packaged in 20 mL vials was used. Provider and Lot No. of materials are not indicated.

Design

This was an open label, single dose administration, single center, exploratory study. The patients received ranolazine by intravenous infusion for 8 h (at a rate of 45 mg/h for the first 3 h followed by a rate of 90 mg/h for the subsequent 5 h). The 90 mg infusion rate was expected to generate a mean plasma concentration level at the end of the infusion of approximately 2200 ng/mL, a value close to the average trough ranolazine plasma concentration found in the pivotal trials CVT 3031 and 3033 after bid administration of 1000 mg ranolazine extended release tablets. The patients were institutionalized for 4 days. They were admitted to the clinic on Day -2, pre-dose assessments were conducted on Day-1, the drug infusions were administered on Day 1, and the subjects were discharged on Day 2.

For inclusion in the study the patients could be male or female, must be 18-55 years of age,

had a confirmed genotype of LTQ-3 with the ΔKPQ mutation and a QTc> 470 msec. Women of child bearing potential were to have a negative pregnancy test and be willing to use contraceptive drugs or devices.

Subjects receiving sodium channel blockers, inhibitors or inducers of CYP3A or drugs prolonging the QT interval, subjects with significant chronic hepatic impairment (Child-Pugh Class B or C), severe renal impairment (CLcr <30 mL/min), and subjects with a significant co-morbidity precluding safe participation in the study were excluded from the trial.

On Days -1 and 1 twelve lead ECGs were obtained (on Day-1 every 0.5 for 8 h and at 10 and 12 h and on Day 1 pre-dose and at times matched to those obtained on Day-1 and at 24 h). Continuous 12 lead Holter monitoring (for a minimum of 12 h prior to dosing and for a minimum of 24 h on Day 1) was performed. Echocardiograms were obtained in the patients pre-dose and within 30 minutes prior to the end of the ranolazine infusion.The ECG tracings were read during the ranolazine infusions by the attending investigator/cardiologist for purposes of ensuring patient safety. These open-label interpretations were not used in the efficacy analysis. The efficacy analysis used data from the ECG tracings that were interpreted in a blinded manner by (b) (4). (b) (4) was blinded to subject identification and whether the ECG came from the baseline or on-treatment period. (b) (4) (b) (4) was not involved in either patient treatment or the open-label reading of the ECG during the ranolazine infusion.

Efficacy of the ranolazine infusion was measured through ECG parameters including RR, PR, QRS and QT/QTc and T-wave morphology, Holter parameters (QT/RR relationship, QT variability index) and echocardiogram parameters including the systolic parameters: left vetricular ejection fraction (LVEF), stroke volume (SV), systolic mitral annulus velocity (Sa), and the diastolic parameters: left ventricular isovolumic relaxation time (LV IVRT), peak early mitral annulus velocity (mitral E wave velocity) (E), peak transmitral flow velocity during atrial contraction (mitral A wave velocity) (A), early mitral deceleration time (mitral E wave deceleration) (DT) and peak early diastolic mitral annulus velocity (mitral annular velocity) (E')

Pharmacokinetic Profiling

Scheduled blood samples were taken for the measurement of the plasma concentrations of ranolazine pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 h after start of the infusion.

Bioassay

A validated LC/MS/MS method with an internal standard and a calibration range of 50.0 ng/mL-10 000 ng/mL was used. The coefficient of determination for the linear regression is ≥ 0.999. The accuracy ranged between -0.125 and 5.0% and the precision is ≤ 5%.

Statistical Analysis

All patients dosed with ranolazine were included in the statistical analysis. The primary efficacy analysis used a mixed effects linear model applied to the change from time-matched baseline values in Fridericia QTc with a fixed effect for time, accounting for repeated measures within subjects. Secondary efficacy analyses were performed using the same methods for the ECG parameters PR, QRS, Q and T-wave morphology, and for the parameters QT/RR relationship and QT variability index derived from the Holter data. The one sample Student's t-test was used to assess the changes from baseline for the echocardiographic parameters.

The Pearson correlation coefficient between each ECG efficacy variable and ranolazine plasma concentration was computed using all the data from all time points within each subject. The across-subject mean and median values of the correlation coefficient were computed.

RESULTS

Demographics

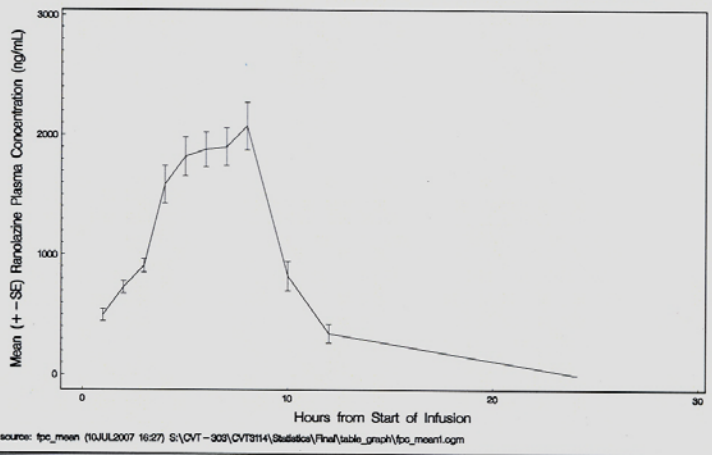
Five Caucasian subjects (4 males, 1 female) in the age range 23 to 55 years enrolled and completed the study. All subjects had a history of LQT-3, 2 had a history of syncope, 2 had an implantable cardioverter/defibrillator and 2 had an atrial pacemaker. Four of the 5 subjects were on nadolol for the treatment of LTQ-3. The patients' median baseline QTc values on Day-1 ranged between 530 and 566 msec.

Results

Pharmacokinetics

The mean plasma concentration profiles of ranolazine are shown in Figure 1 below:

Figure 1 **Mean Ranolazine Plasma Concentrations over Study Nominal Time Points**



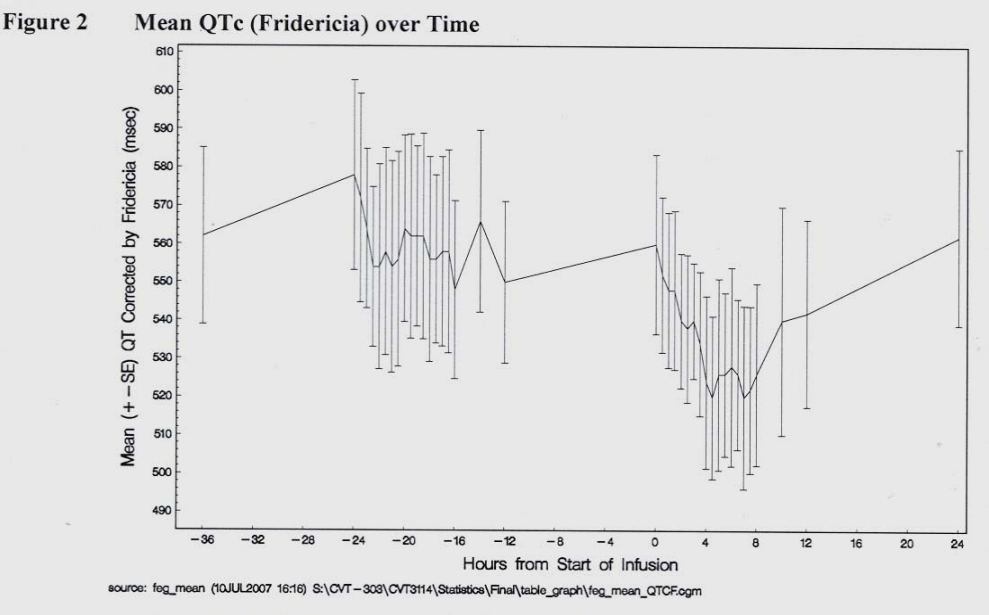
The results indicate that the plasma concentrations of ranolazine after 3 h and 8 h were approximately 900 ng/ml and 2100 ng/mL, respectively, levels that were similar to the mean

trough concentrations observed in the pivotal trials CVT 3031 and 3033 in the target angina population receiving 500 mg and 1000 mg ranolazine extended release tablets bid, respectively.

Pharmacodynamics

The heart rate during the infusion changed from baseline on average by 0.9 (0.54) bpm.
The slope of plots of the QTcF intervals against the RR intervals at baseline are not different from zero indicating that heart rate correction of QT according to Fridericia is appropriate.

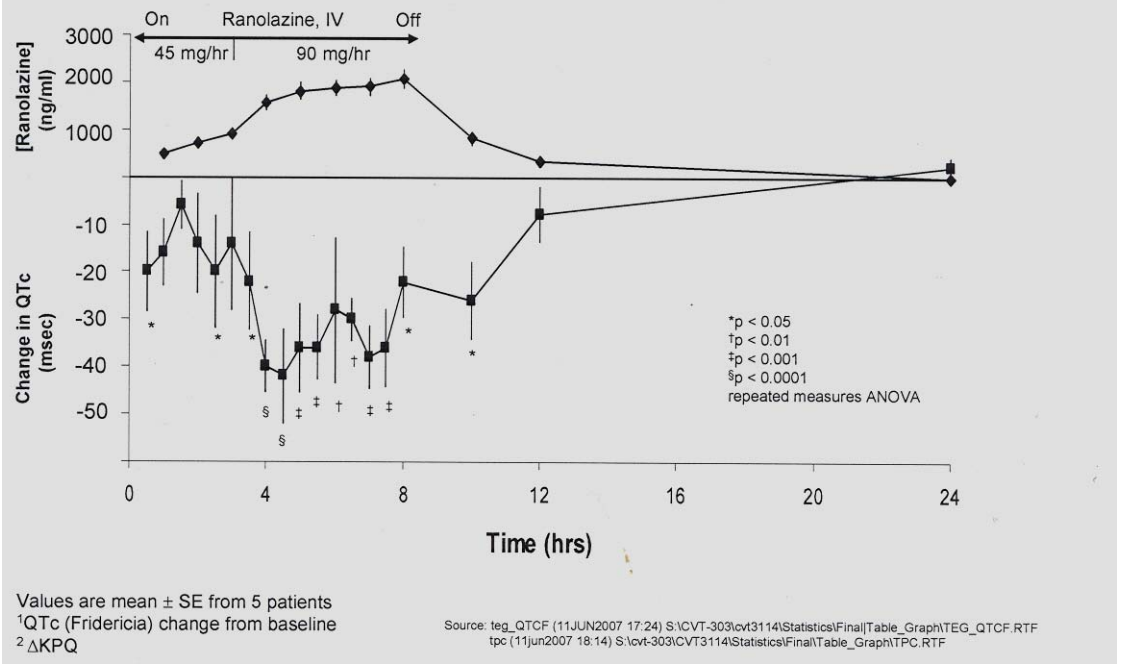
The mean QTc F interval durations at baseline and during ranolazine infusion are shown in Figure 2:



The data suggest that the Friderician QTc intervals on Day 1 during the ranolazine infusion were shorter than the time matched QTc intervals on Day -1. All the mean Fridericia QTc intervals during the ranolazine infusion were statistically significantly shorter than the time matched baseline values. On Day 1 during the initial 3 h infusion period when ranolazine was infused at a rate of 45 mg/h the Fridericia QTc intervals were longer than those observed during the subsequent 5 h infusion period when ranolazine was administered at a rate of 90 mg/h.

Figure 3 shows the effect of ranolazine on QTc and the simultaneously measured plasma concentrations:

Figure 3 Profile over Time of Plasma Ranolazine Concentrations and Changes from Time-Matched Baseline in QTc Interval[1] in LQT3 Subjects[2]



A summary of the median effects of ranolazine on the ECG intervals is shown below:

ECG Interval	Number Subjects Evaluated	Median Overall Change from Baseline, ms		
		Overall during 8 h Infusion	3 h after Infusion Start	8 h after Infusion Start
PR	3	4	20	-10
QRS	5	1	0	0
T	5	-16	0	10
QTc	5	-25	-20	-30

The median change in the interval duration from the time matched baseline was consistent for the QTc interval and indicated a shortening effect of ranolazine. The median change in QTc from the time matched baseline during the initial 3 h of the infusion and the subsequent 5 h of infusion ranged between - 60 ms and 20 ms and -40 ms and 0 ms, respectively. There was a statistically significant correlation between the change in QTc from time matched baseline and the ranolazine plasma concentration (r=0.7 (0.22)). There was a trend for a shortening of the T-interval during the infusions, but the measurements showed more variability. The median change in T wave duration (uncorrected for heart rate) in the subjects 3 h and 8 h after start of the infusion ranged between -40 ms and 30 ms and -20 ms and 40 ms, respectively. The T-wave amplitude appeared

not to be impacted by ranolazine. Also, ranolazine appeared not to affect the QRS or PR interval. However, it should be noted that the latter interval was only evaluable in 3 of the 5 subjects (2 patients had atrial pacemakers). These results suggest that ranolazine does not affect conduction velocity.

Pharmacokinetics-Pharmacodynamics

There is a statistically significant linear regression of QTc on the ranolazine plasma concentrations measured during the 8 h infusion.

The results on the echocardiographic variables are summarized in Table 3:

Table 3 Echocardiographic Resting Left Ventricular Function

Parameter	Mean ± SD		
	Baseline (n=5)	End of Ranolazine Treatment (n=5)	Change from Baseline (n=5)
Systolic Function			
LVEF (%)	62.4 ± 7.80	59.8 ± 4.60	−2.6 ± 3.21
SV (mL)	79.4 ± 24.84	77.6 ± 26.52	−1.8 ± 10.03
Sa (cm/sec)	9.8 ± 1.25	8.6 ± 0.96	−1.2 ± 1.35
Diastolic Function			
LV IVRT (msec)	125.4 ± 27.36	108.6 ± 35.35	−16.8 ± 9.68*
E (cm/sec)	56.6 ± 7.64	70.8 ± 9.07	14.2 ± 10.69*
A (cm/sec)	50.0 ± 9.90	62.6 ± 12.28	12.6 ± 15.57
E/A	1.2 ± 0.33	1.2 ± 0.26	0.0 ± 0.43
DT (msec)	288.8 ± 79.63	226.2 ± 33.99	−62.6 ± 88.43
E′ (cm/sec)	7.9 ± 3.61	8.7 ± 3.42	0.8 ± 0.91

*Change from baseline statistically significant ($p<0.05$)

Key to acronyms: LVEF = LV ejection fraction; SV = stroke volume; Sa = systolic mitral annulus velocity; LV IVRT = LV isovolumic relaxation time; E = peak early mitral annulus velocity (mitral E wave velocity); A = peak transmitral flow velocity during atrial contraction (mitral A wave velocity); DT = early mitral deceleration time (mitral E wave deceleration time); E′ = peak early diastolic mitral annulus velocity (mitral annular velocity)

Source: Appendix 17 (and a by subject listing of echocardiogram data are provided in Appendix 18)

At the end of the infusion the mean left ventricular iso-volumic relaxation time was 13 % shorter and the peak early transmitral flow velocity increased by 25% compared to the corresponding pre-dose baseline values indicating improved diastolic relaxation. Both differences were statistically significant.

Conclusions

In patients with LTQ-3 syndrome there is a continuous influx of late I_{Na} resulting in a major prolongation of the QTc interval in the absence of drugs. In patients without LQT-3 syndrome ranolazine has been shown to prolong the QTc interval by blocking I_{Kr}.

The present study was not placebo controlled. It assessed the effects of ranolazine in patients with LTQ-3 due to SCN5A ΔPQ mutation by comparing the QTc interval duration and diastolic relaxation at baseline and during ranolazine infusion. The respective plasma concentrations of

ranolazine attained at the end of the first and second infusion were similar to the trough concentrations observed in the pivotal trials when angina patients received 500 mg and 1000 mg extended release tablets bid orally.

The present study shows that the net effect of ranolazine at antianginal effective concentrations is a shortening of the QTc interval in patients with LQT-3. However, treatment with ranolazine does not normalize the QTc interval duration in the LQT-3 patients. The shortening of the QTc interval is correlated with the plasma concentrations of ranolazine. The PR and QRS intervals appear not to be impacted by ranolazine. The shortening of the QTc interval appears to be mainly due to ranolazine's impact on the latter part of the QTc interval (T wave and ST-segment) in accordance with an effect on late I_{Na}. The drug's potency of blocking the late I_{Na} current appears to be greater than that of blocking I_{Kr} in patients with LQT-3. Ranolazine also increases diastolic relaxation in patients with LQT-3 as evidenced by the shortened left ventricular isovolumic relaxation time and increased mitral E wave velocity.

Overall the data support the sponsor's claim that ranolazine at therapeutic concentrations inhibits the late I_{Na+} and improves diastolic relaxation in patients with LQT-3. The relevance of the ECG findings in patients with LTQ-3 syndrome for patients with angina is uncertain. The relevance of the echocardiographic findings in the subpopulation studied would be increased if the sponsor could demonstrate diastolic relaxation of ranolazine in the angina population at the 500 mg and 1000 mg bid levels. Also, demonstration of a correlation between the respective effects on the QTc interval and diastolic relaxation in patients with the LQT-3 syndrome could be helpful in supporting the proposed hypothesis that ranolazine's effect on the late I_{Na} is the primordial action of the drug.

Comments

- The report does not state whether the reader of the echocardiogram was blinded
- The RR interval durations should be added to the summary statistical tables and individual data tables
- The duration of the ECG intervals is reported up two digits after the comma. How can this precision be justified?
- Provider and Lot No. of the ranolazine injected are not indicated

3.3 Study Report CVT 301-19:" A Phase 1, Multiple Dose, Fixed Sequence, Cross-Over, Open Label Study to Evaluate the Effect of Diltiazem 180 mg bid on the Pharmacokinetics, Safety and Tolerability of Ranolazine ER in Healthy Male and Female Subjects with Poor (PM) and Extensive (EM) Metabolizer Genotype for CYP2D6"

Study Investigator and Site

(b) (4)

Background

Ranolazine is predominantly eliminated by non-renal elimination which includes metabolism mainly by CYP3A and partly by CYP2D6. The metabolism mediated by CYP 3A appears to be linear whereas the CYP 2D6 catalyzed metabolism is nonlinear. Ranolazine has been shown to be an inhibitor of CYP2D6.

Objectives

Primary: to evaluate the effect of diltiazem (DLT) 180 mg bid at steady-state on the PK parameters of ranolazine (RAN) 500 mg bid at steady-state in subjects with PM and EM genotypes for CYP2D6

Secondary: 1) to evaluate the PK parameters of RAN 500 mg bid and 1000 mg bid administered alone in subjects with PM genotype for CYP2D6 as compared to subjects with EM genotype; 2) to evaluate the PK parameters of RAN 500 mg bid after the addition of DLT 180 mg bid in subjects with PM genotype for CYP2D6 as compared to the change in subjects with EM genotype; and 3) to evaluate the PK parameters of the metabolites CVT-2512, CVT-2514 and CVT-2738 after administration of RAN 500 mg bid and 1000 mg bid alone and co-administered with DLT 180 mg in subjects with PM and EM genotypes for CYP2D6

Investigational Drugs and Formulations

Film coated ER tablets containing 500 mg ranolazine (Lot Nos. 3H3026 and A18050) were supplied by the sponsor. (b) (4) supplied the diltiazem hydrochloride 90 mg tablets (Tildiem Retard, Sanofi-Sythelabo) (Lot No.:25013) and 7.5 mg in 5 mL dextrometorphan hydrobromide (Robitussin Dry Cough Medicine) (Lot No. 385097).

Design

This was an open-label, multiple dose, cross-over study involving up to 52 healthy male and female volunteers. The treatment phase of the study was to last for 15 days (from the morning of Day 1 to the morning of Day 15) during which subjects were to remain institutionalized in the clinical unit. Starting on the morning of Day 1 and continuing until the morning of Day 4, subjects were to receive an oral dose of RAN 500 mg bid. Starting on the evening of Day 4 and continuing until the morning of Day 8, subjects were to receive RAN 1000 mg bid. Starting on the evening of Day 8, and continuing until the morning of Day 15, subjects were to receive RAN 500 mg bid. Subjects were also to receive an oral dose of DLT 90 mg on the evening of Day 8 and on the morning of Day 9. On the evening of Day 9 until the morning of Day 15, subjects were to receive DLT 180 mg bid. The study ended when the last subject had completed his/her

last study site visit and a 14 day follow-up contact. Originally, the study was designed to include an additional treatment period lasting from the evening of Day 15 to the morning of Day 22, during which subjects were to receive RAN 1000 mg bid concomitantly with DLT 180 mg bid. The protocol was amended after 10 subjects (7 with EM genotype and 3 with PM genotype) had completed the study through Day 22 and 6 subjects (5 with EM genotype and 1 with PM genotype) had withdrawn from the study between Days 15-22. These 16 subjects were considered evaluable under the amended protocol.

The drugs were administered together with 250 mL water. Mouth checks were performed after the drugs were administered to assure that they had been swallowed. Breakfast, lunch, and dinner were to be provided at approximately 1 h, 5 h, and 10 h, respectively, post morning dose.

Subjects were to be classified as EMs or PMs based on their CYP2D6 genotypes. The allele variants *3, *4, *5, and *6, were to be tested that together allow for identification of > 97% of PMs in a predominantly Caucasian population. A dextrometorphan phenotyping test was to be administered prior to initiation of ranolazine to detect possible additional PMs with other allele variants, as well as ultra-rapid metabolizers with gene duplication.

Steady-state for RAN is generally attained within 3 days with a continuous bid regimen. The highest RAN plasma concentrations were predicted not to exceed 8000-10 000 ng/mL, a range that was attained in previous studies with co-administration of RAN and ketoconazole or in a study in which RAN was administered alone by intravenous infusion.

The protocol contained the following precautionary measures: because of the known QTc prolongation associated with administration of RAN subjects with a history of, or risk factors for QTc prolongation were excluded from the study. The ECG was monitored at schedule times throughout the study. A stopping rule of 500 msec for a QTc reading on a single ECG, based on automatic ECG interpretation in conjunction with Investigator interpretation, was to be implemented if necessary. Repeat ECGs were allowed to confirm the measurement if required.

DLT is known to increase the PR interval. During the dose escalation phase of DLT a 12 Lead ECG was to be performed prior to each dose and the following criteria applied:

- If the PR interval was between 120-200 msec the next dose was given
- If the PR interval was greater than 200 msec, but less than 220 msec, the finding was noted and the next scheduled dose given
- If the PR interval was greater than 220 msec, the subject was withdrawn from the study and received no additional doses of DLT

The presence of second degree heart block (Wenckebach (Mobitz I), Mobitz II, or high grade block) constituted a withdrawal criterion.

Prior and concomitant administration of the following drugs was prohibited:

- Class IA anti-arrhythmics (e.g., quinidine)
- Class III anti-arrhythmics (e.g., sotalol, dofetilide)
- Phenothiazide anti-psychotics (e.g., chlorpromazine, mesoridazine, pimozide, thoridazine)
- Quinolone antibiotics (e.g., gatifloxacin, moxifloxacin, sparfloxacin)
- Others: droperidol, mefloquine, pentamidine, levomethadyl, dolasetron, systemic dosing of tacrolimus, arsenic trioxide, terfenadine, astemizole, cisapride
- Other drugs that have a contraindication or boxed warning regarding QT prolongation in the prescribing information

Apart from diltiazem issued as per protocol, medications which affect CYP3A were not allowed; they included, but were not limited to the following:

- Erythromycin, clarithromycin, and troleandomycin
- Ketoconazole and itraconazole (topical agents were permissible)
- Nefazadone
- Protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, saquinavir)
- Diltiazem
- Verapamil

In addition, the following medications and foods were not allowed:

- Agents known to inhibit P-glycoprotein
- Beta blockers
- Calcium antagonists
- Alcohol was not permitted during the 48 h prior to the Screening Visit and was also not permitted from the 48 h prior to admission (Day-1) through discharge from the clinical unit.
- Subjects may not have been smokers who smoked more than five cigarettes per day and must have abstained from smoking as of midnight prior to admission and throughout the residential treatment period
- Caffeine containing products were not permitted during the residential phase of the study
- Grapefruit, grapefruit juice, and grapefruit-containing products, Seville oranges or marmalade, were prohibited within 2 weeks prior to admission through the end of the study

Allowed concomitant medications included the use of multivitamins, paracetamol (maximum 2 g/day), HRT/hormonal contraception and stable thyroxine replacement therapy. Other drugs that did not fall under what is described above may have been allowed if they were judged not to interfere with the objectives of the study.

The inclusion and exclusion criteria applied are listed below:

9.3.1 Inclusion Criteria

To be eligible for enrollment, subjects had to satisfy the following requirements:

- Subject was male or female aged 18 to 70 years, inclusive
- Subject provided a signed informed consent form and patient information sheet
- *For female subjects only:* Subjects must have been post-menopausal or sterilized, or if of childbearing potential, not breastfeeding, have a negative pregnancy test, with no intention of becoming pregnant during the course of

the study, and using adequate contraceptive drugs or devices (defined as usage of any form of hormonal contraception or intra-uterine device, plus usage by at least one of the partners of an additional barrier method of contraception e.g., condoms, spermicide)

- *For male subjects only:* Subjects with female partners of child bearing potential must have been taking adequate contraceptive precautions (defined as usage by the female partner of any form of hormonal contraception or intra-uterine device, plus usage by at least one of the partners of an additional barrier method of contraception e.g., condoms, spermicide)
- Subject's general practitioner (GP) was informed of subject's planned participation in the study
- Subject's body weight was ≥ 60 kilograms
- Subject's body mass index (BMI) was between 18–30 kg/m^2 inclusive
- Subject had no current or past medical history of clinical significance and the Screening Visit physical examination was either normal or revealed no clinically significant abnormalities, including vital signs within the normal ranges (measured supine after 5 min, HR: 45 to 90 bpm; systolic BP: 100 to 140 mm Hg; diastolic BP: 50 to 90 mm Hg. Standing after at least 5 min, HR: 50 to 100 bpm; systolic BP: 100 to 160 mm Hg; diastolic BP: 50 to 90 mm Hg)
- Subject's 12-lead ECG at the Screening Visit was normal, without evidence of conduction or repolarization abnormalities, including a sinus bradycardia less than 45 bpm or any degree of heart block. Other changes should have been deemed not clinically significant by the Investigator.
- Subject's QTc interval at Screening Visit was ≤ 450 msec, as measured by automatic ECG reading, in conjunction with Investigator interpretation
- Subject experienced no clinically significant arrhythmias during approximately 24-h continuous Holter ECG monitoring at the Screening Visit
- Subject's Screening Visit clinical laboratory findings were within the normal range or, if outside the normal range, were not considered clinically significant in the opinion of the Investigator
- Subject was willing and able to comply with the requirements of the protocol and follow directions from the clinic staff

9.3.2 Exclusion Criteria

Subjects were not to be enrolled if any of the following were true:

- Subject had a clinically significant illness in the 4 weeks prior to the Screening Visit at which informed consent was given
- Subject was currently taking any regular prescribed or over-the-counter medication, or was using prescribed or over-the-counter medications in the 2 weeks prior to dosing (with the exception of the following: multi-vitamins, the occasional use of paracetamol [maximum 2 g/day], contraceptive pill, HRT/hormonal contraception, and stable thyroxine replacement therapy)
- Subject had significant history of drug/solvent abuse, or a positive drugs of abuse test
- Subject had a history of alcohol abuse, currently drank in excess of 28 units of alcohol per week if male or 21 units per week if female, or had a positive alcohol breath test (ABT)
- Subject currently smoked more than five cigarettes or equivalent per day, and if otherwise eligible would not have been able to abstain from smoking from midnight prior to admission and throughout the residential session
- Subject was planning to consume grapefruit juice or grapefruit-containing products, Seville oranges or marmalade, from 2 weeks prior to admission to the clinical unit until the end of the study
- Subject was, in the opinion of the Investigator/GP, not suitable to participate in the study
- Subject used any experimental or investigational drug or device within 90 days prior to the first day of dosing
- Subject had a positive result at the Screening Visit for HIV, Hepatitis B, or Hepatitis C
- Subject had history of allergy or hypersensitivity to ranolazine, diltiazem, dextromethorphan or related drugs
- Subject previously had a serious adverse reaction or hypersensitivity to any drug
- Subject had donated blood within the 3 months prior to the Screening Visit
- Subject had any individual or family history of QT prolongation or cardiomyopathy, including a family history of sudden cardiac death
- Subject was a vegetarian or had significantly changed his/her diet in the 2 months prior to the Screening Visit or intended to change his/her diet during the study

The scheduled study activities are shown in the below schemes:

Table 1 Schedule of Events

	Screening	Admit	Treatment Period										
Day of Period	-21 to -1	-1	1	2	3	4	5	6	7	8	9	10	11
Procedures													
Written Informed Consent	X												
Demographic Data	X												
Medical History	X												
Physical Examination[a]	X	X											
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and Weight	X												
12-lead ECG[c]	X	X	X			X				X	X	X	X
Clinical Laboratory Blood and Urine Samples[d]	X	X								X			
Virology	X												
Drugs of Abuse Screen	X	X											
Alcohol Breath Test	X	X											
Urine Pregnancy Test	X	X											
Inclusion/Exclusion	X	X											
Ranolazine Administration[e]			X	X	X	X	X	X	X	X	X	X	X
Diltiazem Administration[f]										X	X	X	X
Dextromethorphan Dose		X											
Urine Sampling[g]		X	X										
PK Blood Sampling[h]			X	X	X	X	X	X	X	X	X	X	X
Holter Monitoring	X									X	X	X	X
Adverse Events/Con Meds[i]	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] A physical examination will be performed at the Screening Visit, on admission and at discharge (Day 15 or Day 22, for Amendment 1 and original protocol, respectively)

[b] Vital signs (supine and standing BP and pulse) will be performed at: the Screening Visit, on admission, on Days 1, 4, 8, 15, 22 (if applicable) at 0, 1, 2, 4, 6, 8, 12 h; Days 2, 3, 5, 6, 7, 9, 10, 11, 12, 13, 14, and Days 16-21 (if applicable) at 0, 4, 8, 12 h; and at follow-up.

[c] ECGs will be performed at: the Screening Visit, on admission, on Days 1, 4, 8, 15, 22 (if applicable) at 0, 1, 2, 4, 6, 8, 12 h; Days 9, 10, 11, 12, 13, 14, and Days 16-21 (if applicable) at 0, 4, 8, 12 h; and at follow-up.

[d] Clinical lab blood and urine samples will be collected at the Screening Visit, on admission, at Day 8, and at discharge (Day 15 or Day 22, for Amendment 1 and original protocol, respectively)

[e] Subjects will receive ranolazine twice daily from the morning of Day 1 until the morning of Day 15 or Day 22, for Amendment 1 and original protocol, respectively.

[f] Subjects will receive diltiazem in the evening of Day 8, in the morning of Day 9 and thereafter twice daily until the morning of Day 15 or Day 22, for Amendment 1 and original protocol, respectively.

[g] Urine samples will be collected cumulatively following dextromethorphan administration on Day –1 until 30 minutes prior to dosing ranolazine administration in the morning of Day 1.

[h] PK samples for ranolazine analysis will be taken on: Day 1, 2, 3 at 0 and 12 h (pre-dose); Days 4, 8, 15, 22 (if applicable) at 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 h (full PK profile) and Days 5, 6, 7, 9, 10, 11, 12, 13, 14, and Days 16-21 (if applicable), with the trough sample taken prior to evening dose at 12 h.

[i] Adverse events were to be collected starting on Day 1

Table 1 Schedule of Events (Cont'd)

	Treatment Period											Follow up
Day of Period	12	13	14	15	16	17	18	19	20	21	22	Follow up
Procedures												
Physical Examination[a]				X							X	
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X
Height and Weight												
12-lead ECG[c]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Blood and Urine Samples[d]				X							X	X
Virology												
Drugs of Abuse Screen												
Alcohol Breath Test (ABT)												X
Urine Pregnancy Test												X
Inclusion/Exclusion												
Ranolazine Administration[e]	X	X	X	X	X	X	X	X	X	X	X	
Diltiazem Administration[f]	X	X	X	X	X	X	X	X	X	X	X	
PK Blood Sampling[g]	X	X	X	X	X	X	X	X	X	X	X	
Holter Monitoring	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events/Con Meds	X	X	X	X	X	X	X	X	X	X	X	X

NB: Shaded columns apply only to subjects enrolled in the original protocol and not Amendment 1.

[a] A physical examination will be performed at the Screening Visit, on admission and at discharge (Day 15 or Day 22, for Amendment 1 and original protocol, respectively)

[b] Vital signs (supine and standing BP and pulse) will be performed at: the Screening Visit, on admission, on Days 1, 4, 8, 15, 22 (if applicable) at 0, 1, 2, 4, 6, 8, 12 h; Days 2, 3, 5, 6, 7, 9, 10, 11, 12, 13, 14, and Days 16-21 (if applicable) at 0, 4, 8, 12 h; and at follow-up.

[c] ECGs will be performed at: the Screening Visit, on admission, on Days 1, 4, 8, 15, 22 (if applicable) at 0, 1, 2, 4, 6, 8, 12 h; Days 9, 10, 11, 12, 13, 14, and Days 16-21 (if applicable) at 0, 4, 8, 12 h; and at follow-up.

[d] Clinical lab blood and urine samples will be collected at the Screening Visit, on admission, at Day 8, and at discharge (Day 15 or Day 22, for Amendment 1 and original protocol, respectively)

[e] Subjects will receive ranolazine twice daily from the morning of Day 1 until the morning of Day 15 or Day 22, for Amendment 1 and original protocol, respectively.

[f] Subjects will receive diltiazem in the evening of Day 8, in the morning of Day 9 and thereafter twice daily until the morning of Day 15 or Day 22, for Amendment 1 and original protocol, respectively.

[g] PK samples for ranolazine analysis will be taken on: Day 1, 2, 3 at 0 and 12 h (pre-dose); Days 4, 8, 15, 22 (if applicable) at 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 h (full PK profile) and Days 5, 6, 7, 9, 10, 11, 12, 13, 14, and Days 16–21 (if applicable), with the trough sample taken prior to evening dose at 12 h.

Safety

Safety was evaluated by collecting AE, identification of serious adverse events, clinical laboratory results, vital signs, physical examination and scheduled 12-Lead ECG measurements. Continuous Holter recordings were obtained from Day 8 through the end of the treatment period (Days 15 or 22), divided into approximate 24 h intervals and evaluated for the occurrence of arrhythmias (b) (4)

Pharmacokinetic Profiling

RAN

Blood samples for the determination of RAN and the metabolites CVT-2514, CVT-2512 and CVT-2738 were collected on:

Days 1, 2 and 3: pre morning (0 h) and evening dose (12 h)
Days 4, 8, 15, 22: pre morning dose, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 h (full profile) after the morning dose
Days 5, 6, 7, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21: pre-evening dose (12 h)
At the time of a clinically significant AE and early withdrawal or discontinuation (if applicable)

Dextrometorphan

A dose of 30 mg dextrometorphan was administered to the subjects on the evening of Day -1. Total urine volumes were collected for a 12 h period starting from the time of dextrometorphan administration and ending approximately 30 min prior to dosing with RAN in the morning of Day 1. The urine pH was to be kept constant by excluding other factors, such as food, during the collection period.

Bioassay

Ranolazine

The plasma concentrations of RAN and the metabolites CVT-2512, CVT-2514 and CVT-2738 were measured by a LC/MS/MS method. The calibration curve is linear for RAN in the range between 50.0-10000 g/mL and the metabolites in the range between 10.0 -2000 ng/mL. The respective correlation coefficients for standards are ≥ 0.998, ≥ 0.995, ≥ 0.996 and ≥ 0.995 for RAN, CVT 2512, CVT 2514 and CVT 2738, respectively. Mean accuracy for RAN ranges between 1.63% and 2.00% and the precision is ≤ 10.6%. Mean accuracy for CVT-2512 ranges between -3.75% and 3.00 % and the precision is ≤ 7.77%. Mean accuracy for CVT-2514 ranges between -4.38% and 5.50% and the precision is ≤ 10.0%. Mean accuracy for CVT-2738 ranges between -5.63% and 5.50 % and the precision is ≤ 10.2%.

Dextrometorphan/Dextrorphan

The report does not indicate the methods used to determine dextrometorphan and dextrorphan and the laboratory performing the assays.

Pharmacokinetic Data Analysis

Cmax, tmax, Cmin, and AUC0-12 were determined for RAN, CVT-2514, CVT-2512 and CVT-2738 using non-compartmental methods. Cmax, tmax and Cmin were obtained directly from the observed concentration time data. AUC 0-12 was obtained by application of the linear trapezoidal rule. The primary parameters for evaluation were Cmax and AUC0-12. WinNonlin Professional (Version 5.0.1 (Pharsight Corporation)) was used.

Pharmacodynamic Data Analysis

All 12-Lead ECGs were to be evaluated for the RR, PR QRS and QT intervals and heart rate. Baseline for each parameter was defined as the average of values measured on Day -1 (admission) and Day 1. Change in each ECG parameter from baseline was calculated for each ECG recording during 0-12 h after the morning dose on the PK profiling Days (Days 4, 8, 16, and 22)

Statistical Analysis

Ranolazine plasma level C_{max} and AUC_{0-12} were transformed for analysis using the natural logarithm. All mean effect estimates and their associated confidence intervals in the log scale were back-transformed to the original scale.

Log-transformed C_{max} and AUC_{0-12} were analyzed using a mixed effects analysis of variance (ANOVA) model with fixed effects for CYP2D6 metabolizer genotype (EM or PM), concomitant administration of diltiazem (present or absent), ranolazine dose (500 mg bid or 1000 mg bid), all two-way interactions of these factors, and the three-factor interaction, and a random effect for subject.

For the primary objective, the ANOVA model was used to estimate the mean effect of diltiazem administration on C_{max} and AUC_{0-12} for the RAN 500 mg bid dose in subjects with PM and EM genotype for CYP2D6, using the least squares-estimated mean difference between ranolazine plus diltiazem and ranolazine alone. The effect of diltiazem was tested for significance using the ANOVA model, and a 90% confidence interval for the treatment effect was provided.

For secondary objective no. 1, the ANOVA model was used to estimate the difference between genotypes in log-transformed C_{max} and AUC_{0-12} following ranolazine alone for each ranolazine dose. For each dose, a 90% confidence interval was estimated and back-transformed to the original scale to provide a confidence interval for the ratio.

For secondary objective no. 2, the ANOVA model was used to estimate the difference between genotypes in the diltiazem vs no-diltiazem differences in log-transformed C_{max} and AUC_{0-12} for the RAN 500 mg bid dose. A 90% confidence interval was estimated and back-transformed to the original scale to provide a confidence interval for the ratio.

For secondary objective no. 3, the same ANOVA model will be applied to the C_{max} and AUC_{0-12} of each of the metabolites CVT-2512, CVT-2514, and CVT-2738, and to the ratio of the AUC_{0-12} for each metabolite to the AUC_{0-12} of ranolazine. The least square mean and its 90% confidence interval of each were described using the ANOVA model.

The parameter t_{max} was analyzed using nonparametric methods. The Wilcoxon signed rank test was used to compare t_{max} in the presence and absence of diltiazem within each combination of genotype and ranolazine dose.

Summary statistics were provided for PK parameters of ranolazine and each of the metabolites CVT-2512, CVT-2514, and CVT-2738 for each combination of genotype, diltiazem administration, and ranolazine dose. Descriptive statistics included the arithmetic mean, geometric mean, SD, %CV, median, minimum, and maximum.

- The statistical analysis methods were updated to correspond to changes in the study design and objectives.
  - For the primary objective, the ANOVA model was to be used to estimate the mean effect of diltiazem administration on C_{max} and AUC_{0-12} for the RAN 500 mg bid dose in subjects with PM and EM genotypes for CYP2D6, using the least squares-estimated mean difference between ranolazine plus diltiazem and ranolazine alone.
  - For secondary objective no. 2, the ANOVA model was to be used to estimate the difference between genotypes in the diltiazem vs no diltiazem differences in log-transformed C_{max} and AUC_{0-12} for the RAN 500 mg bid dose.
- C_{min} was excluded from all analyses.

Sample Size

Based on variability information from a previous study of ranolazine in renally impaired patients (Study CVT 3016), the cohort sizes of 8 evaluable subjects with PM genotype and 8 evaluable subjects with EM genotype, and the use of 90% confidence intervals provide 80% power to conclude that the difference between genotypes in ranolazine AUC_{0-12} is no greater than 36% and in C_{max} no greater than 60%, if in fact there is no effect of genotype on either parameter. If genotype does have an effect, the sample size of 8 subjects with PM genotype and 8 subjects with EM genotype provides 80% power to detect a difference of 42% for AUC_{0-12} and 70% for C_{max} using two-sided tests at the 5% significance level. These differences are below the levels that are considered clinically meaningful. For the purpose of the PK comparison between subjects with PM and EM genotypes, an evaluable subject was defined as one who had completed the Day 15 morning dose with RAN 500 mg bid + DILT 180 mg bid and associated PK sampling.

RESULTS

Demographics

The demographic details of the participating subjects are shown in the below table:

Table 3 Demographic Details for All Dosed Subjects

Variable Mean (SD)	Poor Metabolizer (N = 12)	Extensive Metabolizer (N = 19)
Age (yrs)	34.7 (13.1)	34.1 (11.0)
Range	19–55	20–59
Gender		
Male	9 (75%)	19 (100%)
Female	3 (25%)	0
Race		
Asian	0	2 (11%)
Black	0	1 (5%)
Caucasian	12 (100%)	16 (84%)
Hispanic	0	0
Other	0	0
Height (cm)[a]	171.7 (10.6)	176.0 (7.9)
Weight (kg)[b]	75.7 (14.1)	76.3 (7.2)
BMI (kg/m^2)[a]	25.6 (2.5)	24.7 (2.2)

[a] PM: N = 10; EM: N =14 [b] PM: N = 11; EM: N =14

Disposition of Subjects

Thirty-three (33) adult subjects enrolled in the study; 21 had EM genotype and 12 had PM genotype. All subjects classified as genotypic PMs displayed a dextrometorphan/dextrorphan ratio of >0.3, and all subjects classified a genotypic EMs had a dextrometorphan/dextrorphan ratio <0.3. Thus, there was agreement between phenotype and genotype determinations.

The disposition of the PMs and EMs is shown in the below 2 schemes:

Table 2 Subject Disposition

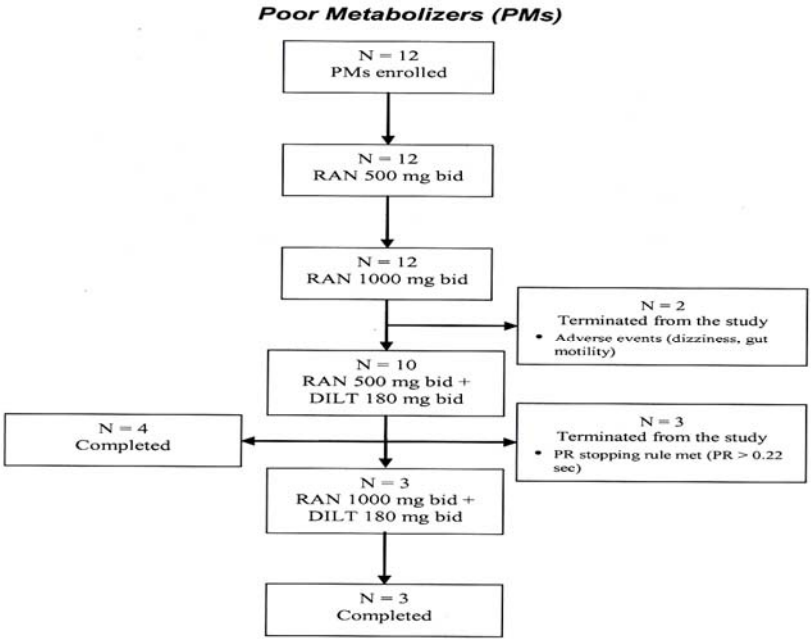
	Poor Metabolizer				Extensive Metabolizer			
	RAN 500 mg bid		RAN 1000 mg bid		RAN 500 mg bid		RAN 1000 mg bid	
	Without DILT (N = 12)	With DILT (N = 10)	Without DILT (N = 12)	With DILT (N = 3)	Without DILT (N = 19)	With DILT (N = 17)	Without DILT (N = 18)	With DILT (N = 12)
No. of subjects completed treatment	12 (100%)	7 (70%)	10 (83%)	3 (100%)	18 (95%)	12 (71%)	17 (94%)	7 (58%)
No. of subjects terminated early	0	3* (30%)	2 (17%)	0	1 (5%)	5 (29%)	1 (6%)	5** (42%)
Primary reason for early termination								
Adverse event	0	0	2 (17%)	0	1 (5%)	2 (12%)	1 (6%)	3 (25%)
PR > 0.22 sec	0	3 (30%)	0	0	0	3 (18%)	0	0
QTc > 500 msec	0	0	0	0	0	0	0	2 (17%)

* One subject, withdrawn from the original protocol on Day 15 after the morning dose, was eligible for inclusion in the PK analysis population as described in Amendment 1.

** Since completion of the RAN 1000 mg bid + DILT 180 mg bid treatment period was not required by Amendment 1, all five of these subjects were eligible for inclusion in the analysis population.

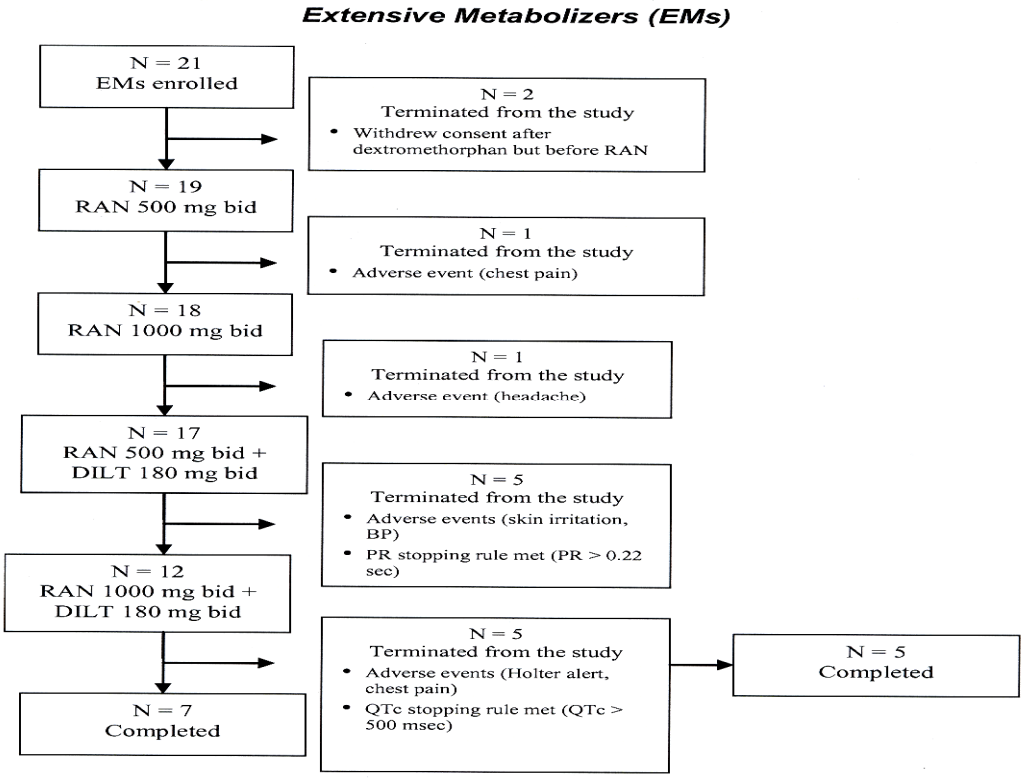
Derived from Section 14.1.1

Figure 1 Subject Disposition



The seven subjects who completed the RAN 500 mg bid + DILT 180 mg bid arm of the study and one subject who withdrew due to PR interval prolongation after the morning dose on Day 15 are included in the PK analysis population.

Figure 1 Subject Disposition (Cont'd)



The 12 subjects who completed the RAN 500 mg bid + DILT 180 mg bid arm of the study are included in the PK analysis population.

PM

Of the 12 PMs enrolled, 4 completed the 500 mg and 1000 mg RAN alone treatments and the 500 mg RAN + 180 mg DLT co-administration treatment and 5 were terminated (2 during the 1000 mg RAN regimen and 3 during the 500 mg RAN + 180 mg DLT regimens. All 3 subjects receiving 1000 mg RAN + 180 mg DLT completed the study.

EM

Of the 21 EMs enrolled in the study 5 completed the 500 mg RAN-, the RAN 1000 mg-, and the 500 mg RAN + 180 mg DLT treatments, 2 subjects were terminated from the study prior to receiving the first treatment with 500 mg RAN alone, 1 subject during treatment with RAN 500 mg alone, 1 subject during treatment with 1000 mg RAN alone and 5 subjects during treatment with RAN 1000 mg + 180 mg DLT. Of the 12 subjects receiving the 1000 mg RAN + 180 mg DLT regimen, 7 completed the study and 5 were terminated. The reasons for early termination are explained in the below table:

Table 11 Reasons for Early Termination

Subject No.	Reason for Termination	AEs or Stopping Criteria for which Drug Was Withdrawn	Last Treatment Administered
Poor Metabolizers			
1913	AE	Diarrhea, palpitations, upper abdominal pain, chest pain, headache, leg tremor, hyperhidrosis	RAN 1000 mg bid
1918	AE	Dizziness, headache	RAN 1000 mg bid
1917	Stopping criteria reached	PR > 0.22 sec	RAN 500 mg bid + DILT 180 mg bid
1927[a]	Stopping criteria reached	PR > 0.22 sec	RAN 500 mg bid + DILT 180 mg bid
1928	Stopping criteria reached	PR > 0.22 sec	RAN 500 mg bid + DILT 180 mg bid
Extensive Metabolizers			
1903	AE	Application site erythema at Holter sticker site	RAN 500 mg bid + DILT 180 mg bid
1909	AE	Headache, arthralgia, neck pain	RAN 1000 mg bid
1910	AE	Hypertension	RAN 500 mg bid + DILT 180 mg bid
1914[a]	AE	Ventricular tachycardia	RAN 1000 mg bid + DILT 180 mg bid[b]
1922[a]	AE	Ventricular tachycardia	RAN 1000 mg bid + DILT 180 mg bid[b]
1923[a]	AE	Chest pain	RAN 1000 mg bid + DILT 180 mg bid
1924	AE	Chest pain	RAN 500 mg bid
1904	Stopping criteria reached	PR > 0.22 sec	RAN 500 mg bid + DILT 180 mg bid
1911	Stopping criteria reached	PR > 0.22 sec	RAN 500 mg bid + DILT 180 mg bid
1915	Stopping criteria reached	PR > 0.22 sec	RAN 500 mg bid + DILT 180 mg bid
1902[a]	Stopping criteria reached	QTc > 500 msec	RAN 1000 mg bid + DILT 180 mg bid
1916[a]	Stopping criteria reached	QTc > 500 msec	RAN 1000 mg bid + DILT 180 mg bid

Derived from Section 16.2.11.

[a] Terminated early under the original protocol, but completed the requirements under Amendment 1 and are included in the PK analysis population.

[b] AE occurred while subject was on RAN 500 mg bid + DILT 180 mg bid

Note: Subjects 1912 and 1926 withdrew consent after receiving dextromethorphan for CYP2D6 phenotyping, but prior to dosing with ranolazine

The table indicates that 9 subjects (2 PMs and 7 EMs) were prematurely discontinued because of an AE and 8 subjects were withdrawn due to meeting a stopping criterion specified in the protocol.

Safety

An overview of the AEs and a summary of the most frequent AEs are provided by the below 3 tables:

Table 9 Overview of Adverse Events

	Poor Metabolizer				Extensive Metabolizer			
	RAN 500 mg bid		RAN 1000 mg bid		RAN 500 mg bid		RAN 1000 mg bid	
	Without DILT (N = 12)	With DILT (N = 10)	Without DILT (N = 12)	With DILT (N = 3)	Without DILT (N = 19)	With DILT (N = 17)	Without DILT (N = 18)	With DILT (N = 12)
No. of subjects with AEs	10 (83%)	8 (80%)	10 (83%)	3 (100%)	8 (42%)	17 (100%)	12 (67%)	11 (92%)
No. of AEs	23	41	48	22	23	67	26	43
No. of subjects with causally-related AEs	9 (75%)	6 (60%)	10 (83%)	3 (100%)	7 (37%)	12 (71%)	10 (56%)	6 (50%)
No. of subjects prematurely withdrawn due to AEs	0	0	2 (17%)	0	1 (5%)	4 (24%)	1 (6%)	1 (8%)
No. of subjects with SAEs	0	0	0	0	0	0	0	0

SOURCE: tae_overview (27MAR2007 15:08) S:\CVT-303\CVT301-19\Statistics\Final\Table_Graph\TAE_OVERVIEW.RTF

Table 10 Summary of Most Frequent* Adverse Events

	Poor Metabolizers				Extensive Metabolizers			
	RAN 500 mg bid		RAN 1000 mg bid		RAN 500 mg bid		RAN 1000 mg bid	
Organ System Class/ Preferred Term	Without DILT (N = 12)	With DILT (N = 10)	Without DILT (N = 12)	With DILT (N = 3)	Without DILT (N = 19)	With DILT (N = 17)	Without DILT (N = 18)	With DILT (N = 12)
Number of Subjects with AEs	10 (83%)	8 (80%)	10 (83%)	3 (100%)	8 (42%)	17 (100%)	12 (67%)	11 (92%)
Cardiac Disorders								
Palpitations	0	1 (10%)	1 (8%)	1 (33%)	0	1 (6%)	0	1 (8%)
Gastrointestinal Disorders								
Constipation	0	1 (10%)	0	1 (33%)	0	2 (12%)	0	0
Flatulence	1 (8%)	2 (20%)	2 (17%)	1 (33%)	1 (5%)	1 (6%)	1 (6%)	0
Nausea	2 (17%)	1 (10%)	1 (8%)	0	0	4 (24%)	3 (17%)	0
General Disorders & Administrative Site Conditions								
Application Site Dermatitis	0	0	0	0	0	2 (12%)	0	3 (25%)
Application Site Erythema	0	4 (40%)	1 (8%)	1 (33%)	0	6 (35%)	0	4 (33%)
Application Site Irritation	0	1 (10%)	0	0	1 (5%)	2 (12%)	0	1 (8%)
Application Site Reaction	0	0	0	0	0	2 (12%)	0	2 (17%)
Chest Pain	1 (8%)	0	2 (17%)	1 (33%)	1 (5%)	4 (24%)	0	4 (33%)
Fatigue	1 (8%)	2 (20%)	1 (8%)	2 (67%)	2 (11%)	1 (6%)	0	0
Feeling Hot	1 (8%)	0	0	1 (33%)	0	0	0	1 (8%)
Injury, Poisoning and Procedural Complications								
Contusion	0	0	0	0	0	2 (12%)	1 (6%)	1 (8%)
Nervous System Disorders								
Dizziness	3 (25%)	3 (30%)	5 (42%)	1 (33%)	0	2 (12%)	2 (11%)	1 (8%)
Dizziness Postural	3 (25%)	0	5 (42%)	1 (33%)	1 (5%)	3 (18%)	3 (17%)	1 (8%)
Headache	1 (8%)	1 (10%)	4 (33%)	1 (33%)	4 (21%)	9 (53%)	6 (33%)	3 (25%)
Lethargy	0	0	0	0	0	0	0	2 (17%)
Paresthesia	1 (8%)	3 (30%)	0	0	0	1 (6%)	0	0
Sensory Disturbance	0	1 (10%)	1 (8%)	0	0	1 (6%)	0	0
Skin & Subcutaneous Tissue Disorders								
Pruritus	0	2 (20%)	1 (8%)	0	0	0	0	0
Rash	0	1 (10%)	0	0	0	1 (6%)	0	1 (8%)

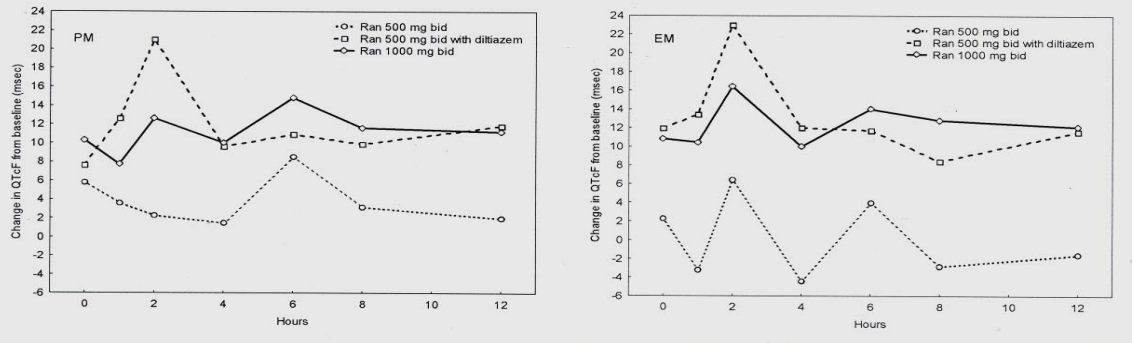
* Experienced by ≥ 2 subjects (PMs and EMs combined) during any 1 of the 4 treatment periods. Derived from Section 14.3.2

Headache, dizziness, postural dizziness, application site erythema (Holter electrodes), chest pain, nausea, and paresthesia were the most frequent AEs recorded. Chest pain and application site erythema were reported more frequently during the co-administration regimens than during the RAN alone treatments. Nine subjects (2 PMs and 7 EMs) discontinued the study because of AEs and 8 others were withdrawn due to meeting a protocol-specified ECG interval stopping criterion. The incidence of dizziness, both unspecified and postural, generally correlated with the RAN plasma concentrations with higher occurrences in PMs than in EMs.

QTc Interval and other ECG Findings

The mean changes from baseline (value measured on the eve of Day 1) in the QTcF interval in PMs and EMs receiving treatments of 500 mg RAN alone, 1000 mg RAN alone and 500 mg RAN+180 mg DLT bid are shown in the below 2 figures:

Figure 7 Change from Baseline in QTcF Interval (PK Evaluable Population)



With the 500 mg RAN bid alone treatment the maximum increase in mean QTc was 8 msec at 6 h post dose in PMs and 6 msec at 2 h post-dose in EMs. The maximum increase in QTc with the 1000 mg RAN alone treatment was 15 msec at 6 h post dose in PMs and 16 msec at 2 h in EMs. With the co-administration treatment the maximum increase in QTcF in PMs was 21 msec at 2 h post dose and 23 msec at 2 h post-dose in EMs. These results suggest that the observed increase in QTcF is exposure related.

(b) (4) sent alert reports to the sponsor for the following events: VT/ventricular fibrillation (VF) with three or more ventricular beats, severe bradycardia with a rate ≤ 35 bpm, AV block type Mobitz II, AV block type III or other advanced block, ventricular asystole or pause ≥ 3 sec, atrial fibrillation or flutter with ventricular rate > 150 bpm, sustained (> 60 sec), SVT with ventricular rate ≥ 180 bpm. In total 7 subjects were judged to have clinically significant abnormalities on Holter Monitoring.

Three PM subjects and 2 EM subjects experienced episodes of severe bradycardia on one or more treatment days (four subjects were on the co-administration treatment of 500 mg RAN+ 180 mg DLT and one subject was on the co-administration treatment with 1000 mg RAN+ 180 mg DLT).

One EM subject had an episode of asymptomatic VT on Day 14 while receiving the co-administration treatment of 500 mg RAN + 180 mg DLT. The subject was withdrawn from the study on Day 16 after receipt of the alert report. The RAN plasma concentration was approximately 1800 ng/ml at the time of the event. Subsequently, the Holter recording was evaluated by (b) (4) (b) (4) His assessment was that the short run of monomorphic VT observed did not correspond to the type usually associated with drug induced VT abnormality (i.e. Torsades de Pointes).

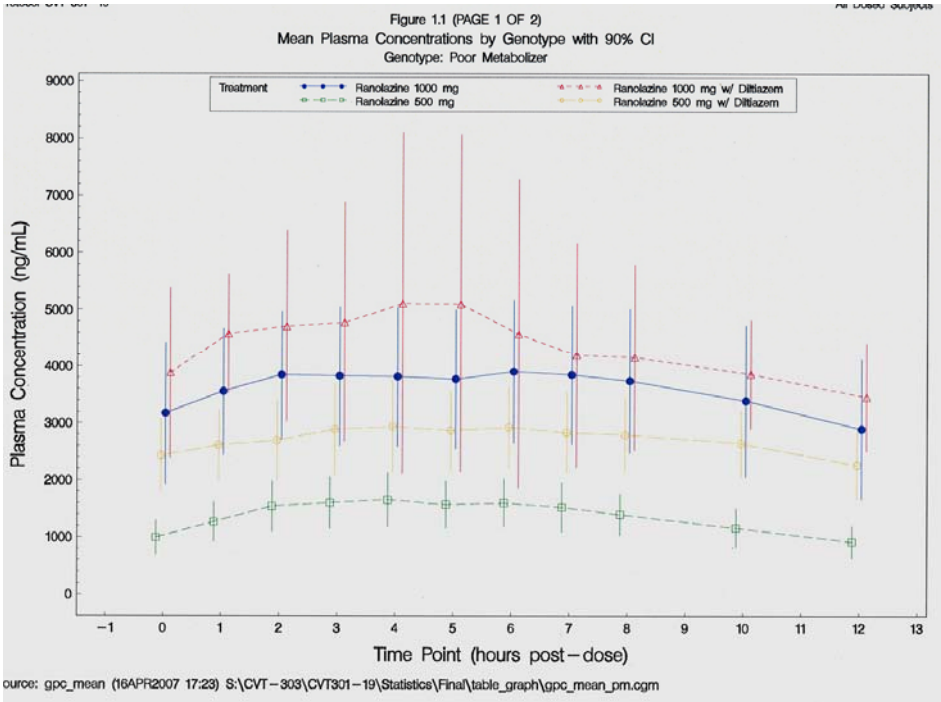
A second EM subject on RAN 500 mg +DLT 180 mg had an episode on Day 14 initially reported as VT. The subject was terminated from the study after receipt of the alert report on Day 16. The subject had no associated symptoms, and the RAN plasma concentration was approximately 1000 ng/mL at the time of the event. Subsequently, the Holter recording was evaluated by (b) (4) (b) (4) His assessment was that the ECG tracing was consistent with an accelerated idioventricular rhythm, a not unusual finding in healthy subjects and not consistent with the known effects of DIL and/or RAN.

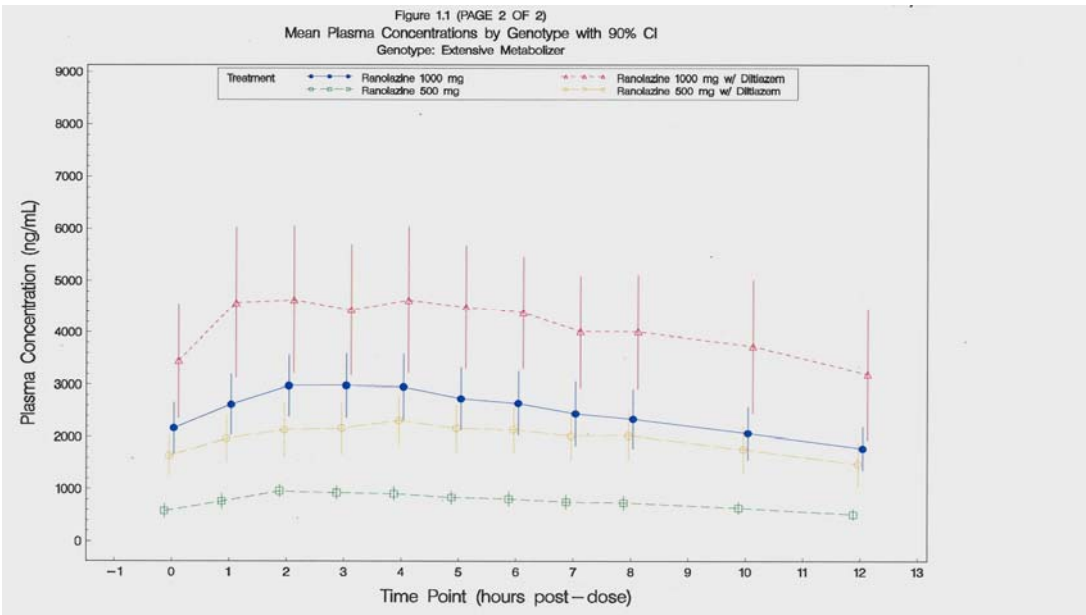
A PM subject who had experienced a severe bradycardia on Day 12, had a 3 beat-run of asymptomatic monomorphic VT at a rate of approximately 120 bpm after midnight on Day 13 while receiving 500 mg RAN+180 mg DLT. The alert report was received immediately prior to the time of the last dose administration on the morning of Day 15. Investigator and sponsor considered the event to be very unlikely drug induced and the subject to continue.

An EM individual experienced a clinically significant increase in blood pressure during the study. The subjects blood pressure at screening was normal (122/83 mmHg). On Day Day 10 blood pressure rose to 220/105 and 194/112 mmHg. The Day 10 evening dose and the Day 11 doses were withheld and the subject withdrawn from the study. Upon discontinuation of study medication, the subject's blood pressure decreased and at the time of the 14 day follow-up the blood pressure was normal.

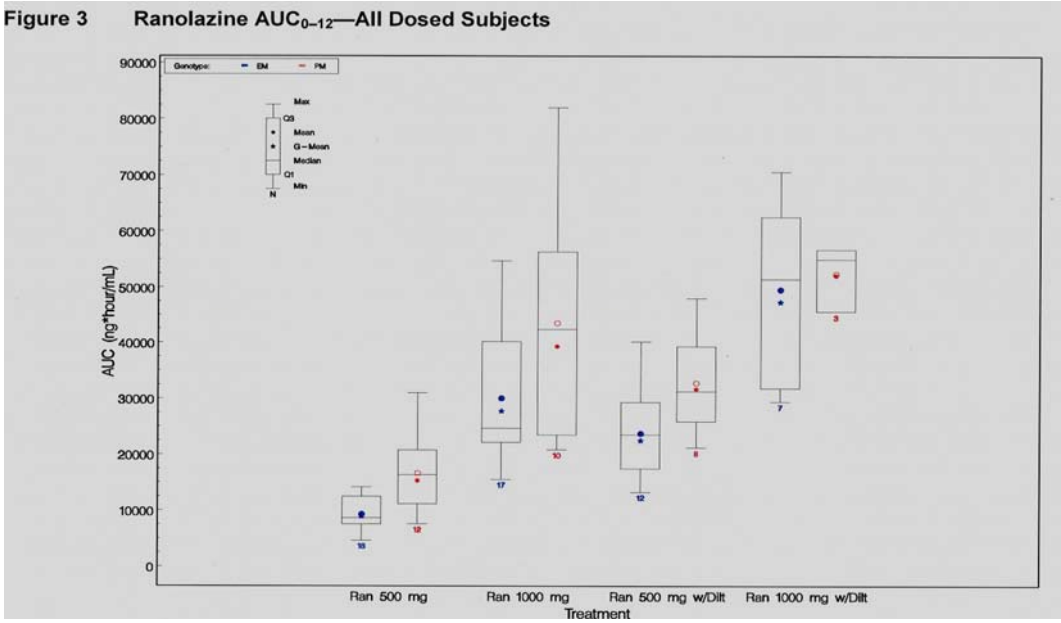
Pharmacokinetics

The mean plasma concentration time profiles of RAN in the presence and absence of DLT in PMs and EMs are shown in the below 2 figures:





The below box plot shows AUC0-12 for all dosed EMs and PMs receiving 500 mg and 1000 mg RAN with or without co-administration of DLT:



The PMs tend to exhibit greater AUC0-12 values than EMs in the RAN alone and in the RAN+ DLT co-administration treatments at both dose levels of RAN.

The below tables list the geometric mean and maximum exposure values of RAN and the metabolites observed with the RAN alone and DLT co-administration treatments:

Impact of the 500 mg Ranolazine alone and Diltiazem Co-Administration Treatments on Exposure (Geometric Mean and Maximum AUC and Cmax) to Ranolazine and Metabolites

	PM				EM			
	-DLT		+ DLT		-DLT		+DLT	
	mean	max	mean	max	mean	max	mean	max
n	12	12	8	8	18	18	12	12
Ranolazine								
AUC_{0-12}, ng·h/mL	15338	30960	31694	48070	8909	14124	22462	40080
Cmax	1695	3310	3158	4680	1036	1490	2391	3640
CVT-2512								
AUC_{0-12}	262	403	240	397	1099	2221	735	1785
Cmax	24.1	37.2	22.0	37.7	100	196	66.9	171
CVT-2514								

AUC_{0-12}	746	1048	1170	1663	4162	7482	5781	8986
Cmax	74.8	111	112	191	424	721	577	837
CVT-2738								
AUC_{0-12}	4765	7754	4756	5494	2535	3820	2375	3029
Cmax	444	724	437	492	245	378	232	359

Impact of the 1000 mg Ranolazine Alone and Diltiazem Co-Administration Treatments on Exposure (Geometric Mean and Maximum AUC and Cmax) to Ranolazine and Metabolites

	PM				EM			
	-DLT		+ DLT		-DLT		+DLT	
	mean	max	mean	max	mean	max	mean	max
n	10	10	3	3	17	17	7	7
Ranolazine								
AUC_{0-12}, ng·h/mL	39308	81975	52158	56725	27736	54710	47379	70570
Cmax	3947	7240	5522	5970	3009	5600	4873	6410
CVT-2512								
AUC_{0-12}	496	718	559	770	1630	3866	1430	2788
Cmax	44.2	63.8	50.7	68.7	148	338	128	241
CVT-2514								
AUC_{0-12}	1512	2328	2080	2511	7686	16901	9703	15325
Cmax	149	204	206	245	745	1660	906	1490
CVT-2738								
AUC_{0-12}	10493	15465	10099	10467	6395	10746	6159	9474
Cmax	976	1370	923	997	600	1010	571	880

The below table reports the ratios of the respective geometric mean values calculated from the above tables for 4 scenarios:

Ratio of the Geometric Mean AUC0-12 and Cmax values at Different Dose Levels of Ranolazine in the Presence and Absence of Diltiazem in PMs and EMs

	Ratio of Geometric Means			
	AUC0-12		Cmax	
	EM	PM	EM	PM
Scenario				
1000 mg RAN/500 mg RAN				
Ranolazine	3.11	2.56	2.90	2.32
CVT-2512	1.48	1.23	1.48	1.83
CVT- 2514	2.26	3.12	2.30	2.73
CVT-2738	2.52	2.20	2.20	2.20
1000 mg RAN*/500 mg RAN*				
Ranolazine	2.11	1.65	2.04	1.75
CVT-2512	1.95	2.33	1.91	2.30
CVT- 2514	1.68	1.78	1.57	1.84
CVT-2738	2.59	2.12	2.46	2.11
500 mg RAN*/500 mg RAN				
Ranolazine	2.52	2.07	2.31	1.86
CVT-2512	0.67	0.92	0.67	0.91
CVT- 2514	1.39	1.57	1.36	1.50
CVT-2738	0.94	1.00	0.95	0.98
1000 mg RAN*/1000 mg RAN				
Ranolazine	1.71	1.33	1.62	1.40
CVT-2512	0.88	1.13	0.86	1.15
CVT- 2514	1.26	1.38	1.22	1.38
CVT-2738	0.96	0.96	0.95	0.95

RAN=ranolazine administered in the absence of diltiazem
*RAN=ranolazine administered in the presence of diltiazem

The results of the statistical evaluation of AUC0-12 and Cmax for ranolazine after RAN 500 mg bid and 1000 mg bid in the absence of DLT in PMs and EMs are shown in the below table:

Table 7 Ranolazine PK Parameters—Difference between Genotypes Following Ranolazine Alone

Treatment Group/ Parameter*	N	LS Mean: Poor Metabolizer	LS Mean: Extensive Metabolizer	Ratio (Poor Metabolizer/ Extensive Metabolizer) (%)	90% CI for the Ratio (%)	Group Difference P-value
Ranolazine 500 mg						
AUC (0-12) (ng*hours/mL)	20	15039.98	9288.99	161.91	122.29 - 214.38	.006
Cmax (ng/mL)	20	1693.33	1087.32	155.73	120.59 - 201.11	.006
Tmax (hours)	20	3.50	3.50			.84
Ranolazine 1000 mg						
AUC (0-12) (ng*hours/mL)	20	36733.94	29281.10	125.45	94.75 - 166.10	.18
Cmax (ng/mL)	20	3668.15	3204.88	114.46	88.63 - 147.81	.38
Tmax (hours)	20	5.50	3.00			.37

Notes: ANOVA with terms for CYP2D6 metabolizer genotype, concomitant administration of diltiazem, ranolazine dose, all two-way interactions of these factors, the three-factor interactions, and subject as a random effect.
* The natural logarithms of AUC and Cmax are used in the ANOVA modeling. Results are reported in the original scale by taking the anti-logarithm.
Wilcoxon rank sum test is used for Tmax difference. Median Tmax values are presented.
Subjects 1928 and 1929, Day 8 Hour 7 samples were not included for the PK parameter calculations since those values were believed to be outliers.

The results of the statistical evaluation of Cmax and AUC0-12 for 500 mg RAN in the presence and absence of 180 mg DLT in EMs and PMs are shown in the below table:

Table 4 Ranolazine PK Parameters—Primary Analysis (PK Evaluable Population)

Treatment Group/ Parameter*	N	LS Mean: With Diltiazem	LS Mean: Without Diltiazem	Ratio (With Diltiazem/Without Diltiazem) (%)	90% CI for the Ratio (%)	Treatment Difference P-value
Poor Metabolizer and Ranolazine 500 mg						
AUC (0-12) (ng*hours/mL)	8	31694.12	15039.98	210.73	179.26 - 247.72	<.001
Cmax (ng/mL)	8	3157.77	1693.33	186.48	157.73 - 220.48	<.001
Tmax (hours)	8	4.00	3.50	0.50	-2.00 - 7.00	.47
Extensive Metabolizer and Ranolazine 500 mg						
AUC (0-12) (ng*hours/mL)	12	22461.81	9288.99	241.81	211.90 - 275.95	<.001
Cmax (ng/mL)	12	2390.69	1087.32	219.87	191.77 - 252.08	<.001
Tmax (hours)	12	3.51	3.50	0.50	-2.00 - 1.83	.65

Notes: ANOVA with terms for CYP2D6 metabolizer genotype, concomitant administration of diltiazem, ranolazine dose, all two-way interactions of these factors, the three-factor interactions, and subject as a random effect.
* The natural logarithms of AUC and Cmax are used in the ANOVA modeling. Results are reported in the original scale by taking the anti-logarithm.
Wilcoxon signed rank test is used for Tmax difference. Median response is used to estimate the values.
Subjects 1928 and 1929, Day 8 Hour 7 samples were not included for the PK parameter calculations since those values were believed to be outliers.

The below table lists the LS means, PM/EM ratios and 90% confidence intervals for RAN when RAN 500 mg was co-administered with 180 mg DLT bid:

Table 5 Ranolazine PK Parameters— Difference between Genotypes in the Diltiazem vs No Diltiazem Ratio (PK Evaluable Population)

Treatment Group/ Parameter*	N	LS Mean: Poor Metabolizer	LS Mean: Extensive Metabolizer	Ratio (Poor Metabolizer/ Extensive Metabolizer) (%)	90% CI for the Ratio (%)	Group Difference P-value
Diltiazem Administration Effect for Ranolazine 500 mg						
AUC (0-12) (ng*hours/mL)	20	210.73	241.81	87.15	70.73 - 107.38	.27
Cmax (ng/mL)	20	186.48	219.87	84.82	68.33 - 105.28	.21
Tmax (hours)	20	1.17	1.17			.43

Notes: ANOVA with terms for CYP2D6 metabolizer genotype, concomitant administration of diltiazem, ranolazine dose, all two-way interactions of these factors, the three-factor interactions, and subject as a random effect.
* The natural logarithms of AUC and Cmax are used in the ANOVA modeling. Results are reported in the original scale by taking the anti-logarithm.
Wilcoxon rank sum test is used for Tmax difference. Median ratio (with Diltiazem/without Diltiazem) are presented.
Subjects 1928 and 1929, Day 8 Hour 7 samples were not included for the PK parameter calculations since those values were believed to be outliers.

The next 2 tables provide the results of the statistical evaluations of the impact of genotype on the exposure to the metabolites after 500 mg and 1000 mg RAN alone with and without considering the AUC0-12 of the parent drug.

Impact of Genotype on Exposure to Metabolites in Subjects Receiving 500 mg and 1000 mg Ranolazine Alone without Considering Simultaneous Exposure to Ranolazine

Ranolazine Dose Level	Ratio of Metabolite AUC0-12 in PMs and EMs LS Mean (90% CI), %
500 mg	
CVT-2512	27 (20-37)*
CVT-2514	18 (14-24)*
CVT 2738	198 (165-238)*
1000 mg	
CVT-2512	32 (23-43)*
CVT-2514	19 (14-26)*
CVT-2738	154 (128-185)*

* Statistically significant treatment effect

Impact of Genotype on Exposure to Metabolites in Subjects Receiving 500 mg and 1000 mg Ranolazine Alone under Consideration of Simultaneous Exposure to Ranolazine

Ranolazine Dose Level	Ratio of Metabolite to Ranolazine for AUC0-12 in Ranolazine Alone Treatments, LS Mean		Impact of Genotype Ratio PM/EM, %
	PM	EM	
500 mg			
CVT-2512	0.018	0.104	17 (10-28)*
CVT-2514	0.047	0.411	11 (7.7-17)*
CVT-2738	0.337	0.275	122 (93-161)
1000 mg			
CVT-2512	0.013	0.052	25 (15-42)*
CVT-2514	0.038	0.250	15 (10-23)*
CVT-2738	0.283	0.230	123 (94-161)

* Statistically significant treatment effect

The final 2 tables list the results of the statistical evaluation of the impact of co-administering DLT and RAN on the exposure to the metabolites

Impact of Diltiazem Co-Administration on Exposure to Metabolites without Considering Simultaneous Exposure to Ranolazine

Ranolazine Dose Level	Ratio of Metabolite AUC0-12 in Presence and Absence of Diltiazem LS Mean (90% CI), %	
	PM	EM
500 mg		
CVT-2512	91 (82-100)	76 (70-82)*
CVT-2514	167 (148-188)*	151 (138-167)*
CVT-2738	94 (86-102)	93 (86-100)

* Statistically significant treatment effect

Impact of Diltiazem Co-Administration on Exposure to Metabolites under Consideration of Simultaneous Exposure to Ranolazine

Ranolazine Dose Level	Metabolite to Ranolazine Ratio for AUC0-12 in Presence and Absence of Diltiazem, LS Mean (90% CI), %	
	PM	EM

500 mg		
CVT-2512	43 (35-53)*	31 (27-37)*
CVT-2514	79 (69-91)*	63 (56-70)*
CVT-2738	45 (39-51)*	38 (35-43)*

* Statistically significant treatment effect

Ranolazine

Among all subjects receiving RAN alone or together with DLT a PM subject receiving RAN 1000 mg alone displayed the highest Cmax (7240 ng/mL) and AUC0-12 (81975 ng·h/mL). Among the subjects receiving 500 mg RAN alone or together with DLT a PM subject receiving RAN + DLT displayed the highest Cmax (4680 ng/mL) and AUC0-12 (48070 ng·h/mL).

AUC0-12 and Cmax after RAN 500 mg alone are statistically significantly greater in PMs than EMs. No statistically significant difference in AUC0-12 or Cmax between PMs and EMs is found after administration of 1000 mg RAN alone. AUC0-12 and Cmax after alone administration of 1000 mg are more than 2 fold greater than after 500 mg RAN alone in EMs and PMs indicating that the PK of RAN are more than dose proportional in both genotypes. Co-administration of DLT 180 mg and RAN 500 mg increases exposure to RAN about 2.4 fold in EMs and about 2.0 fold in PMs. Co-administration of DLT 180 mg and RAN 1000 mg increases exposure to RAN about 1.7 fold in EMs and about 1.4 fold in PMs indicating that the inhibition of the CYP3A mediated metabolism by DLT is smaller at the higher dose level with both genotypes. The extent of inhibition of RAN by DLT is in agreement with the findings in previous studies.

Metabolites

After administration of RAN 500 mg and 1000 mg alone, the respective AUC 0-12 values of CVT-2512 and CVT-2514 are smaller in PMs than in EMs, whereas the exposure to CVT-2738 is greater in PMs than in EMs in agreement with the notion that CVT-2512 and CVT-2514 are metabolized by CYP 2D6 and CVT-2738 by CYP 3A. The respective AUC0-12 values for CVT-2738 normalized for AUC0-12 of the parent drug (normalized AUC0-12/exposure) are not statistically significantly different in the two genotypes. In contrast, the corresponding values for CVT-2512 and CVT-2514 are significantly smaller in PMs than in EMs indicating that the difference in the PK of RAN and metabolites between the genotypes is associated with the CYP 2D6 pathway. Similar to the parent drug, the respective AUC0-12 values for CVT-2514 and CVT-2738 after a dose of 1000 mg RAN alone are more than 2.0 fold greater than those after 500 mg RAN alone in both genotypes. In contrast, AUC0-12 for CVT-2512 at the higher dose level is less than 2.0 fold greater than AUC0-12 at the lower dose level of RAN in both genotypes suggesting that the CYP2D6 mediated pathway generating CVT-2512 is primarily responsible for the non-linearity in the PK of RAN.

Co-administration of DLT and 500 mg RAN decreases AUC0-12 of CVT-2512 in EMs and increases the AUC0-12 of CVT-2514 in both genotypes. Co-administration of DLT and RAN 500 mg does not change AUC0-12 of CVT-2738. The respective normalized AUC0-12 values of CVT-2512, CVT-2514 and CVT-2738 are decreased in both genotypes when DLT is co-administered with RAN 500 mg compared to RAN alone. This finding suggests that the contribution of CYP 2D6 to the elimination of RAN at the plasma concentrations of RAN enhanced by DLT's inhibition of CYP3A is small.

Conclusions

PK

Previous studies have shown that RAN is predominantly eliminated by metabolism. It is known to be a substrate mainly of CYP3A, but also of CYP2D6. Among the measured first generation metabolites of RAN, CVT-2738 is thought to be generated mainly by CYP3A, whereas CVT-2512 and CVT-2514 are thought to be produced in part by CYP2D6. CVT-2738 and CVT-2512 are end-products, whereas CVT-2514 is glucuronidated prior to elimination. As a consequence of the ability of RAN to inhibit CYP2D6, the kinetics of RAN are more than dose proportional at therapeutic levels. The respective contributions of CYP3A to pre-systemic and systemic elimination of RAN from the body are not known. Unknown is also the contribution of enzymes other than CYP3A and 2D6 to the metabolism of RAN.

The present study shows that the PK of RAN are more than dose proportional at therapeutic dose levels. Exposure to RAN at the 500 mg dose level in PMs is greater than in EMs. At the 1000 mg dose level the exposure to RAN is not statistically significantly different between PMs and EMs. Co-administration of DLT 180 mg and RAN 500 mg increases exposure to RAN about 2.4 fold in EMs and about 2.0 fold in PMs. Co-administration of DLT 180 mg and RAN 1000 mg increases exposure to RAN about 1.7 fold in EMs and about 1.4 fold in PMs indicating inhibition of the CYP3A mediated metabolism by DLT is smaller at the higher dose level with both genotypes. The extent of inhibition of RAN by DLT is in agreement with the findings in previous studies.
Normalized exposure to CVT-2738 is similar in PMs and EMs after administration of RAN 500 mg or 1000 mg alone, in contrast to the corresponding values of CVT-2512 and CVT-2514 which are smaller in PMs than in EMs. Co-administration of DLT and 500 mg RAN reduces not only normalized exposure to CVT-2738, but also to CVT-2512 and CVT-2514 in both genotypes. The observed reduction of the normalized exposures to CVT-2512 and CVT-2514 suggests that the increased levels of RAN resulting from inhibition of CYP3A by DLT saturate CYP 2D6 enough so that the respective rates of formation of CVT-2512 and CVT- 2514 relative to the rate of formation of CVT-2738 are not increased.

Safety

Nine subjects (2 PMs and 7 EMs) discontinued the study because of AEs and 8 others were withdrawn due to meeting a protocol-specified ECG interval stopping criterion. The incidence of dizziness, both unspecified and postural, generally correlated with the RAN plasma concentrations with higher occurrences in PMs than in EMs. Three PM subjects and 2 EM

subjects experienced episodes of severe bradycardia on one or more treatment days during the co-administration regimen with 500 mg RAN or 1000 mg + 180 mg DLT bid. Two subjects experienced asymptomatic VT runs, one of which had developed a severe bradycardia the day before and a third subjects showed an idioventricular rhythm. All of these arrhythmia events occurred during the co-administration regimen with 500 mg RAN + 180 mg DLT. The expected exposure dependent prolongations of QTcF of up to 23 msec were seen.

Comments

1. It is well known that the pH of the urine samples influences the dextrometorphan/dextrorphan ratio. The pH in the urine samples used to determine the ratio varied greatly among the individuals potentially biasing the phenotype results. Surprisingly, the genotype and phenotype determinations were in agreement.

2. It is unclear why the evaluation of Cmin was excluded from the analysis of all treatments.

3.4 Study Report CVT 3023: A Double-Blind, Randomized, Parallel-Group Dose Escalation Tolerability Study of Ranolazine ER in Patients with Chronic Angina

Primary Investigator and Study Sites

(b) (4)

Objectives

Primary

To determine the tolerability of ranolazine ER at oral doses up to 3000 mg bid in patients with chronic angina, as assessed by specific adverse events

Secondary

To characterize the adverse events and the changes in vital signs and laboratory parameters associated with ranolazine ER at oral doses up to 3000 mg bid in these patients

Investigational Drugs and Formulations

Design

This was a double-blind, randomized, parallel group, dose escalation study of ranolazine ER; in Part 1 of the study, patients with chronic angina received oral doses ranging from 750 up to 2250

mg bid. Patients were randomized (1:1:1within each center) to one of the three treatment regimens shown in the Table below:

Table 1 Treatment Regimens for Part 1 of the Study

Treatment Regimen (Part 1)	Dose (mg twice a day)		
	Treatment Period 1 Days 1–3	Treatment Period 2 Days 4–7	Treatment Period 3 Days 8–13
750/750/750	750	750	750
750/1500/1500	750	1500	1500
750/1500/2250	750	1500	2250

Each treatment regimen included three treatment periods. At the beginning of each treatment period the dose of ranolazine was potentially increased depending on the treatment regimen. During Period 1, all patients were to receive ranolazine at a dose of 750 mg bid. During the Period 2 the dose of ranolazine for patients in Group 2 and 3 was increased to 1500 mg bid, whereas the patients of Group 1 stayed on 750 mg bid. During Period 3 only the patients of Group 3 received an increased dose of 2250 mg bid, whereas the patients in Groups 1 and 2 remained on their dose of 750 and 1500 mg bid, respectively. The patients were resident in the clinic for 14 days and physical examinations, ECGs, blood pressure and heart rate, and laboratory evaluations were performed. Approximately 14 days after discharge they were contacted to assess their condition, and to record any adverse events.

Safety

The primary tolerability endpoint was the number of patients who experience at least one of the pre-specified adverse events including syncope, diplopia, somnolence, depressed level or loss of consciousness, confusion and disorientation, symptomatic hypotension, dizziness, nausea, and vomiting, experienced any severe event or terminated from the study due to an adverse event.

Pharmacokinetic Profiling

Blood samples for the determination of the plasma concentrations of ranolazine were collected at the following times:

Days 3, 7, and 13: at 4 h after the morning dose of ranolazine (steady-state peak concentrations)

Days 4 and 8: within 15 minutes before the administration of the morning dose (steady-state trough concentration)

Day 14: before discharge and within 15 minutes of the time previously established for the morning dose (steady-state trough concentration)

At the time of early withdrawal or discontinuation from the study (within 2 h from the event leading to withdrawal)

Bioassay

The plasma concentrations of ranolazine were measured by a validated LC/MS/MS method. The LLOQ and ULOQ of the method are 50 and 10000 ng/mL respectively. Precision of the assay is < 5.8% and accuracy ranges between -1.8 % and 2.4 %.

Data Analysis

Mean and standard deviations of the plasma ranolazine levels were calculated for subjects receiving the respective dose regimens.

RESULTS

A total of 37 patients enrolled in the study. Twelve patients were randomized to remain on the initial dose of 750 mg bid for all three periods, 13 patients were randomized to escalate to 1500 mg bid in Periods 2 and 3 and 12 patients were randomized to escalate to 1500 mg bid and 2250 mg bid in Periods 2 and 3, respectively. The demographics of the participating patients are shown in the table below:

Table 4 Demographic and Baseline Characteristics

TABLE 1.2 [T-1.2] (PAGE 1 OF 1)
Demographic and Baseline Characteristics

		Treatment Regimen (mg)			
	Statistics	750/750/750 (n=12)	750/1500/1500 (n=13)	750/1500/2250 (n=12)	Overall (n=37)
Age (years)	n	12	13	12	37
	Mean (SD)	57.4 (8.0)	59.5 (10.5)	56.0 (11.9)	57.7 (10.1)
	Median	57.5	56.0	51.0	54.0
	Min - Max	45.0 - 67.0	46.0 - 82.0	47.0 - 78.0	45.0 - 82.0
Gender					
Male	n (%)	7 (58%)	9 (69%)	7 (58%)	23 (62%)
Female	n (%)	5 (42%)	4 (31%)	5 (42%)	14 (38%)
Race					
Caucasian	n (%)	5 (42%)	7 (54%)	7 (58%)	19 (51%)
Black	n (%)	7 (58%)	6 (46%)	5 (42%)	18 (49%)
Height (cm)	n	12	13	12	37
	Mean (SD)	170.0 (8.4)	169.2 (8.0)	171.6 (13.7)	170.2 (10.1)
	Median	169.3	169.0	172.7	170.5
	Min - Max	154.0 - 188.0	157.0 - 180.3	153.0 - 200.7	153.0 - 200.7
Weight (kg)	n	12	13	12	37
	Mean (SD)	91.8 (8.9)	87.0 (16.4)	103.3 (33.6)	93.8 (22.5)
	Median	94.8	86.0	94.8	92.1
	Min - Max	76.2 - 102.5	63.5 - 118.8	69.3 - 196.4	63.5 - 196.4
BMI (kg/m^2)	n	12	13	12	37
	Mean (SD)	32.0 (4.5)	30.4 (5.1)	34.5 (6.7)	32.2 (5.6)
	Median	32.2	30.1	32.9	32.0
	Min - Max	25.9 - 40.2	22.9 - 38.7	25.5 - 48.8	22.9 - 48.8

Source: tdemog.sas (20DEC2005:16:27 by PSERN) tdemog.doc

Safety

Twenty three patients completed the study. A total of 14 patients withdrew early from the study as shown in the table below:

Table 2 Patient Disposition

	Treatment Regimen (mg)		
	750/750/750 (n=12)	750/1500/1500 (n=13)	750/1500/2250 (n=12)
No. of patients who completed treatment	11 (92%)	7 (54%)	5 (42%)
No. of patients who terminated early	1 (8%)	6 (46%)	7 (58%)
Primary reason for early termination			
QTc prolongation	0	1 (8%)	0
Adverse event(s)	0	1 (8%)	4 (33%)
Death	0	0	0
Protocol Violation	0	0	0
Lost to follow-up	0	0	0
Did not meet entrance criteria	0	1 (8%)	0
Other	1 (8%)	3 (23%)	3 (25%)

Source: tdispo.sas (20DEC2005:16:27 by PSERN) tdispo.doc

A listing of patient disposition information is presented in Section 13.1.

Dose levels and reason for premature termination of the study in the 14 subjects are summarized in the table below:

Table 3 Patients Who Prematurely Terminated from the Study

Patient No.	Last Ranolazine Dose prior to Termination (mg b.i.d.)	Reason for Termination	Comment
750/750/750 Regimen			
14012336	750	Other	The study-site required evacuation for an impending hurricane
750/1500/1500 Regimen			
12122301	1500	QTc prolongation	Withdrawn for QTc prolongation (Withdrawal required per protocol, with a QTc > 500 msec and a change from baseline ≥ 60 msec)
14062306	1500	Adverse event	Withdrawn for nausea, disorientation, and confusion
14012325	1500	Other	Patient withdrew consent
14012334	1500	Other	The study-site required evacuation for an impending hurricane
14012320	750[a]	Other	Patient was discharged by the sponsor when it was realized that the patient was taking a prohibited medication (Effexor)
14012329	750	Did not meet entrance criteria	Patient was discharged by the sponsor when it was realized that on Day -1 the patient had orthostatic hypotension, not satisfying study-entrance criteria
750/1500/2250 Regimen			
12122302	1500	Adverse event	Withdrawn for nausea and vomiting
12122309	1500	Adverse event	Withdrawn for severe involuntary muscle spasms (a serious adverse event [SAE])
14062303	2250	Adverse event	Withdrawn for hematuria (emerged at a ranolazine dose of 2250 mg b.i.d.) and a transient ischemic attack (emerged at a dose of 1500 mg .b.i.d.). Both events were SAEs.
14062304	2250	Adverse event	Withdrawn for nausea and orthostatic hypotension, which emerged at a ranolazine dose of 1500 mg b.i.d.
14012302	1500	Other	Patient withdrew consent
14012305	2250	Other	Patient withdrew consent
14062308	2250	Other	Patient withdrew consent

[a] Patient 14012320 terminated on the morning of the first day of treatment period 2; hence the listings reflect that this patient withdrew during period 2, corresponding to a 1500-mg ranolazine dose. However, the patient had not yet taken study medication for the day, so the last actual dose taken was 750 mg.

Source: The data in this table were obtained from the patient disposition listing in Section 13.1 of this report.

Five patients were withdrawn from the study due to one or more adverse events, and one patient was withdrawn for QTc interval prolongation as per protocol (ΔQTc msec ≥ 60 msec and QTc > 500 msec). Four patients withdrew voluntarily. Two patients were withdrawn by the sponsor (one for not meeting the entrance criteria and one for concomitant use of prohibited medication) and 2 patients were withdrawn, because the study site required evacuation (hurricane 2005)

The below table summarizes the tolerability results:

Table 6 Primary Endpoint Analysis: Tolerability

	Treatment Regimen (mg)		
	750/750/750 (n=12)	750/1500/1500 (n=13)	750/1500/2250 (n=12)
Patients Who Experienced a Primary Endpoint Event*	1 (8%)	6 (46%)	9 (75%)
Study Specific Adverse Events	1 (8%)	6 (46%)	9 (75%)
Syncope	0	0	0
Diplopia	0	0	0
Somnolence	0	1 (8%)	2 (17%)
Depressed level/Loss of consciousness	0	0	0
Confusion/Disorientation	0	1 (8%)	0
Symptomatic Hypotension	0	1 (8%)	1 (8%)
Dizziness	1 (8%)	2 (15%)	5 (42%)
Nausea	0	3 (23%)	6 (50%)
Vomiting	0	1 (8%)	3 (25%)
Severe Adverse Events	0	2 (15%)	2 (17%)
Terminated from the Study Due to an Adverse Event	0	1 (8%)	4 (33%)

Note: * Primary endpoint will be the number of patients who experience syncope, diplopia, somnolence, depressed level/loss of consciousness, confusion/disorientation, symptomatic hypotension, dizziness, nausea, vomiting, or any severe adverse event, or terminate from the study due to an adverse event.

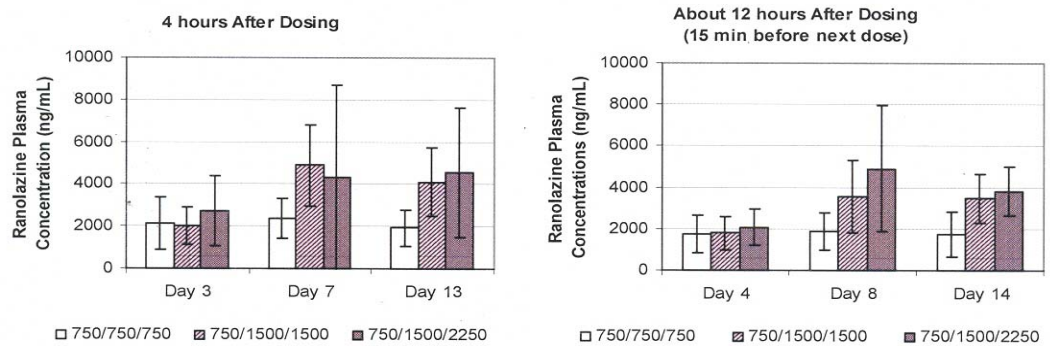
Source: tendpt.sas (20DEC2005:16:27 by PSERN) tendpt.doc

The incidence of somnolence, confusion/disorientation, symptomatic hypotension, dizziness, nausea, or vomitus increase with dose: 8% with the 750 m bid regimen, 46% with the 1500 mg bid regimen and 75% with the 2250 mg bid regimen. The number of subjects terminated from the study because of an adverse event increases also with dose: 0% with the 750 mg bid regimen, 8% with the 1500 mg bid regimen and 33% with the 2250 mg bid regimen. It can be concluded that the 750 mg bid dose regimen is tolerated and the 1500 mg bid and 2250 mg bid dose levels are not.

Pharmacokinetics

The mean peak and trough steady-state plasma concentrations of ranolazine in the patients are shown in the Figure below:

Figure 1 Ranolazine Plasma Concentrations at Scheduled Timepoints



The mean peak concentrations of ranolazine ranged between 1932 ng/mL and 2380 ng/mL and the mean trough concentrations ranged between 1743 ng/mL and 1850 ng/mL in patients receiving the 750/750/750 bid regimen. The concentrations after 750 mg bid in the patients receiving the other two regimens were consistent with those above. For patients taking 1500 mg bid in the 750/1500/1500 mg bid regimen the mean peak concentrations ranged between 4106 ng/mL and 4888 ng/mL and the trough concentrations ranged between 3467 ng/mL and 3551 ng/mL. For patients on the 750/1500/2250 mg bid regimen the peak concentrations after 1500 mg bid were in the range of the concentrations noted above. However, the mean trough concentrations were unexpectedly high, 4884 ng/mL. Finally, patients receiving the 2250 mg bid dose displayed mean peak and trough concentrations of 4540 ng/mL and 3820 ng/mL, respectively. Apart from one exception patients who had a trough concentration ≥ 6000 ng/mL discontinued the study (either being withdrawn by the Investigator or voluntarily withdrawing consent).

The results indicate that the mean plasma concentrations increase with dose, but it appears that the increase in dose from 1500 mg bid to 2250 mg bid is not associated with a proportionate increase of the mean plasma concentration. There is significant inter-subject variation as noted in earlier studies and little difference between mean peak and trough concentrations.

The plasma concentrations of the patients at the time of withdrawal from the study are listed in the table below:

Table 5 Plasma Concentrations at the Time or Following Withdrawal from the Study

Patient No.	Reason for withdrawal	Last ranolazine dose	Plasma concentration	Time since last dose
750/1500/1500 Regimen				
12122301	QTc interval prolongation[a]	1500 mg	7210 ng/mL	~7 hours
14012325	Withdrew consent	1500 mg	6840 ng/mL	~9 hours
14062306	Nausea, disorientation, and confusion	1500 mg	3520 ng/mL	~12 hours
750/1500/2250 Regimen				
12122302	Nausea and vomiting	1500 mg	2120 ng/mL	~24 hours
12122309	Involuntary muscle spasms	1500 mg	14,000 ng/mL	~9.5 hours
14012302	Withdrew consent	1500 mg	BQL	~193 hours
14012305	Withdrew consent	2250 mg	11,800 ng/mL	~12 hours
14062303	Hematuria[b] and transient ischemic attack	2250 mg	12,400 ng/mL	~11 hours
14062304	Nausea, dizziness, and orthostatic hypotension[c]	2250 mg	8800 ng/mL	~11 hours
14062308	Withdrew consent	2250 mg	BQL	~81 hours

[a] The protocol required that a patient be discontinued from the study if the QTc interval both widened to ≥ 60 msec from its baseline duration and was > 500 msec.

[b] The hematuria emerged at the 2250-mg dose, but the transient ischemic attack occurred while the patient was receiving 1500 mg b.i.d.

[c] All events emerged while the patient was receiving 1500 mg b.i.d., but the patient continued dosing and then withdrew while taking 2250 mg b.i.d.

BQL = below the quantitation limit of the assay

Source: Section 13.5

It should be noted that 14 patients withdrew from the study prematurely. Ten (10) of these 14 patients were included in the table. Four (4) patients (2 withdrawn due to study site evacuation and 2 discharged by the sponsor) are not included. Of the 10 patients considered, 7 had plasma samples taken within 12 h of the last dose and of these 7 patients, 6 had trough concentrations > 6000 (6840-14 000) ng/mL. Three (3) patients had plasma concentrations taken only 24 h -193 h after the last ranolazine dose making it difficult to relate the measured concentrations to peak or trough concentrations at steady-state. Of the 6 patients who had trough concentrations > 6000 ng/mL, 5 discontinued the study (either being withdrawn or voluntarily withdrawing consent). One (1) patient in the 750/1500/1500 regimen had trough concentrations of 6580 ng/mL (Day 8) and 4880 ng/mL (Day 14).

Conclusions

Tolerability decreases with increasing doses and plasma concentrations of ranolazine. A regimen with 750 mg ranolazine bid is tolerated. Trough plasma concentrations in excess of 6000 ng/mL were shown to be associated with intolerability. The peak and trough plasma concentrations measured in the angina patients showed considerable variability.

Comments

None.

3.5 Study Report CVT Study 3032 :" A Phase 3, Open-Label, Long Term, Safety Study of Ranolazine SR for Chronic Stable Angina Pectoris at Doses of 750 mg and 1000 mg bid

Study Investigator and Site

45 Investigators at 47 Study Centers in Canada, the Czech Republic, Poland, and the United States

Objectives

The primary objective of this follow up study of CVT study 3031 was to determine the long term safety and tolerability of ranolazine ER 750 mg bid and 1000 mg bid in patients with chronic stable angina during an open label treatment period of up to approximately 10 years duration administered with and without other anti-anginal as needed to control symptoms.

Investigational Drugs and Formulations

Ranolazine ER 375 (lot Nos. 1 H2727A, 3H3022A), 500 mg (Lot Nos. 791771, 898221, 1H2726A, 1K2754A, 3H3026A) and 750 mg (Lot Nos. 791861, 791871) tablets

Design

This was an open-label study in which patients received a treatment with an initial dose of 750 mg of ranolazine ER and may be titrated to 1000 mg ranolazine bid based on clinical response. If at the 1000 mg bid dose level symptoms were not controlled, patients may also have been taken additional anti-anginal therapy such as calcium antagonists or beta-blockers. Patients were seen at weekly intervals until their angina was controlled, then followed up at 1 month after their last titration, and every 3-6 months thereafter. A total of 143 patients enrolled in the study. The patients must have had stable angina and completed Study CVT 3031. Exclusion criteria included NYHA Class III or IV congestive heart failure, second or third degree of atrio-ventricular block, QTc > 500 msec, required medication prolonging the QTc interval, required medication significantly affecting CYP 3A, active acute myocarditis or pericarditis, hypertrophic cardiomyopathy, uncontrolled hypertension, any chronic illness likely to hinder or confuse the follow-up evaluation , or were unwilling to refrain from consumption of grapefruit/ grapefruit juice, clinically significant hepatic disease, end-stage renal disease requiring dialysis or a calculated creatinine clearance < 30 mL/min.

Overall incidences of adverse events, incidence by severity and by relationship to medication were calculated. Continuous laboratory values, vital signs (heart rate blood pressure) and ECG parameters (PR, QRS, QT and QTc) were evaluated and compared to baseline (Visit 2 of CV study 3031). Prolongation of the QTc > 500 msec and ≥ 130% of baseline were considered critical.

The inclusion and exclusion criteria are listed below:

9.3.1 Inclusion Criteria

To be eligible for enrollment, patients had to satisfy the following requirements:

- Patients had completed Study CVT 3031 according to the protocol
- For female patients only: The patient was post-menopausal or sterilized, or if she was of childbearing potential, she was not breast feeding, her pregnancy test was negative, she had no intention of becoming pregnant during the course of the study, and she was using contraceptive drugs or devices
- Patients had signed a consent form for this study approved by the investigator's IRB/IEC

9.3.2 Exclusion Criteria

If patients developed or required any of the listed exclusions below since starting Study CVT 3031, they were not eligible to be entered into Study CVT 3032:

- New York Heart Association (NYHA) Class IV congestive heart failure
- Second or third degree atrioventricular block or uncontrolled clinically significant cardiac arrhythmias
- Corrected QT interval (QTc) > 500 msec
- Required medications which are known to prolong the QTc interval, such as:
  - Class IA anti-arrhythmics and/or Class III anti-arrhythmics (quinidine, procainamide, amiodarone, sotalol, etc.)
  - Seldane (terfenadine)
  - Hismanal (astemizole)
  - Propulsid (cisapride)
- Required medications which significantly affect cytochrome P450 3A4, such as:

  Inhibitors:
  - Erythromycin, Biaxin (clarithromycin), TAO (troleandomycin)
  - Nizoral (ketoconazole), Sporanox (itraconazole)

  Inducers:
  - Dilantin (phenytoin), Tegretol (carbamazepine), phenobarbital, rifampin

  An additional list of medications which affect cytochrome P450 3A4 were listed in the protocol.

  Other medications metabolized by cytochrome P450 such as diltiazem were to be used with caution.
- Unwillingness to refrain from grapefruit/grapefruit juice consumption for the duration of the study (grapefruit juice inhibits cytochrome P450 3A4)
- Active acute myocarditis or pericarditis
- Hypertrophic cardiomyopathy
- Uncontrolled hypertension
- Any chronic illness which was likely to hinder or confuse follow-up evaluation (e.g., cancer, alcoholism, drug dependency or abuse, serious psychiatric illness, uncontrolled or labile diabetes mellitus, etc.)

Prohibited medications included the following:

9.4.5.1 Prohibited Concomitant Medications and Food

- Medications which are known to prolong the QTc interval were not allowed; they included, but were not limited to the following:
  - Class IA anti-arrhythmics (e.g., quinidine, procainamide)
  - Class III anti-arrhythmics (e.g., amiodarone, sotalol, dofetilide)
  - Phenothiazide anti-psychotics: chlorpromazine, mesoridazine, pimozide, thioridazine
  - Quinolone antibiotics: gatifloxacin, moxifloxacin, sparfloxacin
  - Others: droperidol, mefloquine, pentamidine, levomethadyl, dolasetron, systemic dosing of tacrolimus, arsenic trioxide, terfenadine, astemizole, cisapride
  - Other drugs that have a contraindication or boxed warning regarding QT prolongation in the prescribing information
- Medications that are inhibitors or inducers of cytochrome P450 3A4 were not allowed; they included, but were not limited to the following:
  - Erythromycin, clarithromycin, troleandomycin
  - Ketoconazole and itraconazole (topical agents were permissible)
  - Dilantin (phenytoin), Tegretol (carbamazepine), phenobarbital, rifampin
  - Nefazadone
  - Antiviral drugs (delavirdine)
  - Protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir)
  - Cyclosporin

Other medications metabolized by cytochrome P450 such as diltiazem were to be used with caution.

In addition to these concomitant medications, grapefruit/grapefruit juice consumption was prohibited for the duration of the study.

Allowed medications included the following:

9.4.5.2 Allowed Concomitant Medications

- Sublingual nitroglycerin was permitted for treatment of acute angina.
- Aspirin was permitted during the study.
- Any digitalis preparation (e.g., digoxin) was permitted during the study. However, if a patient received digoxin therapy, serum digoxin levels should have been monitored.
- The use of statins was permitted during the study.
- Beta blockers and calcium channel blockers may have been used as anti-hypertensives only if they had been added during the titration phase of the study for control of angina.
- Diuretics and angiotensin converting enzyme (ACE) inhibitors may have been administered as anti-hypertensive therapy.

Use of any concomitant medications should have been documented on the appropriate case report forms (CRFs).

Pharmacokinetic Profiling

Trough plasma concentrations were measured (approximately 12 h after the last dose) beginning after the first long term visit (Visit 3) and at all subsequent maintenance visits at 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69 and 72 months.

Bioassay

The plasma concentrations of ranolazine were measured by a specific LC/MS/MS method**.** The measurements were performed in the [redacted] (b) (4). The calibration curve is linear for ranolazine concentrations ranging from10 ng/mL to 12500 ng/mL. The precision of the assay measured with QC samples is <6.4% and the accuracy is ranging between-2.8% and 9.5%.

PK Data Analysis

Ranolazine plasma concentrations data at the 750 mg and 1000 mg bid dose levels were grouped into time intervals centered around time points every 3 months after start of dosing. If a patient had two plasma concentrations measured within the same time interval the values were averaged. Mean, median, 25th percentile, 75th percentile, minimum and maximum plasma concentrations of ranolazine for the patients were computed for the above time points.

PK-PD Analysis

Plots of QTc versus the ranolazine plasma concentrations were constructed.

RESULTS

Demographics of Subjects

The mean age of the patients was 64 (± 9) years, 75% were male and 92% Caucasians.

Disposition of Subjects

Table 3 Patient Disposition

	Overall n = 143
No. of patients who completed treatment	48 (33.6%)
No. of patients who terminated prematurely	95 (66.4%)
Primary reason for premature termination of the study	
Unacceptable adverse event	43 (30.1%)
Non-compliance	4 (2.8%)
Elective withdrawal	17 (11.9%)
Lost to follow-up	3 (2.1%)
Death	15 (10.5%)
Other	13 (9.1%)

Source: Section 14.1.1

Concomitant Medications

The most common co-medications were: platelet aggregation inhibitors (90%, e.g. acetyl salicylic acid), organic nitrates (73%, e.g. glyceryl trinitrate, isosorbide mono-and dinitrate), HMO Co-A reductase inhibitors (68%, e..g. atorvastatin, simvastatin), α- and β-blocking agents (49%, e..g. atenolol), ACE inhibitors(41%, eg.g lisinopril), diuretics (41%, e.g. furosemide) and calcium channel blockers (32% , 13 % diltiazem, 1.4 % verapamil)

Safety

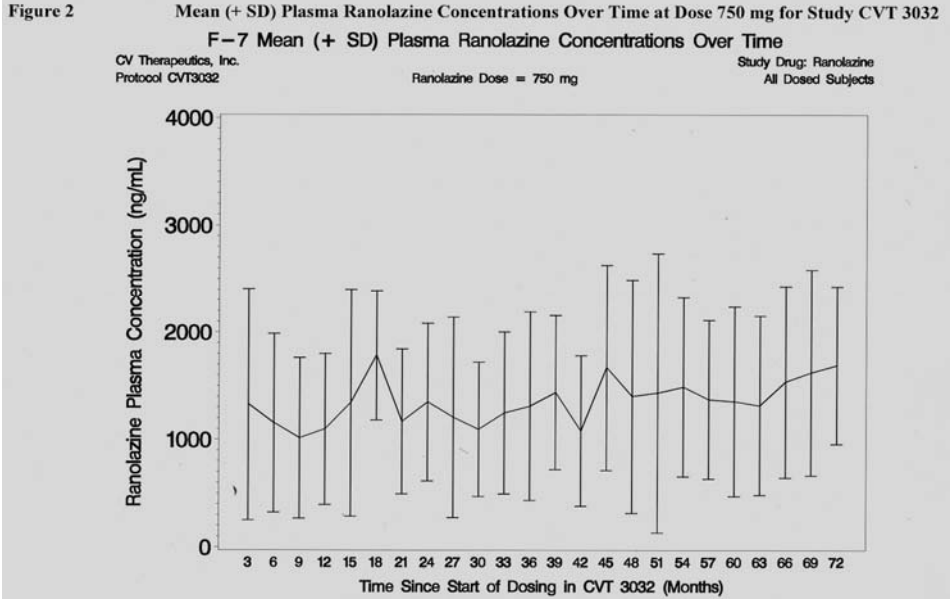
Table 5 Summary of Adverse Events

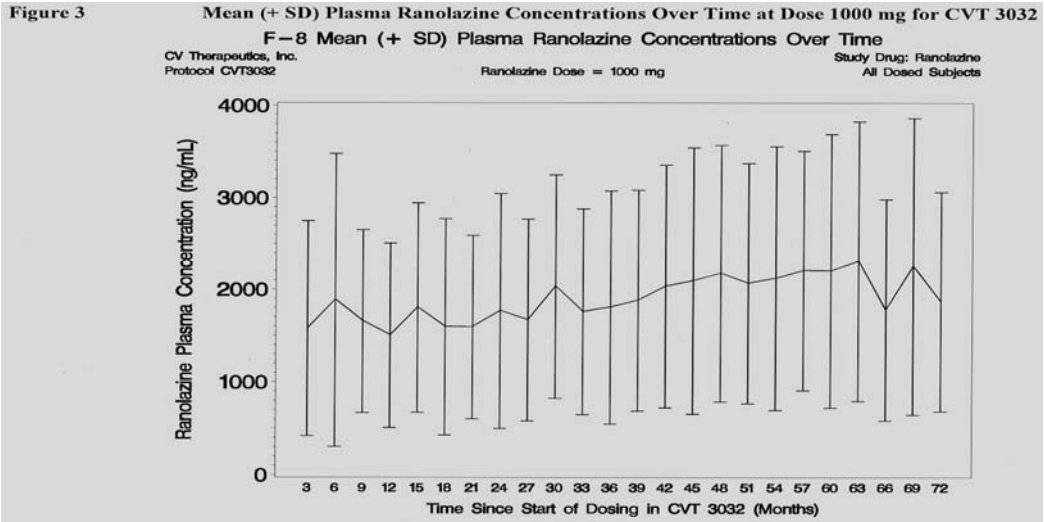
Number of Patients:	Total (n = 143)
Any adverse event	122 (85.3%)
Any potentially study drug related adverse event	51 (35.7%)
Discontinued the study due to an adverse event	53 (37.1%)
Any serious adverse event	87 (60.8%)
Death	17 (11.9%)

Pharmacokinetics

Plots of the mean (SD) trough plasma concentrations of ranolazine over time for the 750 mg bid and 1000 mg bid regimens are shown in the below 2 figures and the corresponding median and individual maximum ranolazine concentrations at each time point are listed in the below 2 tables:

Figure 2 Mean (+ SD) Plasma Ranolazine Concentrations Over Time at Dose 750 mg for Study CVT 3032





The mean trough concentrations and standard deviations show no time dependency even though the number of subjects with information on the plasma concentration of ranolazine decreased over time substantially resulting in a constantly changing population. The large values of the standard deviation point to the known significant inter-subject variation of the exposure to ranolazine. With the 750 mg bid regimen the median trough plasma concentrations over time range between 833 ng/mL and 1705 ng/mL and the individual maximum trough plasma concentrations vary between 2510 ng/mL and 5925 ng/mL. With the 1000 mg bid regimen the trough plasma concentrations over time range between 1350 ng/mL and 2000 ng/mL and the individual maximum trough plasma concentrations vary between 4230 ng/mL and 10800 ng/mL. The median trough plasma concentrations at the 1000 mg dose levels are higher than at the 750 mg dose level. Not surprisingly the plasma concentrations at the 750 and 1000 mg dose level overlap.

Median Trough and Individual Maximum Trough Plasma Concentrations of Ranolazine During a Regimen with 750 mg bid

Month	n Subjects	Median Trough Concentration ng/mL	Maximum Trough Concentration ng/mL
3	41	1090	4240
6	31	927	3540
9	33	833	2840
12	31	1150	2930
15	29	1210	5380
18	30	913	5925
21	26	1143	2510
24	24	1350	2720
27	27	1070	4660
30	23	1000	2545

33	25	1125	3330
36	20	1138	3170
39	21	1470	3510
42	17	1020	2415
45	14	1478	4555
48	13	1315	4420
51	13	1120	4250
54	13	1480	3005
57	11	1500	2605
60	13	1440	3160
63	11	999	2900
66	9	1560	2920
69	8	1705	2860
72	4	1520	2730

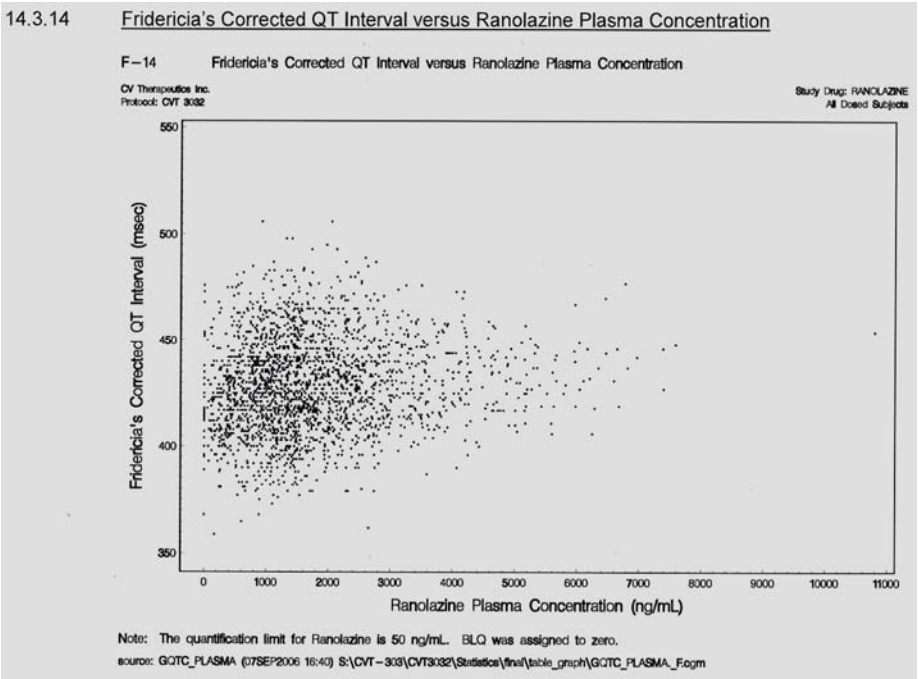
Median Trough and Individual Maximum Trough Plasma Concentrations of Ranolazine During a Regimen with 1000 mg bid

Month	n Subjects	Median Trough Concentration ng/mL	Maximum Trough Concentration ng/mL
3	82	1398	6780
6	74	1450	10800
9	76	1543	5575
12	69	1350	6290
15	70	1558	6350
18	64	1385	5650
21	67	1420	4870
24	63	1560	7590
27	66	1433	5160
30	57	1750	5190
33	62	1528	4710
36	62	1615	5320
39	56	1583	5160
42	60	1700	6070
45	53	1795	6470
48	48	1910	5795
51	43	2000	6135
54	44	1903	6210
57	44	1868	6330
60	42	1903	5370
63	40	1765	6780
66	35	1440	5625
69	27	1920	7400

72	16	1705	4230

Pharmacodynamics

A plot of the QT corrected for heart rate according to Fridericia, QTcF, versus the plasma concentrations of ranolazine is shown below:



The scatter of the data confirms the significant inter-subject variation in QTc ranolazine noted in earlier studies.

Conclusions

PK

The results confirm the significant variation of the exposure to ranolazine in subjects receiving the same dose. There is no evidence for an important time dependence of the pharmacokinetics of and exposure to ranolazine when the drug is administered at a dose of 750 mg or 1000 mg bid for a period of 6 years.

PD

The relationship between QTcF and the plasma concentrations of ranolazine shows the same high variation seen in earlier studies.

Comments

None

3.6 Report of Study CVT 3034 ”A Phase 3, Open-Label, Long-Term, Safety Study of Ranolazine SR for Chronic Stable Angina Pe4ctoris at Doses of 500 mg, 750 mg and 1000 mg Twice a Day Administered in Combination with Antianginal Therapy“

Investigator and Study Sites

This international multi-center study was conducted by 128 Investigators at 128 study centers in Australia, Bulgaria, Canada, the Czech Republic, Georgia, Greece, Israel, New Zealand, Poland Romania, Russia, Spain, the UK and the US.

Objectives

The primary objective of this study was to determine the long-term safety and tolerability of ranolazine ER 500 mg bid, 750 mg bid and 1000 mg bid administered in combination with other anti-anginal therapy(ies) in patients with chronic stable angina during an open-label treatment period of up to 8 years duration.

A secondary objective was to assess the long-term safety and tolerability of ranolazine ER 500 mg bid, 750 mg bid, and 1000 mg bid in patients who had reduced or discontinued concomitant anti-anginal medication(s).

Formulations

Ranolazine ER 375 mg (Lot Nos. 8H2750A, 8H2751A, 9G2715A, 0H2760A, 0H2761A, 1G2704A, 1H2727A, 1I2730A, 2A2760A, 2A2761A, 2D2769A, 1K2756A, 1K2758A, 3H3022A, 3K3051A and Ranolazine 500 mg tablets (Lot Nos. 8H2747A, 8H2749A, 0H2762A, 0H2763A, 1F2701A,1F2702A, 1H2725A, 1I2737A, 1I2738A, 1I2739A, 2D2770A, 1K2755A, 1K2753A, 3H3025A, 3H3027A, A02034A, A02038A.

Design

This was a long-term, open-label safety study of ranolazine ER administered with and without concomitant anti-anginal therapy in patients who had completed either 12 weeks of double-blind therapy in Study CVT 3033 or 6 weeks of double-blind therapy in study CVT 3037. Patients were initially administered the same anti-anginal therapy they received in study CVT 3033 or 3037. The background anti-anginal medications included diltiazem, atenolol, amlodipine with or with long acting nitrates. Once enrolled in study CVT-3034, investigators were permitted to adjust or discontinue background anti-anginals or add other anti-anginals based on the patient’s clinical condition. Patients were seen at weekly intervals for dose titration until their angina was controlled, then followed for 1 month after their last titration, and every 3-6 months thereafter.

The doses of ranolazine could be titrated up and down over a dose range of 500 mg bid, 750 mg bid and 1000 mg bid, based on clinical response.

The inclusion and exclusion criteria are listed below:

9.3.1 Inclusion Criteria

To be eligible for enrollment, patients had to satisfy the following requirements:

- Patients who had completed either Study CVT 3033 (through Visit 6) or Study CVT 3037 (through Visit 5) according to the respective protocol
- For female patients only: The patient was post-menopausal or sterilized, or if she was of childbearing potential, she was not breast feeding, her pregnancy test was negative, she had no intention of becoming pregnant during the course of the study, and she was using contraceptive drugs or devices
- Patients who reviewed the patient information sheet and signed an informed consent form for this study approved by the investigator's IRB or IEC
- Patients who were willing to comply with requirements of the protocol
- Patients who provided HIPAA authorization (U.S. residents only)

9.3.2 Exclusion Criteria

If patients had developed any of the listed exclusions since starting either Study CVT 3033 or Study CVT 3037 they were not be eligible to be entered into Study CVT 3034:

- New York Heart Association (NYHA) Class IV congestive heart failure
- Active acute myocarditis or pericarditis
- Hypertrophic cardiomyopathy
- Uncontrolled hypertension
- Clinically significant hepatic disease
- End-stage renal disease requiring dialysis or a calculated creatinine clearance (CLcr) < 30 mL/min
- Hypersensitivity to ranolazine
- Second or third degree atrioventricular block in the absence of a functioning ventricular pacemaker or uncontrolled clinically significant cardiac arrhythmias or a history of life-threatening ventricular arrhythmias unassociated with acute myocardial infarction (MI)
- Had a QTc interval measurement > 500 msec at Visit 5 of either Study CVT 3033 or Study CVT 3037 as determined by the investigator. Repeat ECGs were allowed to confirm the measurement if required.
- Had a need (or anticipated need) for treatment during the study period with any of the following agents which might interfere with the evaluation of the therapeutic response or safety of the study drug:
  - Agents known to prolong the QT interval, including, but not limited to:
    - Class IA anti-arrhythmics (e.g., quinidine, procainamide)
    - Class III anti-arrhythmics (e.g., amiodarone, sotalol, and dofetilide)
    - Phenothiazide anti-psychotics: chlorpromazine, mesoridazine, pimozide, and thioridazine
    - Quinolone antibiotics: gatifloxacin, moxifloxacin, and sparfloxacin
    - Others: droperidol, mefloquine, pentamidine, levomethadyl, dolasetron, systemic dosing of tacrolimus, arsenic trioxide, terfenadine, astemizole, and cisapride
    - Other drugs that have a contraindication or boxed warning regarding QT prolongation in the prescribing information
  - Agents that were inhibitors or inducers of the cytochrome P450 pathway isoform 3A4, including, but not limited to:
    - Erythromycin, clarithromycin, and troleandomycin
    - Ketoconazole and itraconazole (topical agents were permissible)
    - Phenytoin, carbamezepine, phenobarbital, and rifampin

- Nefazadone
- Antiviral drugs (e.g., delavirdine)
- Protease inhibitors (indinavir, nelfinavir, ritonavir, and saquinavir)
- Cyclosporin

An additional list of medications which affect cytochrome P450 3A4 was presented in the protocol.

- Unwillingness to refrain from grapefruit/grapefruit juice consumption for the duration of the study (grapefruit juice inhibits cytochrome P450 3A4)
- Any chronic illness likely to hinder or confuse compliance with the protocol (e.g., cancer, alcoholism, drug dependency or abuse, serious psychiatric illness, uncontrolled or labile diabetes mellitus, etc.)
- Any condition which might increase the risk to the patient
- Any condition which might decrease the chance of obtaining satisfactory data to achieve the objectives of the study

Prohibited Concomitant Medications included the following:

9.4.5.1 Prohibited Concomitant Medications

Medications which are known to prolong the QTc interval were not allowed to be taken by patients in this study. Prohibited medications included (but were not limited to) the following:

- Class IA anti-arrhythmics (e.g., quinidine, procainamide)
- Class III anti-arrhythmics (e.g., amiodarone, sotalol, dofetilide)
- Phenothiazide anti-psychotics: chlorpromazine, mesoridazine, pimozide, thioridazine
- Quinolone antibiotics: gatifloxacin, moxifloxacin, sparfloxacin
- Others: droperidol, mefloquine, pentamidine, levomethadyl, dolasetron, systemic dosing of tacrolimus, arsenic trioxide, terfenadine, astemizole, cisapride
- Other drugs that have a contraindication or boxed warning regarding QT prolongation in the prescribing information

Medications that are inhibitors or inducers of cytochrome P450 3A4 were not allowed; they included, but were not limited to the following:

- Erythromycin, clarithromycin, and troleandomycin
- Ketoconazole and itraconazole (topical agents were permissible)
- Phenytoin, carbamazepine, phenobarbital, rifampin
- Nefazadone
- Antiviral drugs (delavirdine)
- Protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir)
- Cyclosporin

An additional list of medications that affect cytochrome P450 3A4, was presented in the protocol.

Other medications metabolized by cytochrome P450 such as diltiazem should have been used with caution.

In addition to these concomitant medications, grapefruit/grapefruit juice consumption was prohibited for the duration of the study.

Allowed medications included the following:

9.4.5.2 Allowed Concomitant Medications

- Sublingual nitroglycerin was permitted for treatment of acute angina.
- Aspirin was permitted during the study.
- Any digitalis preparation (e.g., digoxin) was permitted during the study. However, if a patient received digoxin therapy, serum digoxin levels should have been monitored.
- The use of statins was permitted during the study.
- Background antianginal therapy from either Study CVT 3033 (atenolol, amlodipine, or diltiazem), or Study CVT 3037 (amlodipine [and a long-acting nitrate patch or isosorbide mononitrate if applicable]), at the same dose(s) used in Studies CVT 3033/3037, should have been continued initially in Study CVT 3034. Doses of the background antianginal therapy(ies) may have been increased to maximize the therapeutic effect . At the investigator's discretion, if the angina symptoms were controlled on ranolazine ER plus background antianginal medication(s), and/or if the patient experienced AEs which the investigator felt were attributable to the background antianginal medication(s), the background antianginal medication(s) may have been discontinued in Study CVT 3034 according to the titration dose adjustment scheme outlined previously.

Notes:

- Calcium channel blockers and/or beta-blockers should not have been administered solely as anti-hypertensive therapy
- Calcium channel blockers and/or beta blockers may have been used to treat hypertension ONLY if they were being used as concomitant antianginal medications and were being administered to the patient strictly as outlined in the protocol for concomitant antianginal therapy. Diuretics and angiotensin converting enzyme (ACE) inhibitors may have been administered as anti-hypertensive therapy

Use or changes of any/all concomitant medications were to be documented on the appropriate CRF.

Pharmacokinetic Profiling

Blood samples for the determination of ranolazine trough concentrations were collected approximately 12 h after the last study medication beginning at the first long-term maintenance visit (Visit 3) and at all subsequent maintenance visits (i.e. 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69 and 72 months) after start of the long term Maintenance Phase.

Pharmacokinetic Analysis

The ranolazine trough plasma concentrations data were grouped into time intervals centered around time points every 3 months after start of dosing. Mean, median, 25th percentile, 75th percentile, minimum and maximum trough plasma concentrations of ranolazine for the patients were computed for the above time points.

RESULTS

Demographics of Subjects

The mean age of the patients is 63.1 (±9) years, 76% are males and 99% Caucasians.

Disposition of Subjects

Table 2 Patient Disposition

	Overall n = 1,108
No. of patients who completed treatment	814 (73.5%)
No. of patients who terminated prematurely	294 (26.5%)
Primary reason for premature termination of the study	
Unacceptable adverse event	65 (5.9%)
Non-compliance	5 (0.5%)
Elective withdrawal	122 (11.0%)
Lost to follow-up	13 (1.2%)
Death	65 (5.9%)
Other	24 (2.2%)

Source: Section 14.1.1

Concomitant Medications

The most frequently used concomitant medications were platelet aggregation inhibitors (90 % (e.g. acetylsalicylic acid), organic nitrates (90%, e.g. glyceryl trinitrate and isosorbide mono- and dinitrate), calcium channel blockers (81%, e.g. diltiazem 16%, verapamil 1%), ACE inhibitors (53%, e.g. enalapril) HMG CoA reductase inhibitors (50%, e.g. simvastatin and atorvastatin) and α- and β- blocking agents (47%, e.g. atenolol)

Safety

A summary of the adverse events is given in the below table:

Table 4 Summary of Adverse Events (Includes Ongoing Adverse Events Originating in Studies CVT 3033/3037)

Number of Patients:	Total (n = 1,108)
Any adverse event	678 (61.2%)
Any potentially study drug related adverse event	166 (15.0%)
Discontinued the study due to an adverse event	90 (8.1%)
Any serious adverse event	290 (26.2%)
Death	74 (6.7%)

Source: Section 14.3.1

There were no reports of Torsades de Pointes. No patient met the protocol defined criteria for QTc prolongation (QTc > 500 ms and widening of >130 ms from baseline). Four patients experienced QTc prolongations of > 500 ms at one or more time points.

Pharmacokinetics

Plots of the mean (SD) trough plasma concentrations of ranolazine over time for the 500 mg bid, 750 mg bid and 1000 mg bid regimens are shown in the below 3 figures and the corresponding median and individual maximum ranolazine concentrations at each time point are listed in the below 3 tables:

Figure 5 Mean (+SD) Plasma Ranolazine Concentrations Over Time at Dose 500 mg for CVT 3034

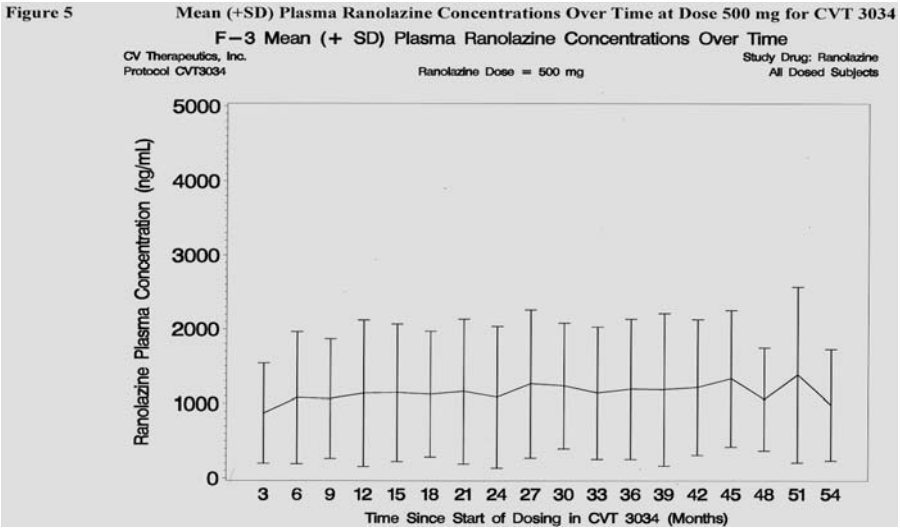


Figure 6 Mean (+SD) Plasma Ranolazine Concentrations Over Time at Dose 750 mg for CVT 3034

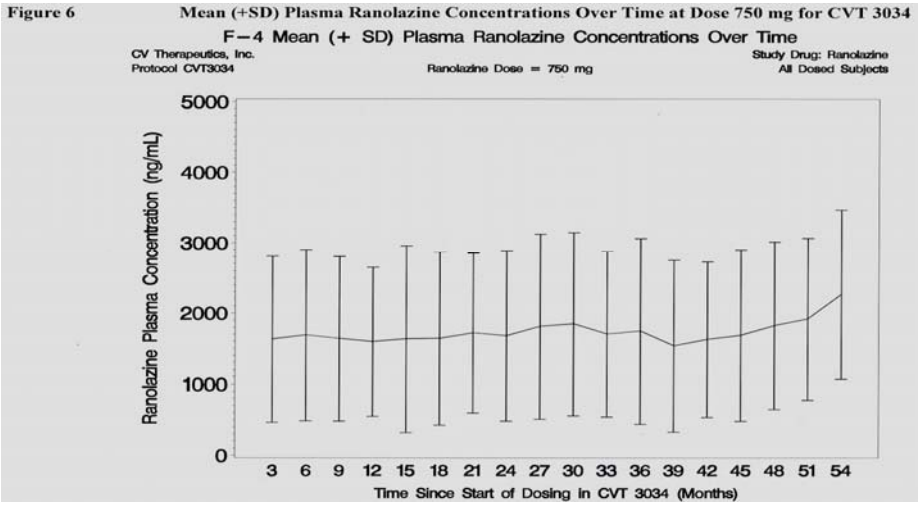
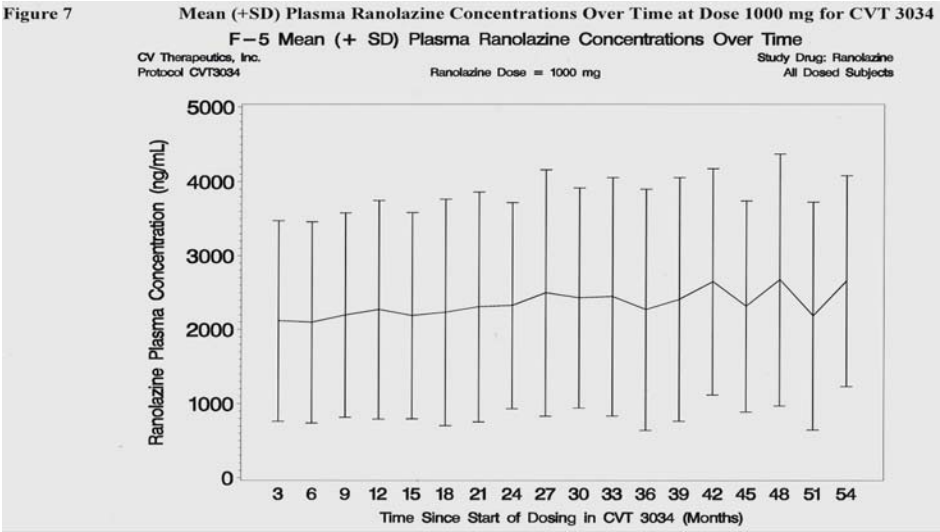


Figure 7 Mean (+SD) Plasma Ranolazine Concentrations Over Time at Dose 1000 mg for CVT 3034



Median Trough and Individual Maximum Trough Plasma Concentrations of Ranolazine During a Regimen with 500 mg bid

Month	n Subjects	Median Trough Concentration ng/mL	Individual Maximum Trough Concentration ng/mL
3	122	805	3900
6	104	948	4340
9	108	800	3690
12	107	952	6340
15	98	941	4730
18	92	1100	5140
21	97	905	4810
24	97	884	5130
27	90	1080	5240
30	89	1110	3740
33	84	996	3740
36	72	988	4150
39	68	1040	5470
42	57	963	4730
45	47	1140	3980
48	36	865	3005
51	13	1290	4560
54	7	965	1930

Median Trough and Individual Maximum Trough Plasma Concentrations of Ranolazine During a Regimen with 750 mg bid

Month	n Subjects	Median Trough Concentration ng/mL	Individual Maximum Trough Concentration ng/mL
3	211	1370	6720
6	222	1450	7200
9	239	1400	6540
12	211	1430	6460
15	208	1320	7210
18	198	1410	6505
21	180	1565	5330
24	163	1470	5750
27	164	1610	8620

30	141	1730	6930
33	128	1445	6380
36	112	1495	6810
39	97	1460	5840
42	87	1450	4450
45	79	1390	6050
48	48	1588	5050
51	30	1890	4540
54	11	2190	4230

Median Trough and Individual Maximum trough Plasma Concentrations of Ranolazine During a Regimen with 1000 mg bid

Month	n Subjects	Median Trough Concentration ng/mL	Individual Maximum Trough Concentration ng/mL
3	202	1930	6590
6	168	1935	6050
9	159	2000	7350
12	170	2265	8430
15	175	2020	7160
18	170	1840	7060
21	180	2170	7870
24	170	2080	5490
27	176	2275	9520
30	167	2230	7530
33	109	2165	7800
36	79	2070	7240
39	73	2390	9580
42	58	2560	6290
45	40	2100	5280
48	23	2650	5660
51	17	2340	4900
54	11	2810	4780

The median and mean trough concentrations as well as the standard deviations show no time dependency, even tough the number of subjects decreased over time. The large values of the standard deviation point to the known significant inter-subject variation of the exposure to ranolazine.

Conclusions

The median trough plasma concentrations measured over a period of 72 months at the 500 mg bid, 750 mg bid and 1000 mg bid levels of ranolazine varied between 800 ng/mL and 1290 ng/mL, 1370 ng/mL and 2190 ng/mL and 1840 ng/mL and 2810 ng/mL, respectively.

Comments

None

4. PARMACOMETRICS REVIEW

NDA	21526
Submission Date(s)	23 September 2007
PDUFA Due Date	23 July 2008
Brand Name	Ranexa®
Generic Name	Ranolazine
Dosage Form	Extended release tablet
Dosage Regimen	500 mg bid increased to 1000 mg bid if needed based on clinical symptoms
Pharmacometrics Reviewer	Nitin Mehrotra, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Clinical Pharmacology Reviewer	Peter Hinderling, M.D.
Clinical Pharmacology Team Leader	Patrick J Marroum, Ph. D.
Sponsor	CV Therapeutics Inc.
Submission Type	NDA Supplement
Proposed indication	Chronic Angina

Executive Summary

The aim of the document is to evaluate if the transition from intravenous infusion to oral dosing in study CVT 3036 resulted in similar exposure of ranolazine in the two dosing periods.

The key question of the present review is:

Did the transition from intravenous infusion to oral extended release formulation resulted in comparable ranolazine plasma levels?

A reasonable population PK model was developed and simulations were conducted both at population and individual level to predict the steady state concentrations after i.v. infusion and compared with observed oral concentrations at steady state. It was seen based on population simulations that the average oral steady state concentrations (calculated based on observed oral data and prior information) were randomly distributed around the mean predicted steady state concentration after i.v. infusion. Similar results were observed after individual level simulations. Thus, it could be concluded that the transition from infusion to oral dosing resulted in comparable exposures.

Recommendation

None

Signatures:

Nitin Mehrotra, Ph.D.	Yaning Wang, Ph.D.
Pharmacometrics Reviewer	Pharmacometrics Team Leader
Office of Clinical Pharmacology	Office of Clinical Pharmacology

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Labeling Statements

There are no relevant statements directly referring to the present population pharmacokinetic analysis and simulations or its implication in the label.

Introduction

Ranolazine (Ranexa®) is approved by the US FDA for the treatment of chronic angina pectoris in combination with amlodipine, β-adrenoceptor antagonists or nitrates in patients who do not respond to other anti-anginals.

Sponsor's Analysis

Study CVT 3036 was conducted to support:

• The use of Ranexa for first-line treatment of chronic angina;

• Reduction of the cautionary language in the Ranexa labeling regarding the observation of QT prolongation; and

(b) (4)

(b) (4)

As part of study CVT 3036 which involved the treatment of ranolazine initiated as a continuous intravenous infusion followed by long term oral administration of the extended release formulation, sponsor developed a population pharmacokinetic model and using simulations showed that the transition from intravenous infusion to oral dosing resulted in comparable exposures of ranolazine.

Population Pharmacokinetics of Ranolazine

Objectives

To evaluate using simulation that the transition from intravenous infusion to oral extended release formulation resulted in similar ranolazine plasma concentrations.

Study Design and Available Data

An i.v. infusion of study drug (ranolazine/placebo) was initiated with 200 mg administered over 1 hour, followed immediately by an 80 mg/h i.v. infusion. The infusion was to be continued for a minimum of 12 hours and up to 96 hours.

The first dose of oral study medication was to be administered prior to termination of the infusion (optimally 1 hour prior to termination); the first dose of oral ranolazine (or matching placebo) was based on the infusion rate at the time of transition, as follows:

Intravenous Dose at Transition	Oral Dose	Preparation
80 mg/h	1000 mg, bid	2 x 500 mg tablet
60 mg/h	750 mg, bid	2 x 375 mg tablet
40 mg/h	500 mg, bid	1 x 500 mg tablet
30 mg/h	375 mg, bid	1 x 375 mg tablet

At selected centers in North America, blood samples were obtained at the following time points for determination of plasma ranolazine levels: 12–16 hours and 24–36 hours after randomization, at the end of the iv infusion, and at trough after oral administration (12 hours after the previous dose) on Day 14 and Month 4.

Of the patients providing pharmacokinetic data, the great majority received the loading infusion of 200 mg over one hour followed by a maintenance infusion of 80 mg/h for approximately 24 hours. Oral doses of 1000 mg bid were thereafter administered throughout the study. A few patients received i.v. infusions of 60 mg/h or 40 mg/h during the maintenance infusion period due to reduced renal function; after the i.v. phase, these patients received oral doses of 750 mg or 500 mg ranolazine bid, respectively.

A total of 220 plasma samples from 112 patients were available for the analysis. In 4 samples, the ranolazine plasma concentration was significantly higher than the rest; these samples were deemed to be outliers and were excluded from the modeling analysis. In addition, 15 samples had duplicate values; the mean data at each time-point were used for the analysis. The final data file included 201 data points from 111 individuals. During the oral dosing period, 273 plasma samples were collected from 132 patients. Of these samples, 22 had no detectable ranolazine concentration, and 1 was deemed as an outlier due to an inordinately high concentration. Six of

the patients were receiving lower ranolazine doses relative to the rest of the group because of low creatinine clearance values; data from these patients were excluded when comparing oral data with the population simulation

Bioanalytical Method

The samples were analyzed using LC/MS/MS validated method (PCB-00-B-M004 amendment 1). The amendment was done to enable use of 96 well plates for extraction and injection as apposed to culture tubes used for sample preparation and HPLC vials for sample injection in the original method. The quantitation limit of the assay was 50 ng/ml with a calibration range of 50-1000 ng/ml. The mean accuracy, expressed as percent relative error ranged between -4.8 and 6% while the precision ranged from 0.7 to 13% across concentrations. The complete details of amendment and the original validated method can be found at \\cdsesub1\evsprod\NDA021526\\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-pcd-00-b-m004\study-pcd-00-b-m004.pdf

Analysis Methods

A mixed effect modeling approach, using NONMEM, version VI ((b) (4)), was used in modeling the i.v. data. During the modeling process, 1- and 2-compartment models were tested. Model selection was based on a drop of 10.8 in the objective function value provided by NONMEM, graphical analysis (using Xpose software), and a predictive check of the model.

The estimated individual i.v. pharmacokinetic parameters were used to simulate an i.v. infusion over the entire study period, which was used to determine the steady-state concentration for each patient. The predicted steady state level during the iv infusion was compared with the observed plasma concentrations after oral dosing at a population and an individual level. In the population simulation, mean population estimates of the iv pharmacokinetic parameters were used to predict the typical concentration-time profile for an iv dosing regimen of 200 mg/h for 1 hour followed by 80 mg/h for over 460 days. This concentration profile was compared with the observed oral administration concentration data from all individuals who received this standard dosing regimen. Results are presented where the predicted steady-state ranolazine plasma concentration levels (with 5th and 95th percentiles) have been extended beyond the actual duration of the i.v.

infusion to facilitate the comparison with the observed concentrations during the oral dosing period. For individual simulations, the empirical bayesian estimates of volume of distribution and clearance were used to simulate the concentration at various time points for which the oral data was available. The difference between simulated infusion concentrations and observed oral concentrations was plotted against individual simulated concentrations.

Results (Sponsor's Analysis)

Population Pharmacokinetics

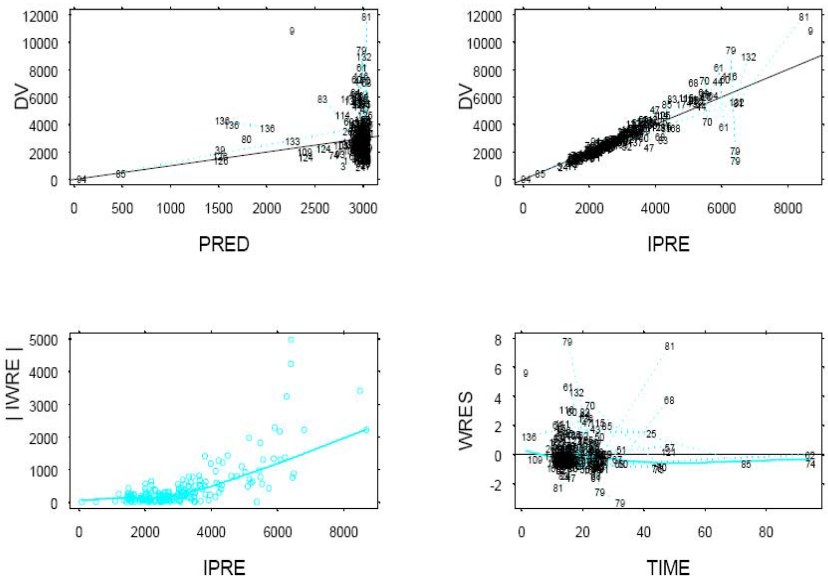
Final Model

The final model was a 1-compartment system with interindividual variability (IIV) in both clearance and volume of distribution parameters, and an exponential error term, using untransformed data. Model parameters are shown in Table 1, and a few diagnostic plots are shown in (Figure 1). A visual predictive check was performed to evaluate the performance of the model (Figure 2).

Table 1: Parameter estimates for the final model.

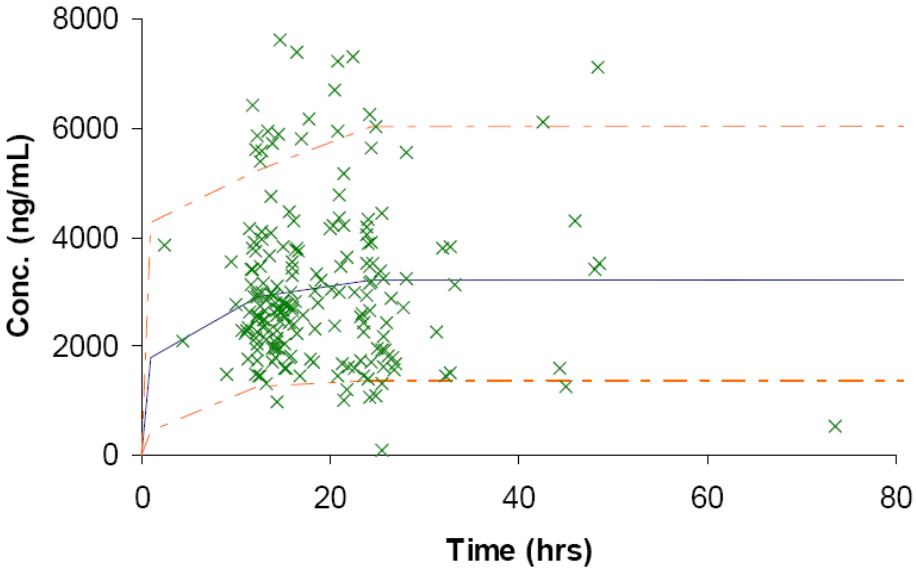
Parameter	Estimate (%RSE)	%Between Subject Variability (%RSE)
Clearance (L/h)	26.3 (5.3)	46 (17)
Volume of distribution (L)	113 (29)	74 (41)
Residual Variability (Proportional Error)	22 (33)	--

Figure 1: Basic goodness of fit diagnostic plots for the Final pharmacokinetic model.



DV = dependent variable (observations), PRED = population prediction, IPRE = individual prediction, IWRE = individual weighted residuals, WRES = weighted residuals

Figure 2: Visual predictive check.



The solid line represents the population prediction, the dashed lines represent the 5th and 95th percentiles. The X's are the observations.

Covariate assessment

No covariate analysis was performed by the sponsor.

Model evaluation

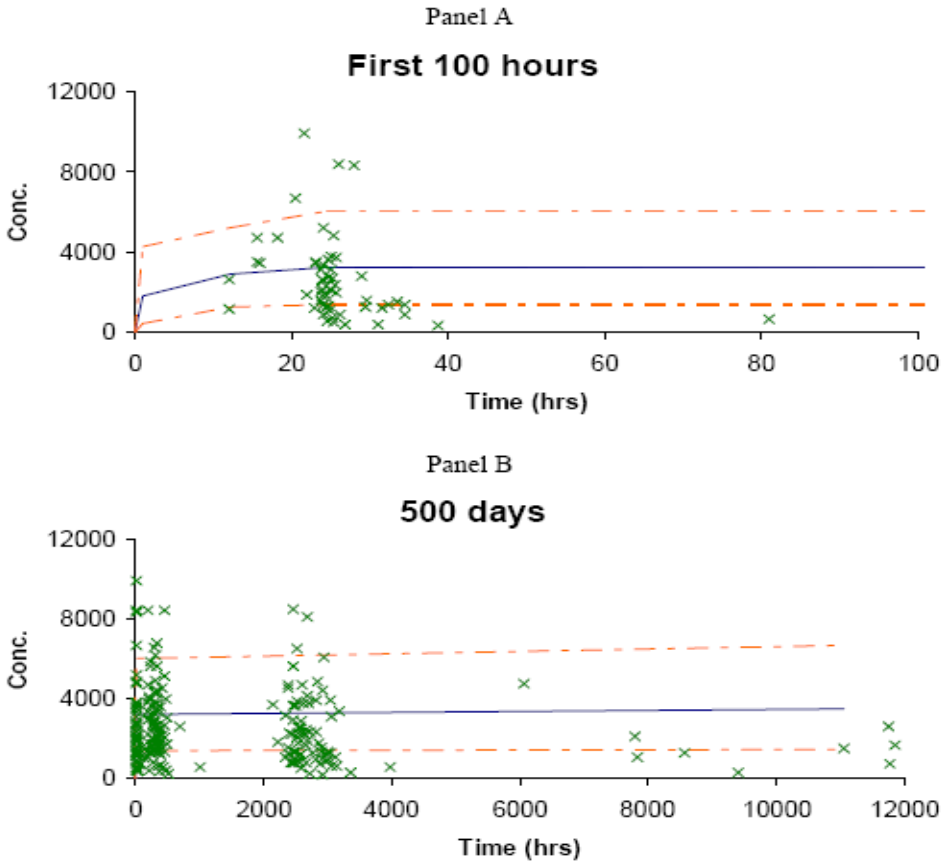
A visual predictive check was performed to evaluate the performance of the model (Figure 2).

Simulation

The simulation results suggest a successful transition from iv infusion dosing to oral dosing, with a majority of the predominantly trough observations during oral dosing falling slightly below the estimated steady state concentrations during the iv phase (Figure 3). The population prediction of the ranolazine concentration at steady-state was 3448 ng/mL, and the arithmetic mean value of all observed concentrations during oral dosing was 2492 ng/mL.

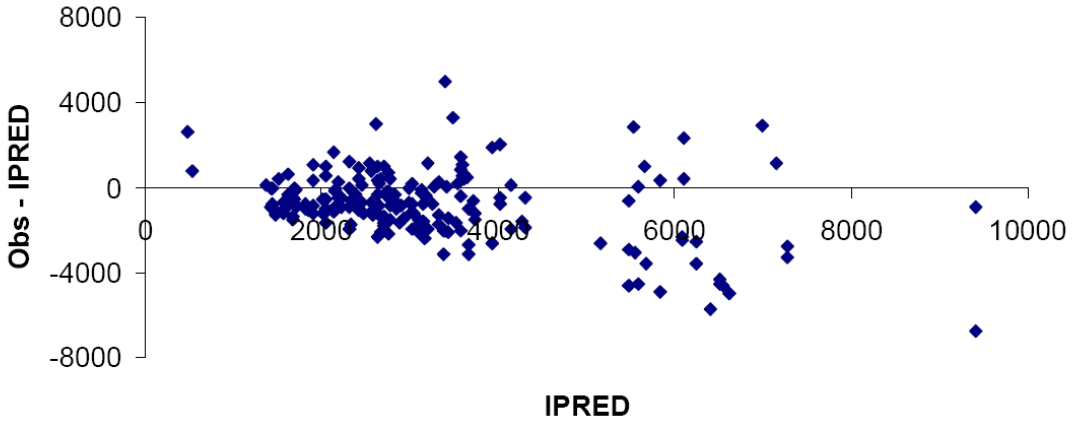
Figure 4 shows individual residuals, i.e. the difference between the actual concentration following oral dosing (oral observation) and the concentration from the simulation of the extended iv infusion (simulated infusion) vs the individual predictions from the simulation. Of the total 201 data points, 151 (75%) are less than 0, while 50 (25%) are greater than 0. The mean deviation between the individually predicted iv steady-state concentration and the observed concentration during the oral phase was −882.

Figure 3: Population Simulation of Intravenous infusion.



Population simulation of iv infusions (200 mg/h for 1 hour followed by 80 mg/h for an extended period of time).
The solid line represents the population prediction, the dashed lines represent the 5th and 95th percentiles. The X's are the observations.
Panel A shows the first 100 hours, and **Panel B** represents a simulated infusion for 500 days.

Figure 4: Individual Residuals (Oral Observation - Simulated Infusion) vs Individual Predictions.



Conclusion

In conclusion, despite a limited number of samples and a rather complex underlying pharmacokinetics of ranolazine, a reasonable i.v. model was developed. The predicted steady state levels were compared with the observed data after oral administration of ranolazine. Study results suggest an adequate transition from the initial i.v. infusion to the long-term oral administration of ranolazine.

Reviewer's comments

The approach of the Sponsor in evaluating the transition from i.v. infusion to oral dosing seems to be reasonable. However, the dataset utilized by the sponsor to build the population PK model was inappropriate. The sponsor had planned to use only intravenous data to build the population model while the dataset (the i.v. infusion dataset) used to develop this model actually includes observations after administration of oral dose. Thus, the reviewer trimmed the dataset to include only those observations after intravenous infusion. The population PK model was re-built with minor modifications, evaluated and population and individual simulations performed again. Furthermore, sponsor compared the predicted intravenous infusion steady state exposures to observed oral trough concentrations which is not a reasonable comparison as trough concentrations would always be lower than the average steady state exposures. Therefore reviewer calculated the average steady state concentrations after oral administration using observed data and prior information, and used these to compare to predicted steady state exposures after i.v. infusion (see simulation for details).

Reviewer's Analysis

Data

Data from 93 patients (114 observations) was used to develop the population PK model such that 80% of patients had only one observation. Considering the sparse nature of the data, it was decided to fix the volume of distribution and it's between subject variability to 110 L (mean population estimate) and 67% respectively which is reported earlier in a population pharmacokinetic analysis.

Analysis Methods

NONMEM VI using FOCE with interaction was utilized to estimate the parameters. One compartment model with interindividual variability in clearance modeled using exponential structure reasonably described the data. Residual variability was also described using exponential error model.

Covariate assessment

Visual inspection of the plots of interindivdual variability in CL (ETA1) vs weight (WT) depicted a clear pattern. Thus, CL was allometrically scaled for weight using power model of 0.75 with weight centered around its median (91.0 kg).

Final Model

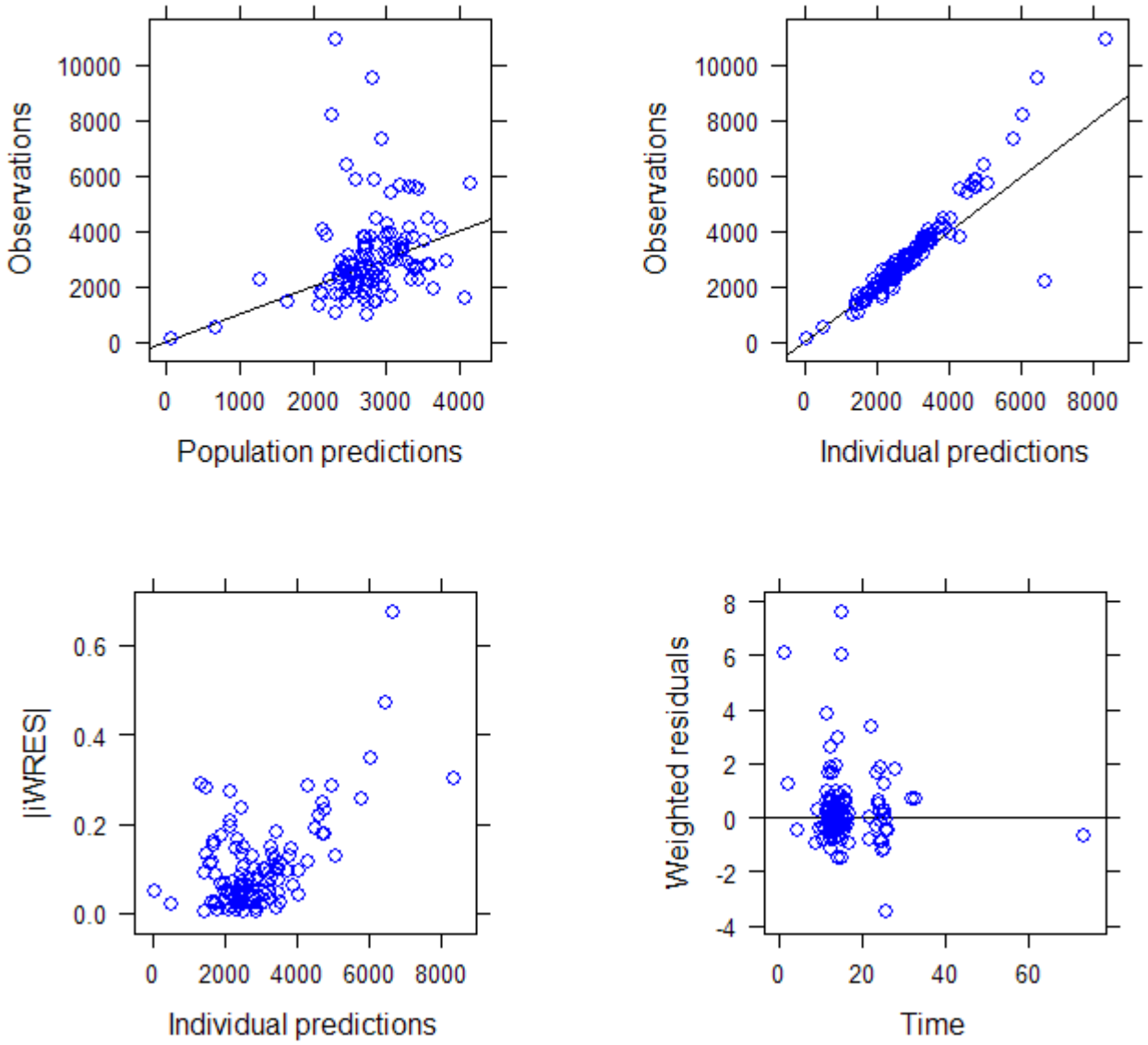
Inclusion of WT as a covariate on CL decreased the objective function by 5.7 and also improved goodness of fit diagnostics (Figure 5).

Moreover, weight was a covariate in the population pharmacokinetic model developed for oral extended release formulation earlier and thus was included in the final model. The final parameter estimates are presented in Table 2 which are similar to sponsor's results (Table 1).

Table 2: Parameter estimates for the Reviewer's final model.

Parameter	Estimate (%RSE)	% Between subject variability (%RSE)
Clearance (L/h)	27.5 (4.4)	37.5 (23.4)
Volume of distribution (L)	110 FIXED	67 FIXED
Residual variability (%) (Exponential Error)	22.4 (48.2)	-

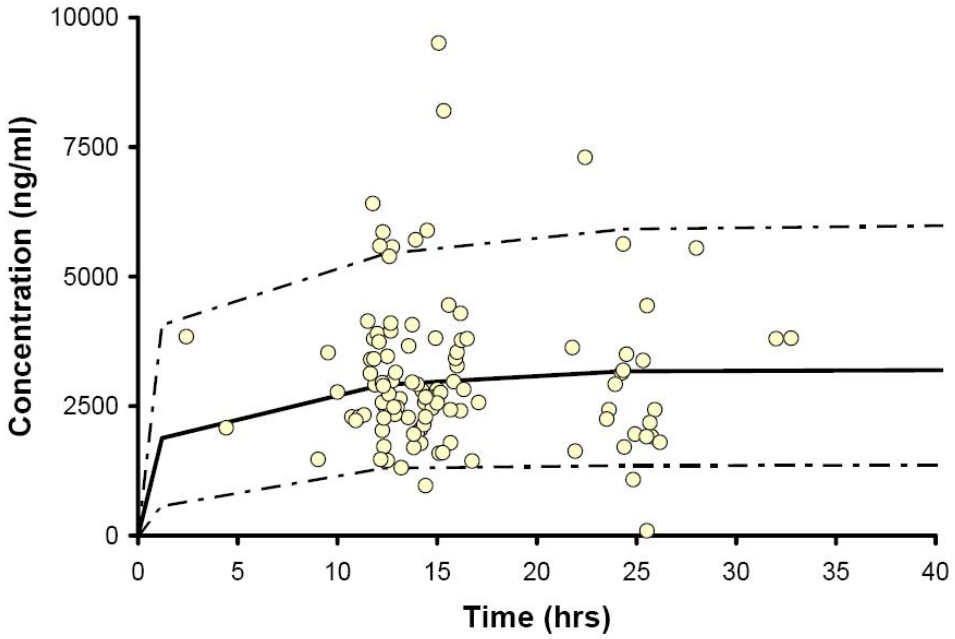
Figure 5: Basic goodness of fit diagnostic plots for the Reviewer's Final pharmacokinetic model. (Solid lines in top two plots represent lines of identity)



Model evaluation

Visual predictive check was performed to evaluate the model which showed that the model provided a reasonable summary of the data in hand (Figure 6).

Figure 6: Visual predictive check (Reviewer's model); Solid line represents the population prediction while dashed lines represent 90% confidence interval; open circles are the observed data available after i.v. infusion.



Simulation

Population and individual simulations were performed in the similar method as described above under Sponsor's Analysis. A factor was calculated as the ratio of the average steady state concentration of ranolazine after 1000 mg bid (obtained from an earlier pharmacokinetic study (RAN0114) to the average (geometric mean) of the observed oral concentrations. All the observed oral concentrations were multiplied by this factor (1.45) to calculate the average steady state concentrations and were used for comparison with predicted steady state exposures after i.v. infusion (Figure 7 and 8).

Figure 7: Population simulation (Reviewer's model); Solid lines represent the population prediction while dashed lines represent 90% confidence interval; open circles are the calculated average steady state concentrations after oral administration based on observed oral data.

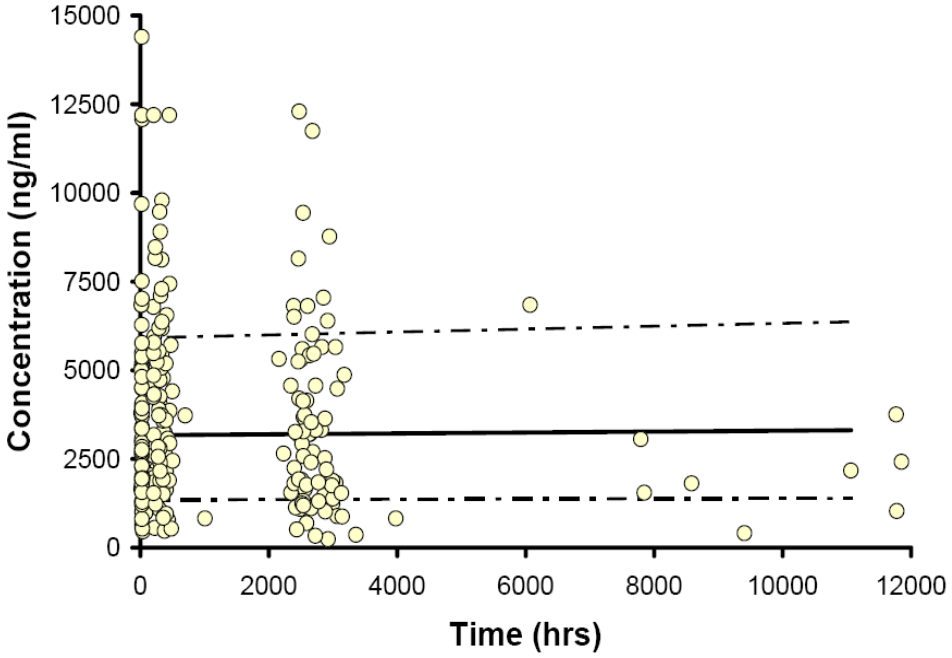
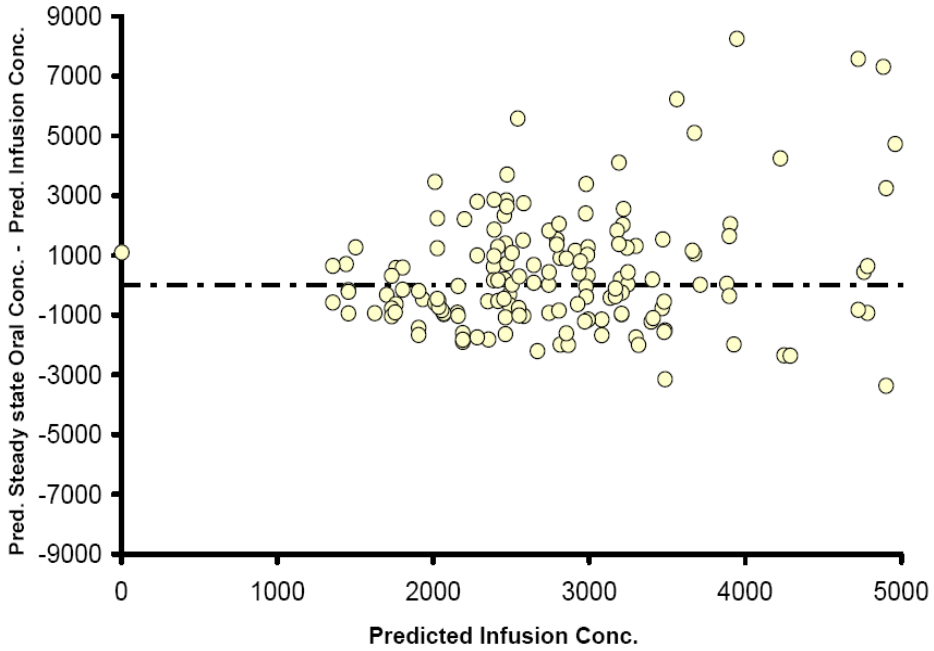


Figure 8: Individual simulation (Reviewer's model); Individual residuals vs predicted concentration after intravenous infusion.



Conclusions

The calculated average steady state concentrations were randomly scattered around mean population predicted steady state concentration after i.v. infusion which is in accordance with individual simulations where approximately 52% of the residuals (Oral-infusion) were more than zero (Figure 7 and 8). Thus, based on these simulation results and also considering higher variability after oral dosing when compared to i.v. infusion, it could be concluded that the transition from i.v. infusion to oral administration resulted in comparable exposures.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	SE 21526	Brand Name	Ranexa
OCPB Division (I, II, III)	I	Generic Name	Ranolazine
Medical Division	DCRP	Drug Class	Antianginal
OCPB Reviewer	Hinderling	Indication(s)	Angina pectoris
OCPB Team Leader	Marroum	Dosage Form	Extended release Tablets
		Dosing Regimen	bid
Date of Submission	September 27, 2007	Route of Administration	oral
Estimated Due Date of OCPB Review	May 1, 2008	Sponsor	CV Therapeutics
PDUFA Due Date	July 27, 2008	Priority Classification	S
Division Due Date	April 20, 2008		

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				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	x	1		

Patients-				
single dose:	x	1		
multiple dose:	x	4		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	1		
In-vivo effects of primary drug:				
In-vitro:	x	1		
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	X	1		
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:		**1**		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:		**1**		
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**5**	**7**		
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 ?	**None**	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**NA**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Peter Hinderling 5-20-08**	
Secondary reviewer Signature and Date	**Patrick Marroum 5-20-08**	

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

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/s/

Peter Hinderling
5/27/2008 11:40:04 AM
BIOPHARMACEUTICS

Nitin Mehrotra
5/27/2008 01:44:43 PM
BIOPHARMACEUTICS

Yaning Wang
5/27/2008 02:58:41 PM
BIOPHARMACEUTICS

Patrick Marroum
5/28/2008 12:28:52 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

Division of Clinical Pharmacology I

NDA 21524 S-004

Type: NDA Supplement
Priority: Standard
Submission Dates: September 27, 2007, December 11, 2008
PDUFA Date: 27 July, 2008
Brand Name: Ranexa
Generic Name: Ranolazine
Dosage Strength: 500 mg and 1000 mg ER tablets
Sponsor: CV Therapeutics
Indications: Chronic Stable Angina
Reviewing Division: Division of Cardiovascular and Renal Products, HFD-110
Reviewers: Peter H. Hinderling, MD
Nitin Mehrotra, Pharmacometrics
Team Leaders: Patrick J. Marroum, Ph.D.
Yaning Wang, Ph.D., Pharmacometrics

Table of Content

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3. Individual Study Reports……..29
4. Pharmacometrics Report……...85

1. EXECUTIVER SUMMARY

The NDA Supplement contained 12 new reports in the Clinical Pharmacology domain: 7 reports including a POPPK analysis reported the results of 6 in vivo studies in humans, 1 report summarized the results from an in vitro study with human liver tissue and 4 reports were assay related. The 7 Clinical Pharmacology reports reported the results from a PK-PD study (CVT-3114) using ranolazine infusions in patients with long QT-3 syndrome, LQT-3; an interaction study (CVT-3119) with diltiazem 180 mg bid co-administered with 500 mg or 1000 mg ranolazine bid in subjects with poor metabolizer (PM) or extensive metabolizer (EM) genotype and phenotype; an ascending dose study with PK information in angina patients (CVT-3023) receiving oral doses of 750 mg, 1500 mg and 2250 mg ranolazine bid; two long term safety studies with measurements of trough plasma concentrations of ranolazine after administration of 750 mg and 1000 mg ranolazine bid (CVT-3032) or 500 mg bid, 750 mg bid and 1000 mg bid ranolazine (CVT-3034); and from an efficacy study CVT-3036 in non-ST elevation (NSTEMI) acute coronary syndrome patients receiving ranolazine initially by intravenous administration followed by oral treatments with ranolazine

375 mg bid, 500 mg bid, 750 mg bid or 1000 mg bid. The POPPK report using sparse sampling information compared the ranolazine levels obtained during the intravenous and oral treatment phases of study CVT-3036.

The 8 reports of the 7 in vivo studies and 1 in vitro study were reviewed. The 4 assay related reports which did not contain relevant new information were not reviewed.

Salient Clinical Pharmacology Findings

Mechanism of Action

The open-label study CVT-3114 in patients with the long QT syndrome (LTQ-3 and ΔKPQ mutation) and continuous influx of sodium through the late (sustained) sodium channel (I_{Na}) showed that ranolazine at therapeutic concentrations decreases QTcF by 25 ms. The finding indicates that ranolazine not only inhibits the rapid inward potassium channel, I_{Kr}, but also I_{Na}, and the inhibition of the latter is greater than that of the former in the patients with LTQ-3.

Pharmacokinetics

The open-label ascending dose study CVT-3023 showed that the tolerability of ranolazine defined by pre-specified endpoints is dose dependent. The incidence of somnolence, confusion/disorientation, symptomatic hypotension, dizziness, nausea, or vomitus increase with dose: 8% with the 750 m bid regimen, 46% with the 1500 mg bid regimen and 75% with the 2250 mg bid regimen. The number of subjects terminated from the study because of an adverse event increases also with dose: 0% with the 750 mg bid regimen, 8% with the 1500 mg bid regimen and 33% with the 2250 mg bid regimen

Two long term open-labeled safety studies with administration of ranolazine 500 mg bid, 750 mg bid or 1000 mg bid in angina patients (CVT-3032 and CVT-3034) and one long term efficacy and safety study with administration of ranolazine 750 mg bid or 1000 mg bid in NSTEMI acute coronary syndrome patients (CVT-3036) measured trough concentrations of ranolazine. In these studies co-administration of calcium antagonists including diltiazem or verapamil was not excluded. In studies CVT-3032 13% and 16% of the subjects received diltiazem and 1.4% and 1.0% verapamil concomitantly with ranolazine. In study CVT-3036 diltiazem and verapamil co-administration occurred in < 2% of the subjects.

The trough plasma concentrations measured in patients with angina in CVT-3032 and CVT-3034 and in patients with NSTEMI acute coronary syndrome in CVT-3036 are shown below:

Comparison of Median Trough and Individual Maximum Trough Plasma Concentrations of Ranolazine in Studies CVT 3032, CVT 3034 and CVT-3036

Study	n Subjects	Dose mg,bid	Plasma Concentration of Ranolazine	
			Median Trough Range	Individual Maximum Trough Range
3032	4-41	750	833-1705	2510- 5925
	16-82	1000	1350- 2000	4230- 10800
3034	7-122	500	800-1290	1930-6340
	11-239	750	1370-2190	4230- 8620
	11-202	1000	1840-2810	4780-9580
3036	92-101	1000*	1510-2030	8410, 8410

*4 subjects received 750 mg bid

The ranges of the median trough concentrations of ranolazine with the 500 and 750 mg bid regimens or the 750 mg and 1000 mg bid regimens are overlapping. Also, the range of the individual maximum trough values in CVT-3032 and CVT-3034 is 2 to 3 fold underlining the marked variability of the plasma concentrations of ranolazine. The trough values of up to 10 000 ng/mL in studies CVT-3032 and CVT-3034 with the angina patients exceed the threshold value of 6000 ng/mL for intolerability determined in CVT-3023.

The large majority of NSTEMI patients in the placebo controlled Phase 3 efficacy and safety study CVT-3036 received a multiple dose regimen of ranolazine 1000 mg bid or placebo that was initiated by intravenous infusion to accelerate attainment of steady-state levels of ranolazine. Less than 2% of the patients had severe renal impairment or were on diltiazem or verapamil and ranolazine. A population PK simulation exercise showed that exposure to ranolazine during the intravenous and oral phases of the regimen is similar (see Pharmacometrics Report p. 85**).**

The open-label study CVT-3114 in healthy subjects genotyped and phenotyped for CYP2D6 polymorphism showed that the exposure to ranolazine at steady-state is significantly greater in PMs than in EMs after 500 mg ranolazine bid. The increased exposure in PMs is associated with an increase in the incidence of adverse events. After 1000 mg ranolazine bid the exposure to ranolazine is not different between PMs and EMs, indicating that the contribution of the CYP 2D6 pathway to the CYP3A dominated metabolic elimination of ranolazine is negligible at the higher dose level.

Co-administration of ranolazine 500 mg bid and diltiazem 180 mg bid increases the exposure to ranolazine by a factor of about 2 in agreement with the results of previous studies. The incidence of adverse events with the co-administration regimen of ranolazine 500 mg bid and diltiazem 180 mg bid appeared to be greater than with ranolazine 500 mg bid alone. Co-administration of ranolazine 1000 mg bid and diltiazem 180 mg is not tolerated by the healthy subjects.

An in vitro study, CVT-303.049N, using human liver microsomes showed that ranolazine at therapeutically effective concentrations does not relevantly inhibit CYP2C8.

Salient Clinical Findings

The efficacy and safety study CVT-3036 in patients with NSTEMI acute coronary syndrome using the composite of time to first occurrence of cardiovascular death, MI, or recurrent ischemia shows that ranolazine is not superior to placebo (standard care) [relative risk ranolazine: placebo= 0.919 (95% confidence interval 0.83, 1.02), p=0.11]. Additional safety related findings were that a) incidence and frequency of symptomatic documented arrhythmias (documented by any form of ECG and resulting in prolongation of hospitalization or being medically important) are not statistically different between ranolazine and placebo; and b) the number of clinically significant arrhythmias during 7-day Holter monitoring in the ranolazine treated patients is lower than in placebo treated patients. These results suggest that ranolazine up to 1000 mg bid despite its QT/QTc prolonging effect does not exhibit pro-arrhythmic activity.

Deficiencies

There are no deficiencies. However, there are issues related to the revised label proposed by the sponsor.

<u>Contraindications</u>

In the present label contraindications for ranolazine include 1) administration of ranolazine to patients with pre-existing QT/QTc prolongation 2) co-administration of ranolazine and QT/QTCc prolonging drugs 3) co-administration of ranolazine with strong and moderate CYP3A inhibitors including diltiazem 4) administration of ranolazine to patients with liver impairment Child-Pugh Class A (mild), B (moderate) and C (severe). (b) (4)

The double-blind, placebo controlled efficacy and safety study CVT-3036 in patients with NSTEMI acute coronary syndrome showed that ranolazine 1000 mg bid is not pro-arrythmic, despite its QT/QTc prolonging effect. However, in study CVT-3036 subjects with pre-existing QT/QTc prolongation, with clinically significant liver disease or on QT/QTc prolonging drugs were excluded. Pertinent other new information was not contained in the submission. (b) (4)

Strong and Moderate CYP3A Inhibitors including Diltiazem

The short term ascending dose tolerability study CVT-3023 in angina patients showed that ranolazine is tolerated in doses up to 1500 mg bid alone. However, study CVT-3031 (MARISA) in the original NDA submission showed an increase in adverse events at dose

levels of Ranexa 1500 mg bid, and the present label states that doses in excess of 1000 mg Ranexa twice daily should not be administered. In agreement with previous studies, study CVT-3119 showed that co-administration of ranolazine 500 mg bid and diltiazem 180 mg bid increases the plasma concentration of ranolazine about 2 fold. Study CVT-3119 also indicated that in PMs of CYP 2D6 the exposure to ranolazine 500 mg bid is only slightly greater than in EMs. In the open label, long term safety study CVT-3034 16% of the subjects received diltiazem in addition to ranolazine with no overt tolerability problems. In the double-blind and placebo controlled efficacy and safety study CVT 3036 patients on strong CYP3A inhibitors or moderate CYP3A inhibitors other than diltiazem or verapamil were excluded from participating in the study. However, co-administration of ranolazine with diltiazem or verapamil, although permitted, occurred in less than 5% of the subjects.

The results from studies CVT-3036 showing an absence of a pro-arrhythmic liability of Ranexa, and from CVT-3031, CVT-3023, CVT-3119 and CVT-3034 and the present label providing quantitative tolerability information, suggest that co-administration of 500 mg ranolazine and 180 mg diltiazem bid is tolerated by a substantial portion of angina patients. Close supervision with ECG monitoring of angina patients in the initial phase of co-administration treatments of Ranexa with diltiazem is recommended. Co-administration of ranolazine in doses greater than 500 mg bid and diltiazem greater than 180 mg remains contraindicated. Co-administration of ranolazine with strong CYP 3A inhibitors or moderate CYP3A inhibitors other than diltiazem remains contraindicated as well. In conclusion, the evidence provided by the sponsor does not justify a removal of contraindication 4, i.e. co-administration of Ranexa with strong and moderate CYP3A inhibitors. However, after ranolazine has been shown not to be pro-arrhythmic, co-administration of the moderate CYP3A inhibitor diltiazem can be justified, because its quantitative impact on the exposure to ranolazine is known from clinical studies. Also known is that Ranexa, a CYP 3A inhibitor, does not affect the pharmacokinetics of diltiazem, a substrate of CYP 3A, when co-administered. Verapamil 120 mg three times a day increases the plasma levels of ranolazine about 2 fold similar to diltiazem. However, the sponsor has not evaluated the possible impact of ranolazine, a CYP3A inhibitor, on the exposure to verapamil, a CYP3A substrate. Thus, the use of Ranexa in patients on verapamil should be avoided. The impact of other moderate CYP3A inhibitors on the exposure to ranolazine is unknown and thus co-administration of Ranexa with moderate CYP-3A inhibitors other than diltiazem remains contraindicated.

Renal Impairment

(b) (4)

1. 1. RECOMMENDATION

From a Clinical Pharmacology view point the submission is acceptable.

2. LABEL

(b) (4)

22 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

3. INDIVIDUAL STUDY REPORTS

3.1. Technical Report CVT 303.049N: In Vitro Evaluation of Ranolazine as an Inhibitor of CYP2C8

Investigator and Study Site

(b) (4)

Objectives

To evaluate the ability of ranolazine to directly inhibit CYP2C8 with the aim to of ascertaining the potential of ranolazine to inhibit the metabolism of other drugs that are substrates of CYP2C8.

Materials and Methods

The study was designed to determine the inhibitory constant (IC50) of ranolazine for direct inhibition of CYP2C8**.** The CYP2C8 activity was measured by determining the 6α-hydroxylation of paclitaxel, a known substrate of CYP2C8. Human liver microsomes from sixteen donated livers were pooled. In initial experiments Km and Vmax of paclitaxel were determined to select

the concentrations of the marker substrate and the incubation conditions. The results are shown in the below table:

Appendix 2: Characterization of the test system

CYP activities in a pool of sixteen individuals

		Pool of sixteen	
		Observed Vmax[a]	Observed Km[a]
Enzyme	CYP Reaction	(pmol/mg protein/min)	(μM)
CYP2C8	Paclitaxel 6α-hydroxylation	570 ± 40	11 ± 2

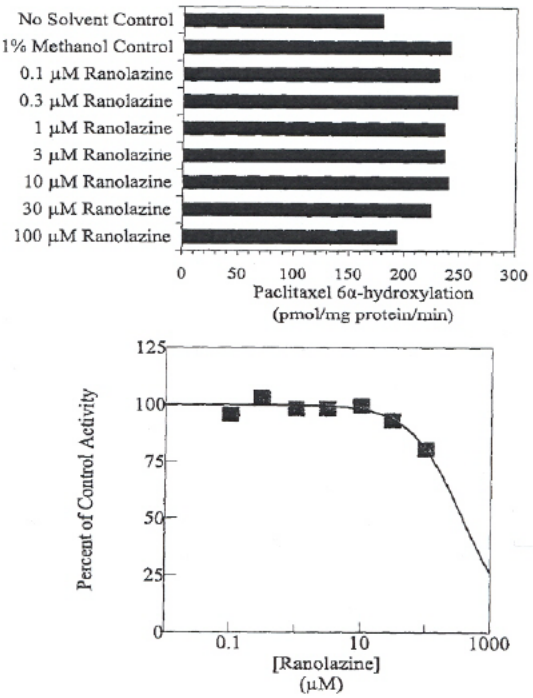
[a] The kinetic constants for the pool of human liver microsomes used for this study were determined in (b) (4) Constants are shown ± standard error (where constants are rounded to two significant figures, and standard errors are rounded to the same degree of accuracy as the constant). They were calculated using the GraFit software, which utilized rates of product formation (triplicate data, with some exceptions) at 13 substrate concentrations. A standard error of 0 indicates the standard error of less than 1% of the mean.

The incubations were conducted at approximately 37° C on 400 μL incubation mixtures (target pH 7.4) containing high purity water, potassium phosphate buffer (50 mM), $MgCl_2$ (3 mM), EDTA (1mM), an NADPH generating system [NADP (1 mM), glucose-6-phosphate dehydrogenase (1 unit/mL)] and marker substrate. Because of a possible binding of ranolazine to protein or lipids, the experiments were designed to keep the microsomal protein concentration low (0.05 mg/mL) and the incubation time short (5min). Under these conditions the rate of reaction was measured under initial rate conditions; i.e. the product formation increased with increased protein concentration and incubation time, such that the percent metabolism of the marker substrate did not exceed 20%. Preliminary experiments conducted at half and twice the normal protein concentration and half and twice the normal incubation period demonstrated linearity of the metabolic rate with protein concentration and incubation time. The incubation concentration of paclitaxel corresponded to the Km value (10 μM). The target concentrations of ranolazine were 0.1, 0.3, 1, 3, 10, 30 and 100 μM. 1% Methanol (4 μL) was used as solvent for ranolazine. Quercetin 20 μM in methanol (0.1% v/v), a known CYP2C8 inhibitor, was used as a positive control. Quercetin inhibited the metabolism of paclitaxel by 90%. Controls were run without solvent and with 1% methanol.
The concentrations of 6α- hydroxy-paclitaxel were measured by a validated HPLC/MS/MS method using (b) (4) as internal standard.

RESULTS

Ranolazine at the highest concentrations tested (100 μM) inhibited the metabolism of paclitaxel by less than 20% (IC50 > 100 μM) as shown in the below figure:

Figure 1: Inhibition of CYP2C8 (paclitaxel 6α-hydroxylation) by Ranolazine: IC50 determination



Parameter	Value	Std. Error
IC50 (μM)	> 100 μM	NA
Slope Factor	NA	NA

Conclusions

Ranolazine at a concentration of 100 μM (44 μg/mL) inhibits CYP2C8 by 20 %. Total (bound+ unbound) trough concentrations of the drug in plasma up to 7 μg/mL have been observed in clinical trials after oral administration of ranolazine. Corresponding peak plasma concentrations were not measured, but can be estimated to be less than 2 fold greater than the trough concentrations Thus, at therapeutic concentrations ranolazine is not expected to impact substrates of CY2C8 in vivo.

Comments

Estimating IC50 based on data with a maximum inhibition of 20 % is not appropriate.

3.2 Report of Study CVT 3114:"An Open Label, Exploratory Study of Ranolazine IV in Subjects with Long QT-3 with the SCN5A ΔPQ Mutation"

Clinical Site and Investigator: (b) (4)

Objectives

Primary: to evaluate the effect of ranolazine to shorten the QTc interval in subjects with long QT-3 syndrome (LQT-3) who have QTc prolongation secondary to the ΔKPQ deletion in the SCN5A sodium channel gene.

Secondary: to evaluate the safety of ranolazine

Study Rationale

The long QT syndrome (LTQS) is a familial genetic disorder characterized by prolonged ventricular repolarization on the ECG and a propensity to syncope, polymorphic ventricular tachycardia (TdP) and sudden death. One of the seven LQTS genes, SN5A, encodes for the cardiac sodium channel; a deletion of the ΔKPQ region within this gene leads to persistent sodium entry into myocardial cells, which results in marked prolongation of ventricular repolarization, manifesting as a prolonged QT interval.

The sponsor claims, based on preclinical data, that ranolazine is a selective inhibitor of the late (sustained) sodium current and has only minimal blocking effect on the peak sodium current during phase 0 of the action potential. If the preclinical data are predictive ranolazine in patients with LQT-3 with the SCN5A ΔPQ mutation should reduce the prolongation of the cardiac repolarization and shorten the QTc interval. Since a persistent sodium current can lead to calcium overload and impairment of cardiac relaxation, the sponsor expects that ranolazine improves LV relaxation.

Investigational Drugs and Formulations

Ranolazine injection formulated at 25 mg/mL and packaged in 20 mL vials was used. Provider and Lot No. of materials are not indicated.

Design

This was an open label, single dose administration, single center, exploratory study. The patients received ranolazine by intravenous infusion for 8 h (at a rate of 45 mg/h for the first 3 h followed by a rate of 90 mg/h for the subsequent 5 h). The 90 mg infusion rate was expected to generate a mean plasma concentration level at the end of the infusion of approximately 2200 ng/mL, a value close to the average trough ranolazine plasma concentration found in the pivotal trials CVT 3031 and 3033 after bid administration of 1000 mg ranolazine extended release tablets. The patients were institutionalized for 4 days. They were admitted to the clinic on Day -2, pre-dose assessments were conducted on Day-1, the drug infusions were administered on Day 1, and the subjects were discharged on Day 2.

For inclusion in the study the patients could be male or female, must be 18-55 years of age,

had a confirmed genotype of LTQ-3 with the ΔKPQ mutation and a QTc> 470 msec. Women of child bearing potential were to have a negative pregnancy test and be willing to use contraceptive drugs or devices.

Subjects receiving sodium channel blockers, inhibitors or inducers of CYP3A or drugs prolonging the QT interval, subjects with significant chronic hepatic impairment (Child-Pugh Class B or C), severe renal impairment (CLcr <30 mL/min), and subjects with a significant co-morbidity precluding safe participation in the study were excluded from the trial.

On Days -1 and 1 twelve lead ECGs were obtained (on Day-1 every 0.5 for 8 h and at 10 and 12 h and on Day 1 pre-dose and at times matched to those obtained on Day-1 and at 24 h). Continuous 12 lead Holter monitoring (for a minimum of 12 h prior to dosing and for a minimum of 24 h on Day 1) was performed. Echocardiograms were obtained in the patients pre-dose and within 30 minutes prior to the end of the ranolazine infusion.The ECG tracings were read during the ranolazine infusions by the attending investigator/cardiologist for purposes of ensuring patient safety. These open-label interpretations were not used in the efficacy analysis. The efficacy analysis used data from the ECG tracings that were interpreted in a blinded manner by (b) (4). (b) (4) was blinded to subject identification and whether the ECG came from the baseline or on-treatment period. (b) (4) (b) (4) was not involved in either patient treatment or the open-label reading of the ECG during the ranolazine infusion.

Efficacy of the ranolazine infusion was measured through ECG parameters including RR, PR, QRS and QT/QTc and T-wave morphology, Holter parameters (QT/RR relationship, QT variability index) and echocardiogram parameters including the systolic parameters: left vetricular ejection fraction (LVEF), stroke volume (SV), systolic mitral annulus velocity (Sa), and the diastolic parameters: left ventricular isovolumic relaxation time (LV IVRT), peak early mitral annulus velocity (mitral E wave velocity) (E), peak transmitral flow velocity during atrial contraction (mitral A wave velocity) (A), early mitral deceleration time (mitral E wave deceleration) (DT) and peak early diastolic mitral annulus velocity (mitral annular velocity) (E')

Pharmacokinetic Profiling

Scheduled blood samples were taken for the measurement of the plasma concentrations of ranolazine pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 h after start of the infusion.

Bioassay

A validated LC/MS/MS method with an internal standard and a calibration range of 50.0 ng/mL-10 000 ng/mL was used. The coefficient of determination for the linear regression is ≥ 0.999. The accuracy ranged between -0.125 and 5.0% and the precision is ≤ 5%.

Statistical Analysis

All patients dosed with ranolazine were included in the statistical analysis. The primary efficacy analysis used a mixed effects linear model applied to the change from time-matched baseline values in Fridericia QTc with a fixed effect for time, accounting for repeated measures within subjects. Secondary efficacy analyses were performed using the same methods for the ECG parameters PR, QRS, Q and T-wave morphology, and for the parameters QT/RR relationship and QT variability index derived from the Holter data. The one sample Student's t-test was used to assess the changes from baseline for the echocardiographic parameters.

The Pearson correlation coefficient between each ECG efficacy variable and ranolazine plasma concentration was computed using all the data from all time points within each subject. The across-subject mean and median values of the correlation coefficient were computed.

RESULTS

Demographics

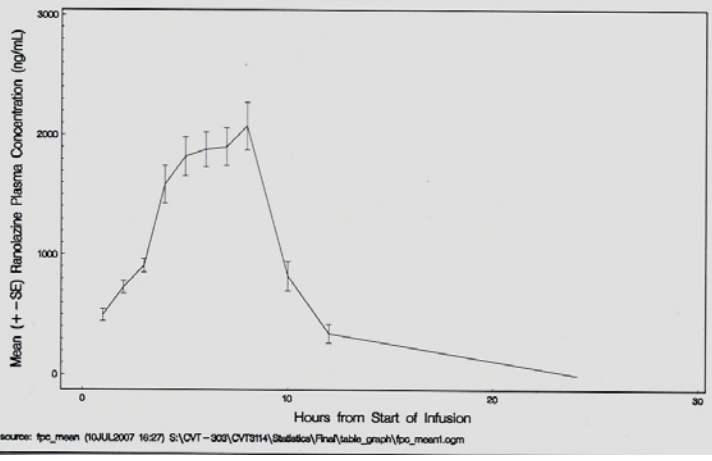
Five Caucasian subjects (4 males, 1 female) in the age range 23 to 55 years enrolled and completed the study. All subjects had a history of LQT-3, 2 had a history of syncope, 2 had an implantable cardioverter/defibrillator and 2 had an atrial pacemaker. Four of the 5 subjects were on nadolol for the treatment of LTQ-3. The patients' median baseline QTc values on Day-1 ranged between 530 and 566 msec.

Results

Pharmacokinetics

The mean plasma concentration profiles of ranolazine are shown in Figure 1 below:

Figure 1 **Mean Ranolazine Plasma Concentrations over Study Nominal Time Points**



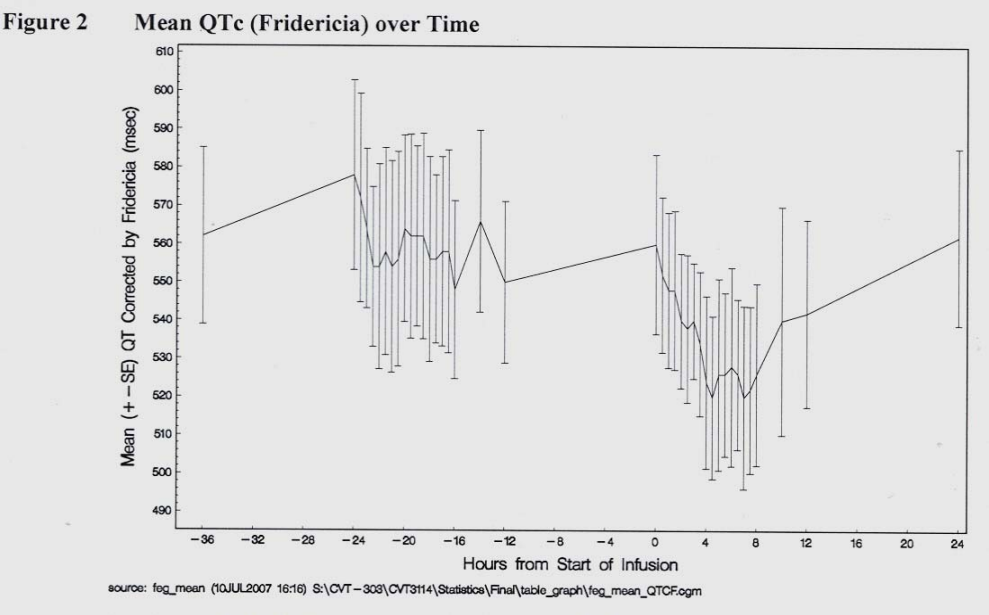
The results indicate that the plasma concentrations of ranolazine after 3 h and 8 h were approximately 900 ng/ml and 2100 ng/mL, respectively, levels that were similar to the mean

trough concentrations observed in the pivotal trials CVT 3031 and 3033 in the target angina population receiving 500 mg and 1000 mg ranolazine extended release tablets bid, respectively.

Pharmacodynamics

The heart rate during the infusion changed from baseline on average by 0.9 (0.54) bpm.
The slope of plots of the QTcF intervals against the RR intervals at baseline are not different from zero indicating that heart rate correction of QT according to Fridericia is appropriate.

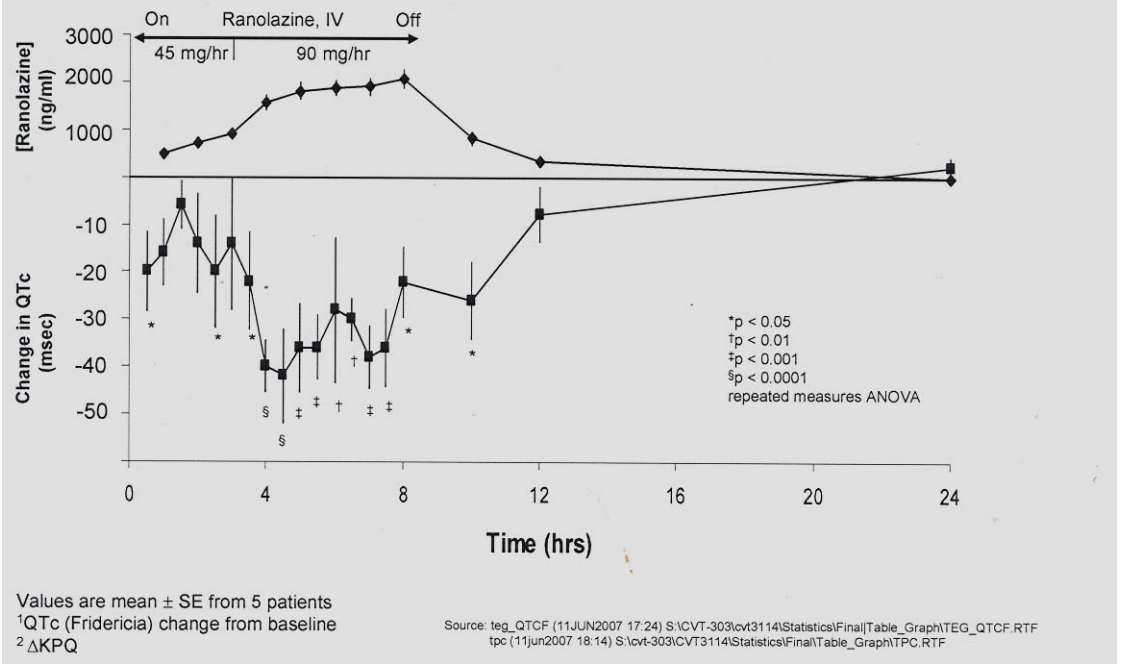
The mean QTc F interval durations at baseline and during ranolazine infusion are shown in Figure 2:



The data suggest that the Friderician QTc intervals on Day 1 during the ranolazine infusion were shorter than the time matched QTc intervals on Day -1. All the mean Fridericia QTc intervals during the ranolazine infusion were statistically significantly shorter than the time matched baseline values. On Day 1 during the initial 3 h infusion period when ranolazine was infused at a rate of 45 mg/h the Fridericia QTc intervals were longer than those observed during the subsequent 5 h infusion period when ranolazine was administered at a rate of 90 mg/h.

Figure 3 shows the effect of ranolazine on QTc and the simultaneously measured plasma concentrations:

Figure 3 Profile over Time of Plasma Ranolazine Concentrations and Changes from Time-Matched Baseline in QTc Interval[1] in LQT3 Subjects[2]



A summary of the median effects of ranolazine on the ECG intervals is shown below:

ECG Interval	Number Subjects Evaluated	Median Overall Change from Baseline, ms		
		Overall during 8 h Infusion	3 h after Infusion Start	8 h after Infusion Start
PR	3	4	20	-10
QRS	5	1	0	0
T	5	-16	0	10
QTc	5	-25	-20	-30

The median change in the interval duration from the time matched baseline was consistent for the QTc interval and indicated a shortening effect of ranolazine. The median change in QTc from the time matched baseline during the initial 3 h of the infusion and the subsequent 5 h of infusion ranged between - 60 ms and 20 ms and -40 ms and 0 ms, respectively. There was a statistically significant correlation between the change in QTc from time matched baseline and the ranolazine plasma concentration (r=0.7 (0.22)). There was a trend for a shortening of the T-interval during the infusions, but the measurements showed more variability. The median change in T wave duration (uncorrected for heart rate) in the subjects 3 h and 8 h after start of the infusion ranged between -40 ms and 30 ms and -20 ms and 40 ms, respectively. The T-wave amplitude appeared

not to be impacted by ranolazine. Also, ranolazine appeared not to affect the QRS or PR interval. However, it should be noted that the latter interval was only evaluable in 3 of the 5 subjects (2 patients had atrial pacemakers). These results suggest that ranolazine does not affect conduction velocity.

Pharmacokinetics-Pharmacodynamics

There is a statistically significant linear regression of QTc on the ranolazine plasma concentrations measured during the 8 h infusion.

The results on the echocardiographic variables are summarized in Table 3:

Table 3 Echocardiographic Resting Left Ventricular Function

Parameter	Mean ± SD		
	Baseline (n=5)	End of Ranolazine Treatment (n=5)	Change from Baseline (n=5)
Systolic Function			
LVEF (%)	62.4 ± 7.80	59.8 ± 4.60	−2.6 ± 3.21
SV (mL)	79.4 ± 24.84	77.6 ± 26.52	−1.8 ± 10.03
Sa (cm/sec)	9.8 ± 1.25	8.6 ± 0.96	−1.2 ± 1.35
Diastolic Function			
LV IVRT (msec)	125.4 ± 27.36	108.6 ± 35.35	−16.8 ± 9.68*
E (cm/sec)	56.6 ± 7.64	70.8 ± 9.07	14.2 ± 10.69*
A (cm/sec)	50.0 ± 9.90	62.6 ± 12.28	12.6 ± 15.57
E/A	1.2 ± 0.33	1.2 ± 0.26	0.0 ± 0.43
DT (msec)	288.8 ± 79.63	226.2 ± 33.99	−62.6 ± 88.43
E′ (cm/sec)	7.9 ± 3.61	8.7 ± 3.42	0.8 ± 0.91

*Change from baseline statistically significant ($p<0.05$)

Key to acronyms: LVEF = LV ejection fraction; SV = stroke volume; Sa = systolic mitral annulus velocity; LV IVRT = LV isovolumic relaxation time; E = peak early mitral annulus velocity (mitral E wave velocity); A = peak transmitral flow velocity during atrial contraction (mitral A wave velocity); DT = early mitral deceleration time (mitral E wave deceleration time); E′ = peak early diastolic mitral annulus velocity (mitral annular velocity)

Source: Appendix 17 (and a by subject listing of echocardiogram data are provided in Appendix 18)

At the end of the infusion the mean left ventricular iso-volumic relaxation time was 13 % shorter and the peak early transmitral flow velocity increased by 25% compared to the corresponding pre-dose baseline values indicating improved diastolic relaxation. Both differences were statistically significant.

Conclusions

In patients with LTQ-3 syndrome there is a continuous influx of late I_{Na} resulting in a major prolongation of the QTc interval in the absence of drugs. In patients without LQT-3 syndrome ranolazine has been shown to prolong the QTc interval by blocking I_{Kr}.

The present study was not placebo controlled. It assessed the effects of ranolazine in patients with LTQ-3 due to SCN5A ΔPQ mutation by comparing the QTc interval duration and diastolic relaxation at baseline and during ranolazine infusion. The respective plasma concentrations of

ranolazine attained at the end of the first and second infusion were similar to the trough concentrations observed in the pivotal trials when angina patients received 500 mg and 1000 mg extended release tablets bid orally.

The present study shows that the net effect of ranolazine at antianginal effective concentrations is a shortening of the QTc interval in patients with LQT-3. However, treatment with ranolazine does not normalize the QTc interval duration in the LQT-3 patients. The shortening of the QTc interval is correlated with the plasma concentrations of ranolazine. The PR and QRS intervals appear not to be impacted by ranolazine. The shortening of the QTc interval appears to be mainly due to ranolazine's impact on the latter part of the QTc interval (T wave and ST-segment) in accordance with an effect on late I_{Na}. The drug's potency of blocking the late I_{Na} current appears to be greater than that of blocking I_{Kr} in patients with LQT-3. Ranolazine also increases diastolic relaxation in patients with LQT-3 as evidenced by the shortened left ventricular isovolumic relaxation time and increased mitral E wave velocity.

Overall the data support the sponsor's claim that ranolazine at therapeutic concentrations inhibits the late I_{Na+} and improves diastolic relaxation in patients with LQT-3. The relevance of the ECG findings in patients with LTQ-3 syndrome for patients with angina is uncertain. The relevance of the echocardiographic findings in the subpopulation studied would be increased if the sponsor could demonstrate diastolic relaxation of ranolazine in the angina population at the 500 mg and 1000 mg bid levels. Also, demonstration of a correlation between the respective effects on the QTc interval and diastolic relaxation in patients with the LQT-3 syndrome could be helpful in supporting the proposed hypothesis that ranolazine's effect on the late I_{Na} is the primordial action of the drug.

Comments

- The report does not state whether the reader of the echocardiogram was blinded
- The RR interval durations should be added to the summary statistical tables and individual data tables
- The duration of the ECG intervals is reported up two digits after the comma. How can this precision be justified?
- Provider and Lot No. of the ranolazine injected are not indicated

3.3 Study Report CVT 301-19:" A Phase 1, Multiple Dose, Fixed Sequence, Cross-Over, Open Label Study to Evaluate the Effect of Diltiazem 180 mg bid on the Pharmacokinetics, Safety and Tolerability of Ranolazine ER in Healthy Male and Female Subjects with Poor (PM) and Extensive (EM) Metabolizer Genotype for CYP2D6"

Study Investigator and Site

(b) (4)

Background

Ranolazine is predominantly eliminated by non-renal elimination which includes metabolism mainly by CYP3A and partly by CYP2D6. The metabolism mediated by CYP 3A appears to be linear whereas the CYP 2D6 catalyzed metabolism is nonlinear. Ranolazine has been shown to be an inhibitor of CYP2D6.

Objectives

Primary: to evaluate the effect of diltiazem (DLT) 180 mg bid at steady-state on the PK parameters of ranolazine (RAN) 500 mg bid at steady-state in subjects with PM and EM genotypes for CYP2D6

Secondary: 1) to evaluate the PK parameters of RAN 500 mg bid and 1000 mg bid administered alone in subjects with PM genotype for CYP2D6 as compared to subjects with EM genotype; 2) to evaluate the PK parameters of RAN 500 mg bid after the addition of DLT 180 mg bid in subjects with PM genotype for CYP2D6 as compared to the change in subjects with EM genotype; and 3) to evaluate the PK parameters of the metabolites CVT-2512, CVT-2514 and CVT-2738 after administration of RAN 500 mg bid and 1000 mg bid alone and co-administered with DLT 180 mg in subjects with PM and EM genotypes for CYP2D6

Investigational Drugs and Formulations

Film coated ER tablets containing 500 mg ranolazine (Lot Nos. 3H3026 and A18050) were supplied by the sponsor. (b) (4) supplied the diltiazem hydrochloride 90 mg tablets (Tildiem Retard, Sanofi-Sythelabo) (Lot No.:25013) and 7.5 mg in 5 mL dextrometorphan hydrobromide (Robitussin Dry Cough Medicine) (Lot No. 385097).

Design

This was an open-label, multiple dose, cross-over study involving up to 52 healthy male and female volunteers. The treatment phase of the study was to last for 15 days (from the morning of Day 1 to the morning of Day 15) during which subjects were to remain institutionalized in the clinical unit. Starting on the morning of Day 1 and continuing until the morning of Day 4, subjects were to receive an oral dose of RAN 500 mg bid. Starting on the evening of Day 4 and continuing until the morning of Day 8, subjects were to receive RAN 1000 mg bid. Starting on the evening of Day 8, and continuing until the morning of Day 15, subjects were to receive RAN 500 mg bid. Subjects were also to receive an oral dose of DLT 90 mg on the evening of Day 8 and on the morning of Day 9. On the evening of Day 9 until the morning of Day 15, subjects were to receive DLT 180 mg bid. The study ended when the last subject had completed his/her

last study site visit and a 14 day follow-up contact. Originally, the study was designed to include an additional treatment period lasting from the evening of Day 15 to the morning of Day 22, during which subjects were to receive RAN 1000 mg bid concomitantly with DLT 180 mg bid. The protocol was amended after 10 subjects (7 with EM genotype and 3 with PM genotype) had completed the study through Day 22 and 6 subjects (5 with EM genotype and 1 with PM genotype) had withdrawn from the study between Days 15-22. These 16 subjects were considered evaluable under the amended protocol.

The drugs were administered together with 250 mL water. Mouth checks were performed after the drugs were administered to assure that they had been swallowed. Breakfast, lunch, and dinner were to be provided at approximately 1 h, 5 h, and 10 h, respectively, post morning dose.

Subjects were to be classified as EMs or PMs based on their CYP2D6 genotypes. The allele variants *3, *4, *5, and *6, were to be tested that together allow for identification of > 97% of PMs in a predominantly Caucasian population. A dextrometorphan phenotyping test was to be administered prior to initiation of ranolazine to detect possible additional PMs with other allele variants, as well as ultra-rapid metabolizers with gene duplication.

Steady-state for RAN is generally attained within 3 days with a continuous bid regimen. The highest RAN plasma concentrations were predicted not to exceed 8000-10 000 ng/mL, a range that was attained in previous studies with co-administration of RAN and ketoconazole or in a study in which RAN was administered alone by intravenous infusion.

The protocol contained the following precautionary measures: because of the known QTc prolongation associated with administration of RAN subjects with a history of, or risk factors for QTc prolongation were excluded from the study. The ECG was monitored at schedule times throughout the study. A stopping rule of 500 msec for a QTc reading on a single ECG, based on automatic ECG interpretation in conjunction with Investigator interpretation, was to be implemented if necessary. Repeat ECGs were allowed to confirm the measurement if required.

DLT is known to increase the PR interval. During the dose escalation phase of DLT a 12 Lead ECG was to be performed prior to each dose and the following criteria applied:

- If the PR interval was between 120-200 msec the next dose was given
- If the PR interval was greater than 200 msec, but less than 220 msec, the finding was noted and the next scheduled dose given
- If the PR interval was greater than 220 msec, the subject was withdrawn from the study and received no additional doses of DLT

The presence of second degree heart block (Wenckebach (Mobitz I), Mobitz II, or high grade block) constituted a withdrawal criterion.

Prior and concomitant administration of the following drugs was prohibited:

- Class IA anti-arrhythmics (e.g., quinidine)
- Class III anti-arrhythmics (e.g., sotalol, dofetilide)
- Phenothiazide anti-psychotics (e.g., chlorpromazine, mesoridazine, pimozide, thoridazine)
- Quinolone antibiotics (e.g., gatifloxacin, moxifloxacin, sparfloxacin)
- Others: droperidol, mefloquine, pentamidine, levomethadyl, dolasetron, systemic dosing of tacrolimus, arsenic trioxide, terfenadine, astemizole, cisapride
- Other drugs that have a contraindication or boxed warning regarding QT prolongation in the prescribing information

Apart from diltiazem issued as per protocol, medications which affect CYP3A were not allowed; they included, but were not limited to the following:

- Erythromycin, clarithromycin, and troleandomycin
- Ketoconazole and itraconazole (topical agents were permissible)
- Nefazadone
- Protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, saquinavir)
- Diltiazem
- Verapamil

In addition, the following medications and foods were not allowed:

- Agents known to inhibit P-glycoprotein
- Beta blockers
- Calcium antagonists
- Alcohol was not permitted during the 48 h prior to the Screening Visit and was also not permitted from the 48 h prior to admission (Day-1) through discharge from the clinical unit.
- Subjects may not have been smokers who smoked more than five cigarettes per day and must have abstained from smoking as of midnight prior to admission and throughout the residential treatment period
- Caffeine containing products were not permitted during the residential phase of the study
- Grapefruit, grapefruit juice, and grapefruit-containing products, Seville oranges or marmalade, were prohibited within 2 weeks prior to admission through the end of the study

Allowed concomitant medications included the use of multivitamins, paracetamol (maximum 2 g/day), HRT/hormonal contraception and stable thyroxine replacement therapy. Other drugs that did not fall under what is described above may have been allowed if they were judged not to interfere with the objectives of the study.

The inclusion and exclusion criteria applied are listed below:

9.3.1 Inclusion Criteria

To be eligible for enrollment, subjects had to satisfy the following requirements:

- Subject was male or female aged 18 to 70 years, inclusive
- Subject provided a signed informed consent form and patient information sheet
- *For female subjects only:* Subjects must have been post-menopausal or sterilized, or if of childbearing potential, not breastfeeding, have a negative pregnancy test, with no intention of becoming pregnant during the course of

the study, and using adequate contraceptive drugs or devices (defined as usage of any form of hormonal contraception or intra-uterine device, plus usage by at least one of the partners of an additional barrier method of contraception e.g., condoms, spermicide)

- *For male subjects only:* Subjects with female partners of child bearing potential must have been taking adequate contraceptive precautions (defined as usage by the female partner of any form of hormonal contraception or intra-uterine device, plus usage by at least one of the partners of an additional barrier method of contraception e.g., condoms, spermicide)
- Subject's general practitioner (GP) was informed of subject's planned participation in the study
- Subject's body weight was ≥ 60 kilograms
- Subject's body mass index (BMI) was between 18–30 kg/m^2 inclusive
- Subject had no current or past medical history of clinical significance and the Screening Visit physical examination was either normal or revealed no clinically significant abnormalities, including vital signs within the normal ranges (measured supine after 5 min, HR: 45 to 90 bpm; systolic BP: 100 to 140 mm Hg; diastolic BP: 50 to 90 mm Hg. Standing after at least 5 min, HR: 50 to 100 bpm; systolic BP: 100 to 160 mm Hg; diastolic BP: 50 to 90 mm Hg)
- Subject's 12-lead ECG at the Screening Visit was normal, without evidence of conduction or repolarization abnormalities, including a sinus bradycardia less than 45 bpm or any degree of heart block. Other changes should have been deemed not clinically significant by the Investigator.
- Subject's QTc interval at Screening Visit was ≤ 450 msec, as measured by automatic ECG reading, in conjunction with Investigator interpretation
- Subject experienced no clinically significant arrhythmias during approximately 24-h continuous Holter ECG monitoring at the Screening Visit
- Subject's Screening Visit clinical laboratory findings were within the normal range or, if outside the normal range, were not considered clinically significant in the opinion of the Investigator
- Subject was willing and able to comply with the requirements of the protocol and follow directions from the clinic staff

9.3.2 Exclusion Criteria

Subjects were not to be enrolled if any of the following were true:

- Subject had a clinically significant illness in the 4 weeks prior to the Screening Visit at which informed consent was given
- Subject was currently taking any regular prescribed or over-the-counter medication, or was using prescribed or over-the-counter medications in the 2 weeks prior to dosing (with the exception of the following: multi-vitamins, the occasional use of paracetamol [maximum 2 g/day], contraceptive pill, HRT/hormonal contraception, and stable thyroxine replacement therapy)
- Subject had significant history of drug/solvent abuse, or a positive drugs of abuse test
- Subject had a history of alcohol abuse, currently drank in excess of 28 units of alcohol per week if male or 21 units per week if female, or had a positive alcohol breath test (ABT)
- Subject currently smoked more than five cigarettes or equivalent per day, and if otherwise eligible would not have been able to abstain from smoking from midnight prior to admission and throughout the residential session
- Subject was planning to consume grapefruit juice or grapefruit-containing products, Seville oranges or marmalade, from 2 weeks prior to admission to the clinical unit until the end of the study
- Subject was, in the opinion of the Investigator/GP, not suitable to participate in the study
- Subject used any experimental or investigational drug or device within 90 days prior to the first day of dosing
- Subject had a positive result at the Screening Visit for HIV, Hepatitis B, or Hepatitis C
- Subject had history of allergy or hypersensitivity to ranolazine, diltiazem, dextromethorphan or related drugs
- Subject previously had a serious adverse reaction or hypersensitivity to any drug
- Subject had donated blood within the 3 months prior to the Screening Visit
- Subject had any individual or family history of QT prolongation or cardiomyopathy, including a family history of sudden cardiac death
- Subject was a vegetarian or had significantly changed his/her diet in the 2 months prior to the Screening Visit or intended to change his/her diet during the study

The scheduled study activities are shown in the below schemes:

Table 1 Schedule of Events

	Screening	Admit	Treatment Period										
Day of Period	-21 to -1	-1	1	2	3	4	5	6	7	8	9	10	11
Procedures													
Written Informed Consent	X												
Demographic Data	X												
Medical History	X												
Physical Examination[a]	X	X											
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and Weight	X												
12-lead ECG[c]	X	X	X			X				X	X	X	X
Clinical Laboratory Blood and Urine Samples[d]	X	X								X			
Virology	X												
Drugs of Abuse Screen	X	X											
Alcohol Breath Test	X	X											
Urine Pregnancy Test	X	X											
Inclusion/Exclusion	X	X											
Ranolazine Administration[e]			X	X	X	X	X	X	X	X	X	X	X
Diltiazem Administration[f]										X	X	X	X
Dextromethorphan Dose		X											
Urine Sampling[g]		X	X										
PK Blood Sampling[h]			X	X	X	X	X	X	X	X	X	X	X
Holter Monitoring	X									X	X	X	X
Adverse Events/Con Meds[i]	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] A physical examination will be performed at the Screening Visit, on admission and at discharge (Day 15 or Day 22, for Amendment 1 and original protocol, respectively)

[b] Vital signs (supine and standing BP and pulse) will be performed at: the Screening Visit, on admission, on Days 1, 4, 8, 15, 22 (if applicable) at 0, 1, 2, 4, 6, 8, 12 h; Days 2, 3, 5, 6, 7, 9, 10, 11, 12, 13, 14, and Days 16-21 (if applicable) at 0, 4, 8, 12 h; and at follow-up.

[c] ECGs will be performed at: the Screening Visit, on admission, on Days 1, 4, 8, 15, 22 (if applicable) at 0, 1, 2, 4, 6, 8, 12 h; Days 9, 10, 11, 12, 13, 14, and Days 16-21 (if applicable) at 0, 4, 8, 12 h; and at follow-up.

[d] Clinical lab blood and urine samples will be collected at the Screening Visit, on admission, at Day 8, and at discharge (Day 15 or Day 22, for Amendment 1 and original protocol, respectively)

[e] Subjects will receive ranolazine twice daily from the morning of Day 1 until the morning of Day 15 or Day 22, for Amendment 1 and original protocol, respectively.

[f] Subjects will receive diltiazem in the evening of Day 8, in the morning of Day 9 and thereafter twice daily until the morning of Day 15 or Day 22, for Amendment 1 and original protocol, respectively.

[g] Urine samples will be collected cumulatively following dextromethorphan administration on Day –1 until 30 minutes prior to dosing ranolazine administration in the morning of Day 1.

[h] PK samples for ranolazine analysis will be taken on: Day 1, 2, 3 at 0 and 12 h (pre-dose); Days 4, 8, 15, 22 (if applicable) at 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 h (full PK profile) and Days 5, 6, 7, 9, 10, 11, 12, 13, 14, and Days 16-21 (if applicable), with the trough sample taken prior to evening dose at 12 h.

[i] Adverse events were to be collected starting on Day 1

Table 1 Schedule of Events (Cont'd)

	Treatment Period											Follow up
Day of Period	12	13	14	15	16	17	18	19	20	21	22	Follow up
Procedures												
Physical Examination[a]				X							X	
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X
Height and Weight												
12-lead ECG[c]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Blood and Urine Samples[d]				X							X	X
Virology												
Drugs of Abuse Screen												
Alcohol Breath Test (ABT)												X
Urine Pregnancy Test												X
Inclusion/Exclusion												
Ranolazine Administration[e]	X	X	X	X	X	X	X	X	X	X	X	
Diltiazem Administration[f]	X	X	X	X	X	X	X	X	X	X	X	
PK Blood Sampling[g]	X	X	X	X	X	X	X	X	X	X	X	
Holter Monitoring	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events/Con Meds	X	X	X	X	X	X	X	X	X	X	X	X

NB: Shaded columns apply only to subjects enrolled in the original protocol and not Amendment 1.

[a] A physical examination will be performed at the Screening Visit, on admission and at discharge (Day 15 or Day 22, for Amendment 1 and original protocol, respectively)

[b] Vital signs (supine and standing BP and pulse) will be performed at: the Screening Visit, on admission, on Days 1, 4, 8, 15, 22 (if applicable) at 0, 1, 2, 4, 6, 8, 12 h; Days 2, 3, 5, 6, 7, 9, 10, 11, 12, 13, 14, and Days 16-21 (if applicable) at 0, 4, 8, 12 h; and at follow-up.

[c] ECGs will be performed at: the Screening Visit, on admission, on Days 1, 4, 8, 15, 22 (if applicable) at 0, 1, 2, 4, 6, 8, 12 h; Days 9, 10, 11, 12, 13, 14, and Days 16-21 (if applicable) at 0, 4, 8, 12 h; and at follow-up.

[d] Clinical lab blood and urine samples will be collected at the Screening Visit, on admission, at Day 8, and at discharge (Day 15 or Day 22, for Amendment 1 and original protocol, respectively)

[e] Subjects will receive ranolazine twice daily from the morning of Day 1 until the morning of Day 15 or Day 22, for Amendment 1 and original protocol, respectively.

[f] Subjects will receive diltiazem in the evening of Day 8, in the morning of Day 9 and thereafter twice daily until the morning of Day 15 or Day 22, for Amendment 1 and original protocol, respectively.

[g] PK samples for ranolazine analysis will be taken on: Day 1, 2, 3 at 0 and 12 h (pre-dose); Days 4, 8, 15, 22 (if applicable) at 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 h (full PK profile) and Days 5, 6, 7, 9, 10, 11, 12, 13, 14, and Days 16–21 (if applicable), with the trough sample taken prior to evening dose at 12 h.

Safety

Safety was evaluated by collecting AE, identification of serious adverse events, clinical laboratory results, vital signs, physical examination and scheduled 12-Lead ECG measurements. Continuous Holter recordings were obtained from Day 8 through the end of the treatment period (Days 15 or 22), divided into approximate 24 h intervals and evaluated for the occurrence of arrhythmias (b) (4)

Pharmacokinetic Profiling

RAN

Blood samples for the determination of RAN and the metabolites CVT-2514, CVT-2512 and CVT-2738 were collected on:

Days 1, 2 and 3: pre morning (0 h) and evening dose (12 h)
Days 4, 8, 15, 22: pre morning dose, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 h (full profile) after the morning dose
Days 5, 6, 7, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21: pre-evening dose (12 h)
At the time of a clinically significant AE and early withdrawal or discontinuation (if applicable)

Dextrometorphan

A dose of 30 mg dextrometorphan was administered to the subjects on the evening of Day -1. Total urine volumes were collected for a 12 h period starting from the time of dextrometorphan administration and ending approximately 30 min prior to dosing with RAN in the morning of Day 1. The urine pH was to be kept constant by excluding other factors, such as food, during the collection period.

Bioassay

Ranolazine

The plasma concentrations of RAN and the metabolites CVT-2512, CVT-2514 and CVT-2738 were measured by a LC/MS/MS method. The calibration curve is linear for RAN in the range between 50.0-10000 g/mL and the metabolites in the range between 10.0 -2000 ng/mL. The respective correlation coefficients for standards are ≥ 0.998, ≥ 0.995, ≥ 0.996 and ≥ 0.995 for RAN, CVT 2512, CVT 2514 and CVT 2738, respectively. Mean accuracy for RAN ranges between 1.63% and 2.00% and the precision is ≤ 10.6%. Mean accuracy for CVT-2512 ranges between -3.75% and 3.00 % and the precision is ≤ 7.77%. Mean accuracy for CVT-2514 ranges between -4.38% and 5.50% and the precision is ≤ 10.0%. Mean accuracy for CVT-2738 ranges between -5.63% and 5.50 % and the precision is ≤ 10.2%.

Dextrometorphan/Dextrorphan

The report does not indicate the methods used to determine dextrometorphan and dextrorphan and the laboratory performing the assays.

Pharmacokinetic Data Analysis

Cmax, tmax, Cmin, and AUC0-12 were determined for RAN, CVT-2514, CVT-2512 and CVT-2738 using non-compartmental methods. Cmax, tmax and Cmin were obtained directly from the observed concentration time data. AUC 0-12 was obtained by application of the linear trapezoidal rule. The primary parameters for evaluation were Cmax and AUC0-12. WinNonlin Professional (Version 5.0.1 (Pharsight Corporation)) was used.

Pharmacodynamic Data Analysis

All 12-Lead ECGs were to be evaluated for the RR, PR QRS and QT intervals and heart rate. Baseline for each parameter was defined as the average of values measured on Day -1 (admission) and Day 1. Change in each ECG parameter from baseline was calculated for each ECG recording during 0-12 h after the morning dose on the PK profiling Days (Days 4, 8, 16, and 22)

Statistical Analysis

Ranolazine plasma level C_{max} and AUC_{0-12} were transformed for analysis using the natural logarithm. All mean effect estimates and their associated confidence intervals in the log scale were back-transformed to the original scale.

Log-transformed C_{max} and AUC_{0-12} were analyzed using a mixed effects analysis of variance (ANOVA) model with fixed effects for CYP2D6 metabolizer genotype (EM or PM), concomitant administration of diltiazem (present or absent), ranolazine dose (500 mg bid or 1000 mg bid), all two-way interactions of these factors, and the three-factor interaction, and a random effect for subject.

For the primary objective, the ANOVA model was used to estimate the mean effect of diltiazem administration on C_{max} and AUC_{0-12} for the RAN 500 mg bid dose in subjects with PM and EM genotype for CYP2D6, using the least squares-estimated mean difference between ranolazine plus diltiazem and ranolazine alone. The effect of diltiazem was tested for significance using the ANOVA model, and a 90% confidence interval for the treatment effect was provided.

For secondary objective no. 1, the ANOVA model was used to estimate the difference between genotypes in log-transformed C_{max} and AUC_{0-12} following ranolazine alone for each ranolazine dose. For each dose, a 90% confidence interval was estimated and back-transformed to the original scale to provide a confidence interval for the ratio.

For secondary objective no. 2, the ANOVA model was used to estimate the difference between genotypes in the diltiazem vs no-diltiazem differences in log-transformed C_{max} and AUC_{0-12} for the RAN 500 mg bid dose. A 90% confidence interval was estimated and back-transformed to the original scale to provide a confidence interval for the ratio.

For secondary objective no. 3, the same ANOVA model will be applied to the C_{max} and AUC_{0-12} of each of the metabolites CVT-2512, CVT-2514, and CVT-2738, and to the ratio of the AUC_{0-12} for each metabolite to the AUC_{0-12} of ranolazine. The least square mean and its 90% confidence interval of each were described using the ANOVA model.

The parameter t_{max} was analyzed using nonparametric methods. The Wilcoxon signed rank test was used to compare t_{max} in the presence and absence of diltiazem within each combination of genotype and ranolazine dose.

Summary statistics were provided for PK parameters of ranolazine and each of the metabolites CVT-2512, CVT-2514, and CVT-2738 for each combination of genotype, diltiazem administration, and ranolazine dose. Descriptive statistics included the arithmetic mean, geometric mean, SD, %CV, median, minimum, and maximum.

- The statistical analysis methods were updated to correspond to changes in the study design and objectives.
  - For the primary objective, the ANOVA model was to be used to estimate the mean effect of diltiazem administration on C_{max} and AUC_{0-12} for the RAN 500 mg bid dose in subjects with PM and EM genotypes for CYP2D6, using the least squares-estimated mean difference between ranolazine plus diltiazem and ranolazine alone.
  - For secondary objective no. 2, the ANOVA model was to be used to estimate the difference between genotypes in the diltiazem vs no diltiazem differences in log-transformed C_{max} and AUC_{0-12} for the RAN 500 mg bid dose.
- C_{min} was excluded from all analyses.

Sample Size

Based on variability information from a previous study of ranolazine in renally impaired patients (Study CVT 3016), the cohort sizes of 8 evaluable subjects with PM genotype and 8 evaluable subjects with EM genotype, and the use of 90% confidence intervals provide 80% power to conclude that the difference between genotypes in ranolazine AUC_{0-12} is no greater than 36% and in C_{max} no greater than 60%, if in fact there is no effect of genotype on either parameter. If genotype does have an effect, the sample size of 8 subjects with PM genotype and 8 subjects with EM genotype provides 80% power to detect a difference of 42% for AUC_{0-12} and 70% for C_{max} using two-sided tests at the 5% significance level. These differences are below the levels that are considered clinically meaningful. For the purpose of the PK comparison between subjects with PM and EM genotypes, an evaluable subject was defined as one who had completed the Day 15 morning dose with RAN 500 mg bid + DILT 180 mg bid and associated PK sampling.

RESULTS

Demographics

The demographic details of the participating subjects are shown in the below table:

Table 3 Demographic Details for All Dosed Subjects

Variable Mean (SD)	Poor Metabolizer (N = 12)	Extensive Metabolizer (N = 19)
Age (yrs)	34.7 (13.1)	34.1 (11.0)
Range	19–55	20–59
Gender		
Male	9 (75%)	19 (100%)
Female	3 (25%)	0
Race		
Asian	0	2 (11%)
Black	0	1 (5%)
Caucasian	12 (100%)	16 (84%)
Hispanic	0	0
Other	0	0
Height (cm)[a]	171.7 (10.6)	176.0 (7.9)
Weight (kg)[b]	75.7 (14.1)	76.3 (7.2)
BMI (kg/m^2)[a]	25.6 (2.5)	24.7 (2.2)

[a] PM: N = 10; EM: N =14 [b] PM: N = 11; EM: N =14

Disposition of Subjects

Thirty-three (33) adult subjects enrolled in the study; 21 had EM genotype and 12 had PM genotype. All subjects classified as genotypic PMs displayed a dextrometorphan/dextrorphan ratio of >0.3, and all subjects classified a genotypic EMs had a dextrometorphan/dextrorphan ratio <0.3. Thus, there was agreement between phenotype and genotype determinations.

The disposition of the PMs and EMs is shown in the below 2 schemes:

Table 2 Subject Disposition

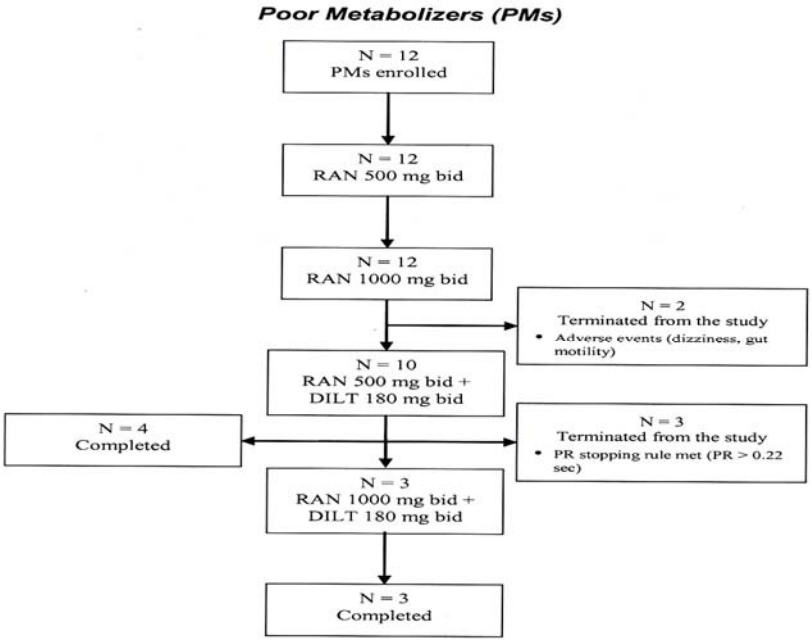
	Poor Metabolizer				Extensive Metabolizer			
	RAN 500 mg bid		RAN 1000 mg bid		RAN 500 mg bid		RAN 1000 mg bid	
	Without DILT (N = 12)	With DILT (N = 10)	Without DILT (N = 12)	With DILT (N = 3)	Without DILT (N = 19)	With DILT (N = 17)	Without DILT (N = 18)	With DILT (N = 12)
No. of subjects completed treatment	12 (100%)	7 (70%)	10 (83%)	3 (100%)	18 (95%)	12 (71%)	17 (94%)	7 (58%)
No. of subjects terminated early	0	3* (30%)	2 (17%)	0	1 (5%)	5 (29%)	1 (6%)	5** (42%)
Primary reason for early termination								
Adverse event	0	0	2 (17%)	0	1 (5%)	2 (12%)	1 (6%)	3 (25%)
PR > 0.22 sec	0	3 (30%)	0	0	0	3 (18%)	0	0
QTc > 500 msec	0	0	0	0	0	0	0	2 (17%)

* One subject, withdrawn from the original protocol on Day 15 after the morning dose, was eligible for inclusion in the PK analysis population as described in Amendment 1.

** Since completion of the RAN 1000 mg bid + DILT 180 mg bid treatment period was not required by Amendment 1, all five of these subjects were eligible for inclusion in the analysis population.

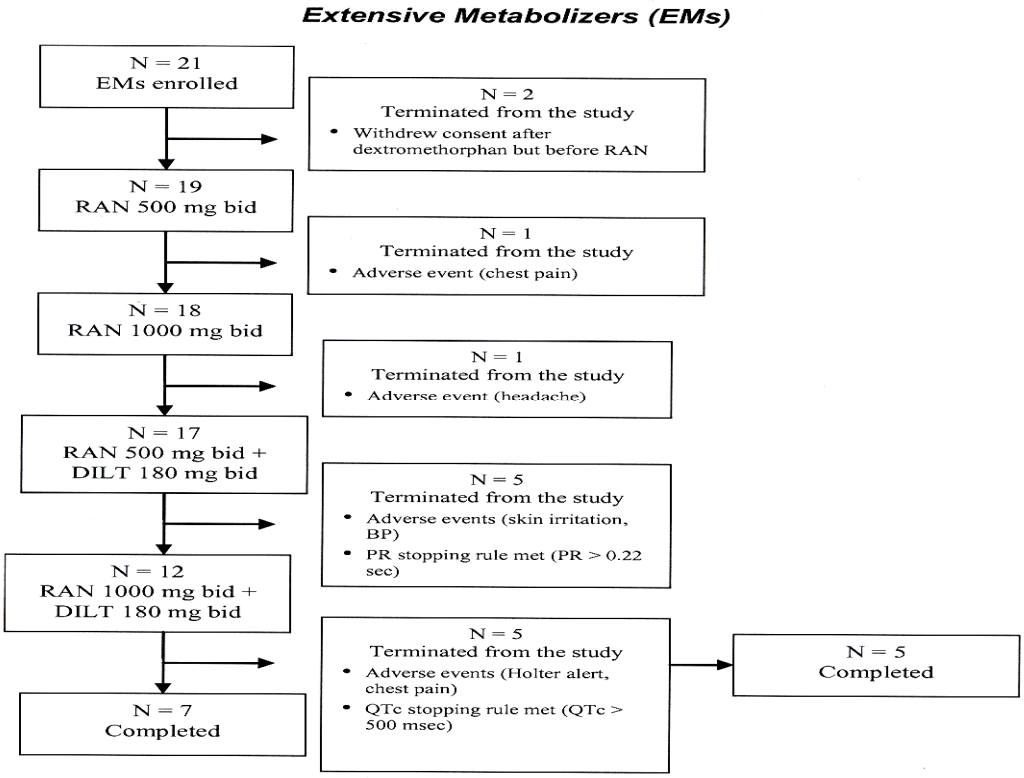
Derived from Section 14.1.1

Figure 1 Subject Disposition



The seven subjects who completed the RAN 500 mg bid + DILT 180 mg bid arm of the study and one subject who withdrew due to PR interval prolongation after the morning dose on Day 15 are included in the PK analysis population.

Figure 1 Subject Disposition (Cont'd)



The 12 subjects who completed the RAN 500 mg bid + DILT 180 mg bid arm of the study are included in the PK analysis population.

PM

Of the 12 PMs enrolled, 4 completed the 500 mg and 1000 mg RAN alone treatments and the 500 mg RAN + 180 mg DLT co-administration treatment and 5 were terminated (2 during the 1000 mg RAN regimen and 3 during the 500 mg RAN + 180 mg DLT regimens. All 3 subjects receiving 1000 mg RAN + 180 mg DLT completed the study.

EM

Of the 21 EMs enrolled in the study 5 completed the 500 mg RAN-, the RAN 1000 mg-, and the 500 mg RAN + 180 mg DLT treatments, 2 subjects were terminated from the study prior to receiving the first treatment with 500 mg RAN alone, 1 subject during treatment with RAN 500 mg alone, 1 subject during treatment with 1000 mg RAN alone and 5 subjects during treatment with RAN 1000 mg + 180 mg DLT. Of the 12 subjects receiving the 1000 mg RAN + 180 mg DLT regimen, 7 completed the study and 5 were terminated. The reasons for early termination are explained in the below table:

Table 11 Reasons for Early Termination

Subject No.	Reason for Termination	AEs or Stopping Criteria for which Drug Was Withdrawn	Last Treatment Administered
Poor Metabolizers			
1913	AE	Diarrhea, palpitations, upper abdominal pain, chest pain, headache, leg tremor, hyperhidrosis	RAN 1000 mg bid
1918	AE	Dizziness, headache	RAN 1000 mg bid
1917	Stopping criteria reached	PR > 0.22 sec	RAN 500 mg bid + DILT 180 mg bid
1927[a]	Stopping criteria reached	PR > 0.22 sec	RAN 500 mg bid + DILT 180 mg bid
1928	Stopping criteria reached	PR > 0.22 sec	RAN 500 mg bid + DILT 180 mg bid
Extensive Metabolizers			
1903	AE	Application site erythema at Holter sticker site	RAN 500 mg bid + DILT 180 mg bid
1909	AE	Headache, arthralgia, neck pain	RAN 1000 mg bid
1910	AE	Hypertension	RAN 500 mg bid + DILT 180 mg bid
1914[a]	AE	Ventricular tachycardia	RAN 1000 mg bid + DILT 180 mg bid[b]
1922[a]	AE	Ventricular tachycardia	RAN 1000 mg bid + DILT 180 mg bid[b]
1923[a]	AE	Chest pain	RAN 1000 mg bid + DILT 180 mg bid
1924	AE	Chest pain	RAN 500 mg bid
1904	Stopping criteria reached	PR > 0.22 sec	RAN 500 mg bid + DILT 180 mg bid
1911	Stopping criteria reached	PR > 0.22 sec	RAN 500 mg bid + DILT 180 mg bid
1915	Stopping criteria reached	PR > 0.22 sec	RAN 500 mg bid + DILT 180 mg bid
1902[a]	Stopping criteria reached	QTc > 500 msec	RAN 1000 mg bid + DILT 180 mg bid
1916[a]	Stopping criteria reached	QTc > 500 msec	RAN 1000 mg bid + DILT 180 mg bid

Derived from Section 16.2.11.

[a] Terminated early under the original protocol, but completed the requirements under Amendment 1 and are included in the PK analysis population.

[b] AE occurred while subject was on RAN 500 mg bid + DILT 180 mg bid

Note: Subjects 1912 and 1926 withdrew consent after receiving dextromethorphan for CYP2D6 phenotyping, but prior to dosing with ranolazine

The table indicates that 9 subjects (2 PMs and 7 EMs) were prematurely discontinued because of an AE and 8 subjects were withdrawn due to meeting a stopping criterion specified in the protocol.

Safety

An overview of the AEs and a summary of the most frequent AEs are provided by the below 3 tables:

Table 9 Overview of Adverse Events

	Poor Metabolizer				Extensive Metabolizer			
	RAN 500 mg bid		RAN 1000 mg bid		RAN 500 mg bid		RAN 1000 mg bid	
	Without DILT (N = 12)	With DILT (N = 10)	Without DILT (N = 12)	With DILT (N = 3)	Without DILT (N = 19)	With DILT (N = 17)	Without DILT (N = 18)	With DILT (N = 12)
No. of subjects with AEs	10 (83%)	8 (80%)	10 (83%)	3 (100%)	8 (42%)	17 (100%)	12 (67%)	11 (92%)
No. of AEs	23	41	48	22	23	67	26	43
No. of subjects with causally-related AEs	9 (75%)	6 (60%)	10 (83%)	3 (100%)	7 (37%)	12 (71%)	10 (56%)	6 (50%)
No. of subjects prematurely withdrawn due to AEs	0	0	2 (17%)	0	1 (5%)	4 (24%)	1 (6%)	1 (8%)
No. of subjects with SAEs	0	0	0	0	0	0	0	0

SOURCE: tae_overview (27MAR2007 15:08) S:\CVT-303\CVT301-19\Statistics\Final\Table_Graph\TAE_OVERVIEW.RTF

Table 10 Summary of Most Frequent* Adverse Events

	Poor Metabolizers				Extensive Metabolizers			
	RAN 500 mg bid		RAN 1000 mg bid		RAN 500 mg bid		RAN 1000 mg bid	
Organ System Class/ Preferred Term	Without DILT (N = 12)	With DILT (N = 10)	Without DILT (N = 12)	With DILT (N = 3)	Without DILT (N = 19)	With DILT (N = 17)	Without DILT (N = 18)	With DILT (N = 12)
Number of Subjects with AEs	10 (83%)	8 (80%)	10 (83%)	3 (100%)	8 (42%)	17 (100%)	12 (67%)	11 (92%)
Cardiac Disorders								
Palpitations	0	1 (10%)	1 (8%)	1 (33%)	0	1 (6%)	0	1 (8%)
Gastrointestinal Disorders								
Constipation	0	1 (10%)	0	1 (33%)	0	2 (12%)	0	0
Flatulence	1 (8%)	2 (20%)	2 (17%)	1 (33%)	1 (5%)	1 (6%)	1 (6%)	0
Nausea	2 (17%)	1 (10%)	1 (8%)	0	0	4 (24%)	3 (17%)	0
General Disorders & Administrative Site Conditions								
Application Site Dermatitis	0	0	0	0	0	2 (12%)	0	3 (25%)
Application Site Erythema	0	4 (40%)	1 (8%)	1 (33%)	0	6 (35%)	0	4 (33%)
Application Site Irritation	0	1 (10%)	0	0	1 (5%)	2 (12%)	0	1 (8%)
Application Site Reaction	0	0	0	0	0	2 (12%)	0	2 (17%)
Chest Pain	1 (8%)	0	2 (17%)	1 (33%)	1 (5%)	4 (24%)	0	4 (33%)
Fatigue	1 (8%)	2 (20%)	1 (8%)	2 (67%)	2 (11%)	1 (6%)	0	0
Feeling Hot	1 (8%)	0	0	1 (33%)	0	0	0	1 (8%)
Injury, Poisoning and Procedural Complications								
Contusion	0	0	0	0	0	2 (12%)	1 (6%)	1 (8%)
Nervous System Disorders								
Dizziness	3 (25%)	3 (30%)	5 (42%)	1 (33%)	0	2 (12%)	2 (11%)	1 (8%)
Dizziness Postural	3 (25%)	0	5 (42%)	1 (33%)	1 (5%)	3 (18%)	3 (17%)	1 (8%)
Headache	1 (8%)	1 (10%)	4 (33%)	1 (33%)	4 (21%)	9 (53%)	6 (33%)	3 (25%)
Lethargy	0	0	0	0	0	0	0	2 (17%)
Paresthesia	1 (8%)	3 (30%)	0	0	0	1 (6%)	0	0
Sensory Disturbance	0	1 (10%)	1 (8%)	0	0	1 (6%)	0	0
Skin & Subcutaneous Tissue Disorders								
Pruritus	0	2 (20%)	1 (8%)	0	0	0	0	0
Rash	0	1 (10%)	0	0	0	1 (6%)	0	1 (8%)

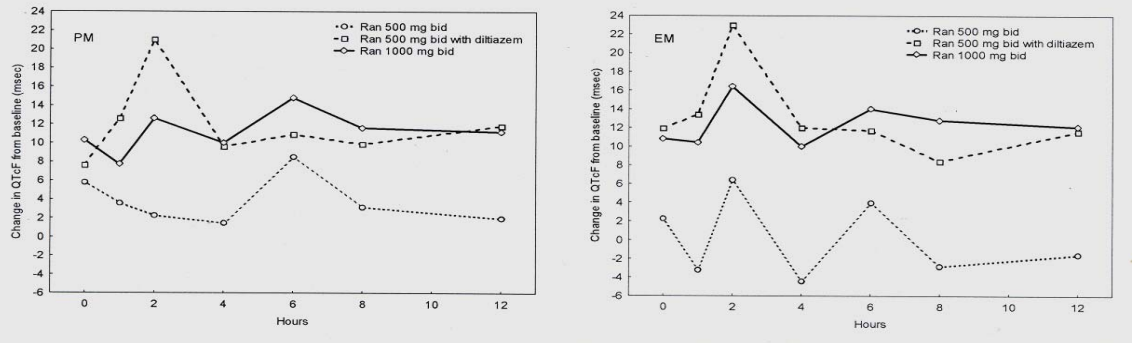
* Experienced by ≥ 2 subjects (PMs and EMs combined) during any 1 of the 4 treatment periods. Derived from Section 14.3.2

Headache, dizziness, postural dizziness, application site erythema (Holter electrodes), chest pain, nausea, and paresthesia were the most frequent AEs recorded. Chest pain and application site erythema were reported more frequently during the co-administration regimens than during the RAN alone treatments. Nine subjects (2 PMs and 7 EMs) discontinued the study because of AEs and 8 others were withdrawn due to meeting a protocol-specified ECG interval stopping criterion. The incidence of dizziness, both unspecified and postural, generally correlated with the RAN plasma concentrations with higher occurrences in PMs than in EMs.

QTc Interval and other ECG Findings

The mean changes from baseline (value measured on the eve of Day 1) in the QTcF interval in PMs and EMs receiving treatments of 500 mg RAN alone, 1000 mg RAN alone and 500 mg RAN+180 mg DLT bid are shown in the below 2 figures:

Figure 7 Change from Baseline in QTcF Interval (PK Evaluable Population)



With the 500 mg RAN bid alone treatment the maximum increase in mean QTc was 8 msec at 6 h post dose in PMs and 6 msec at 2 h post-dose in EMs. The maximum increase in QTc with the 1000 mg RAN alone treatment was 15 msec at 6 h post dose in PMs and 16 msec at 2 h in EMs. With the co-administration treatment the maximum increase in QTcF in PMs was 21 msec at 2 h post dose and 23 msec at 2 h post-dose in EMs. These results suggest that the observed increase in QTcF is exposure related.

(b) (4) sent alert reports to the sponsor for the following events: VT/ventricular fibrillation (VF) with three or more ventricular beats, severe bradycardia with a rate ≤ 35 bpm, AV block type Mobitz II, AV block type III or other advanced block, ventricular asystole or pause ≥ 3 sec, atrial fibrillation or flutter with ventricular rate > 150 bpm, sustained (> 60 sec), SVT with ventricular rate ≥ 180 bpm. In total 7 subjects were judged to have clinically significant abnormalities on Holter Monitoring.

Three PM subjects and 2 EM subjects experienced episodes of severe bradycardia on one or more treatment days (four subjects were on the co-administration treatment of 500 mg RAN+ 180 mg DLT and one subject was on the co-administration treatment with 1000 mg RAN+ 180 mg DLT).

One EM subject had an episode of asymptomatic VT on Day 14 while receiving the co-administration treatment of 500 mg RAN + 180 mg DLT. The subject was withdrawn from the study on Day 16 after receipt of the alert report. The RAN plasma concentration was approximately 1800 ng/ml at the time of the event. Subsequently, the Holter recording was evaluated by (b) (4) (b) (4) His assessment was that the short run of monomorphic VT observed did not correspond to the type usually associated with drug induced VT abnormality (i.e. Torsades de Pointes).

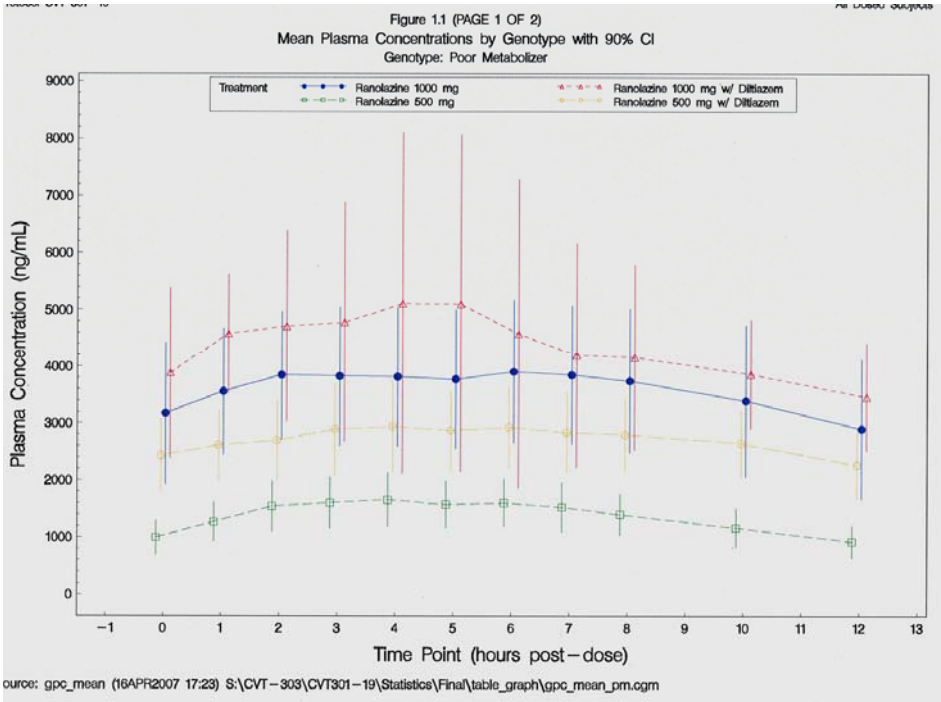
A second EM subject on RAN 500 mg +DLT 180 mg had an episode on Day 14 initially reported as VT. The subject was terminated from the study after receipt of the alert report on Day 16. The subject had no associated symptoms, and the RAN plasma concentration was approximately 1000 ng/mL at the time of the event. Subsequently, the Holter recording was evaluated by (b) (4) (b) (4) His assessment was that the ECG tracing was consistent with an accelerated idioventricular rhythm, a not unusual finding in healthy subjects and not consistent with the known effects of DIL and/or RAN.

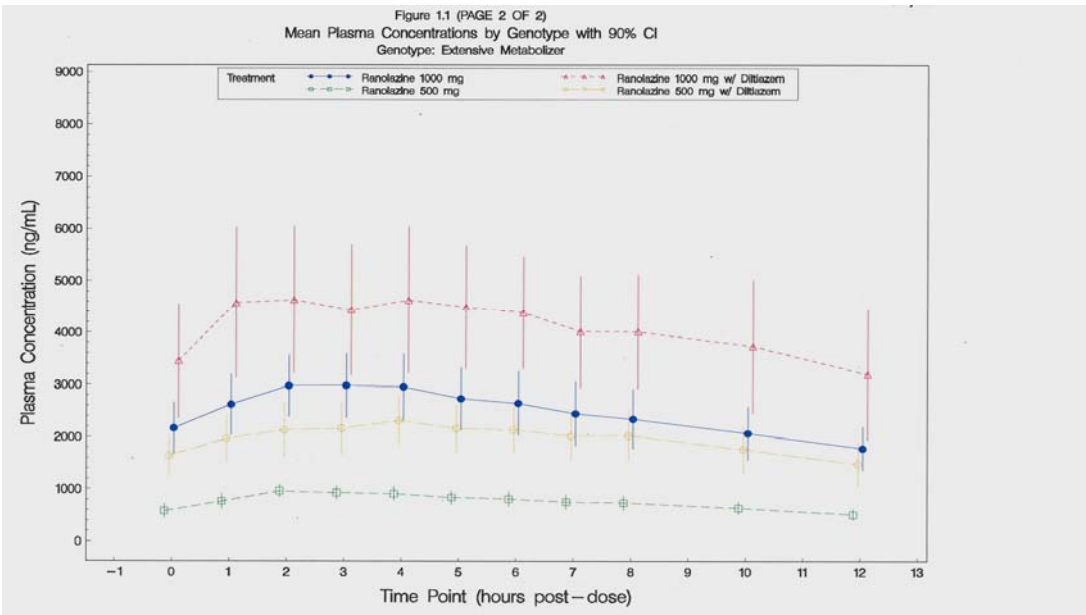
A PM subject who had experienced a severe bradycardia on Day 12, had a 3 beat-run of asymptomatic monomorphic VT at a rate of approximately 120 bpm after midnight on Day 13 while receiving 500 mg RAN+180 mg DLT. The alert report was received immediately prior to the time of the last dose administration on the morning of Day 15. Investigator and sponsor considered the event to be very unlikely drug induced and the subject to continue.

An EM individual experienced a clinically significant increase in blood pressure during the study. The subjects blood pressure at screening was normal (122/83 mmHg). On Day Day 10 blood pressure rose to 220/105 and 194/112 mmHg. The Day 10 evening dose and the Day 11 doses were withheld and the subject withdrawn from the study. Upon discontinuation of study medication, the subject's blood pressure decreased and at the time of the 14 day follow-up the blood pressure was normal.

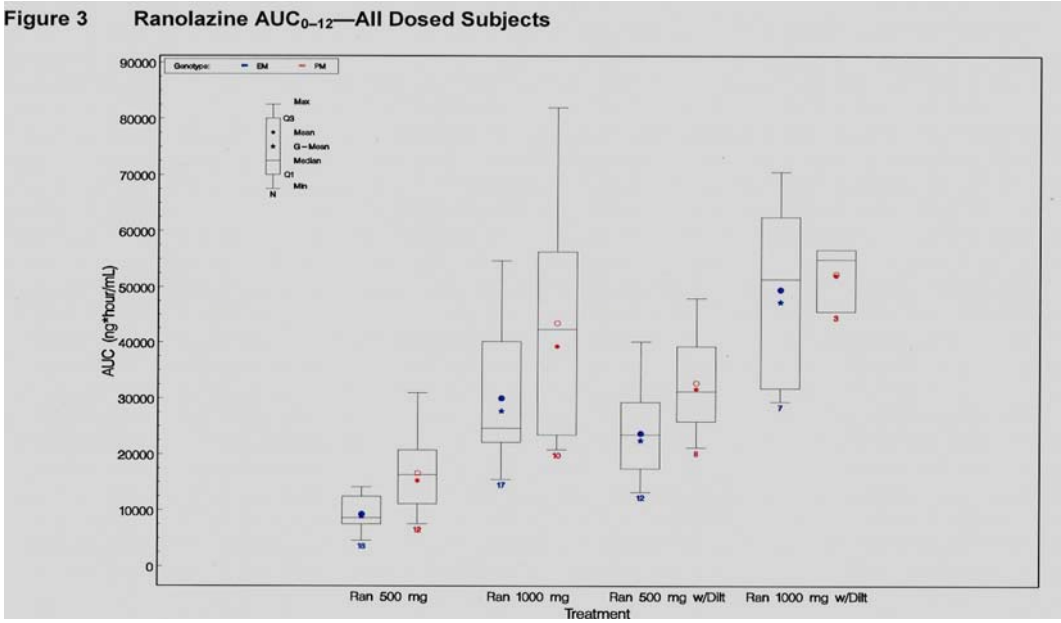
Pharmacokinetics

The mean plasma concentration time profiles of RAN in the presence and absence of DLT in PMs and EMs are shown in the below 2 figures:





The below box plot shows AUC0-12 for all dosed EMs and PMs receiving 500 mg and 1000 mg RAN with or without co-administration of DLT:



The PMs tend to exhibit greater AUC0-12 values than EMs in the RAN alone and in the RAN+ DLT co-administration treatments at both dose levels of RAN.

The below tables list the geometric mean and maximum exposure values of RAN and the metabolites observed with the RAN alone and DLT co-administration treatments:

Impact of the 500 mg Ranolazine alone and Diltiazem Co-Administration Treatments on Exposure (Geometric Mean and Maximum AUC and Cmax) to Ranolazine and Metabolites

	PM				EM			
	-DLT		+ DLT		-DLT		+DLT	
	mean	max	mean	max	mean	max	mean	max
n	12	12	8	8	18	18	12	12
Ranolazine								
AUC_{0-12}, ng·h/mL	15338	30960	31694	48070	8909	14124	22462	40080
Cmax	1695	3310	3158	4680	1036	1490	2391	3640
CVT-2512								
AUC_{0-12}	262	403	240	397	1099	2221	735	1785
Cmax	24.1	37.2	22.0	37.7	100	196	66.9	171
CVT-2514								

AUC_{0-12}	746	1048	1170	1663	4162	7482	5781	8986
Cmax	74.8	111	112	191	424	721	577	837
CVT-2738								
AUC_{0-12}	4765	7754	4756	5494	2535	3820	2375	3029
Cmax	444	724	437	492	245	378	232	359

Impact of the 1000 mg Ranolazine Alone and Diltiazem Co-Administration Treatments on Exposure (Geometric Mean and Maximum AUC and Cmax) to Ranolazine and Metabolites

	PM				EM			
	-DLT		+ DLT		-DLT		+DLT	
	mean	max	mean	max	mean	max	mean	max
n	10	10	3	3	17	17	7	7
Ranolazine								
AUC_{0-12}, ng·h/mL	39308	81975	52158	56725	27736	54710	47379	70570
Cmax	3947	7240	5522	5970	3009	5600	4873	6410
CVT-2512								
AUC_{0-12}	496	718	559	770	1630	3866	1430	2788
Cmax	44.2	63.8	50.7	68.7	148	338	128	241
CVT-2514								
AUC_{0-12}	1512	2328	2080	2511	7686	16901	9703	15325
Cmax	149	204	206	245	745	1660	906	1490
CVT-2738								
AUC_{0-12}	10493	15465	10099	10467	6395	10746	6159	9474
Cmax	976	1370	923	997	600	1010	571	880

The below table reports the ratios of the respective geometric mean values calculated from the above tables for 4 scenarios:

Ratio of the Geometric Mean AUC0-12 and Cmax values at Different Dose Levels of Ranolazine in the Presence and Absence of Diltiazem in PMs and EMs

	Ratio of Geometric Means			
	AUC0-12		Cmax	
	EM	PM	EM	PM
Scenario				
1000 mg RAN/500 mg RAN				
Ranolazine	3.11	2.56	2.90	2.32
CVT-2512	1.48	1.23	1.48	1.83
CVT- 2514	2.26	3.12	2.30	2.73
CVT-2738	2.52	2.20	2.20	2.20
1000 mg RAN*/500 mg RAN*				
Ranolazine	2.11	1.65	2.04	1.75
CVT-2512	1.95	2.33	1.91	2.30
CVT- 2514	1.68	1.78	1.57	1.84
CVT-2738	2.59	2.12	2.46	2.11
500 mg RAN*/500 mg RAN				
Ranolazine	2.52	2.07	2.31	1.86
CVT-2512	0.67	0.92	0.67	0.91
CVT- 2514	1.39	1.57	1.36	1.50
CVT-2738	0.94	1.00	0.95	0.98
1000 mg RAN*/1000 mg RAN				
Ranolazine	1.71	1.33	1.62	1.40
CVT-2512	0.88	1.13	0.86	1.15
CVT- 2514	1.26	1.38	1.22	1.38
CVT-2738	0.96	0.96	0.95	0.95

RAN=ranolazine administered in the absence of diltiazem
*RAN=ranolazine administered in the presence of diltiazem

The results of the statistical evaluation of AUC0-12 and Cmax for ranolazine after RAN 500 mg bid and 1000 mg bid in the absence of DLT in PMs and EMs are shown in the below table:

Table 7 Ranolazine PK Parameters—Difference between Genotypes Following Ranolazine Alone

Treatment Group/ Parameter*	N	LS Mean: Poor Metabolizer	LS Mean: Extensive Metabolizer	Ratio (Poor Metabolizer/ Extensive Metabolizer) (%)	90% CI for the Ratio (%)	Group Difference P-value
Ranolazine 500 mg						
AUC (0-12) (ng*hours/mL)	20	15039.98	9288.99	161.91	122.29 - 214.38	.006
Cmax (ng/mL)	20	1693.33	1087.32	155.73	120.59 - 201.11	.006
Tmax (hours)	20	3.50	3.50			.84
Ranolazine 1000 mg						
AUC (0-12) (ng*hours/mL)	20	36733.94	29281.10	125.45	94.75 - 166.10	.18
Cmax (ng/mL)	20	3668.15	3204.88	114.46	88.63 - 147.81	.38
Tmax (hours)	20	5.50	3.00			.37

Notes: ANOVA with terms for CYP2D6 metabolizer genotype, concomitant administration of diltiazem, ranolazine dose, all two-way interactions of these factors, the three-factor interactions, and subject as a random effect.
* The natural logarithms of AUC and Cmax are used in the ANOVA modeling. Results are reported in the original scale by taking the anti-logarithm.
Wilcoxon rank sum test is used for Tmax difference. Median Tmax values are presented.
Subjects 1928 and 1929, Day 8 Hour 7 samples were not included for the PK parameter calculations since those values were believed to be outliers.

The results of the statistical evaluation of Cmax and AUC0-12 for 500 mg RAN in the presence and absence of 180 mg DLT in EMs and PMs are shown in the below table:

Table 4 Ranolazine PK Parameters—Primary Analysis (PK Evaluable Population)

Treatment Group/ Parameter*	N	LS Mean: With Diltiazem	LS Mean: Without Diltiazem	Ratio (With Diltiazem/Without Diltiazem) (%)	90% CI for the Ratio (%)	Treatment Difference P-value
Poor Metabolizer and Ranolazine 500 mg						
AUC (0-12) (ng*hours/mL)	8	31694.12	15039.98	210.73	179.26 - 247.72	<.001
Cmax (ng/mL)	8	3157.77	1693.33	186.48	157.73 - 220.48	<.001
Tmax (hours)	8	4.00	3.50	0.50	-2.00 - 7.00	.47
Extensive Metabolizer and Ranolazine 500 mg						
AUC (0-12) (ng*hours/mL)	12	22461.81	9288.99	241.81	211.90 - 275.95	<.001
Cmax (ng/mL)	12	2390.69	1087.32	219.87	191.77 - 252.08	<.001
Tmax (hours)	12	3.51	3.50	0.50	-2.00 - 1.83	.65

Notes: ANOVA with terms for CYP2D6 metabolizer genotype, concomitant administration of diltiazem, ranolazine dose, all two-way interactions of these factors, the three-factor interactions, and subject as a random effect.
* The natural logarithms of AUC and Cmax are used in the ANOVA modeling. Results are reported in the original scale by taking the anti-logarithm.
Wilcoxon signed rank test is used for Tmax difference. Median response is used to estimate the values.
Subjects 1928 and 1929, Day 8 Hour 7 samples were not included for the PK parameter calculations since those values were believed to be outliers.

The below table lists the LS means, PM/EM ratios and 90% confidence intervals for RAN when RAN 500 mg was co-administered with 180 mg DLT bid:

Table 5 Ranolazine PK Parameters— Difference between Genotypes in the Diltiazem vs No Diltiazem Ratio (PK Evaluable Population)

Treatment Group/ Parameter*	N	LS Mean: Poor Metabolizer	LS Mean: Extensive Metabolizer	Ratio (Poor Metabolizer/ Extensive Metabolizer) (%)	90% CI for the Ratio (%)	Group Difference P-value
Diltiazem Administration Effect for Ranolazine 500 mg						
AUC (0-12) (ng*hours/mL)	20	210.73	241.81	87.15	70.73 - 107.38	.27
Cmax (ng/mL)	20	186.48	219.87	84.82	68.33 - 105.28	.21
Tmax (hours)	20	1.17	1.17			.43

Notes: ANOVA with terms for CYP2D6 metabolizer genotype, concomitant administration of diltiazem, ranolazine dose, all two-way interactions of these factors, the three-factor interactions, and subject as a random effect.
* The natural logarithms of AUC and Cmax are used in the ANOVA modeling. Results are reported in the original scale by taking the anti-logarithm.
Wilcoxon rank sum test is used for Tmax difference. Median ratio (with Diltiazem/without Diltiazem) are presented.
Subjects 1928 and 1929, Day 8 Hour 7 samples were not included for the PK parameter calculations since those values were believed to be outliers.

The next 2 tables provide the results of the statistical evaluations of the impact of genotype on the exposure to the metabolites after 500 mg and 1000 mg RAN alone with and without considering the AUC0-12 of the parent drug.

Impact of Genotype on Exposure to Metabolites in Subjects Receiving 500 mg and 1000 mg Ranolazine Alone without Considering Simultaneous Exposure to Ranolazine

Ranolazine Dose Level	Ratio of Metabolite AUC0-12 in PMs and EMs LS Mean (90% CI), %
500 mg	
CVT-2512	27 (20-37)*
CVT-2514	18 (14-24)*
CVT 2738	198 (165-238)*
1000 mg	
CVT-2512	32 (23-43)*
CVT-2514	19 (14-26)*
CVT-2738	154 (128-185)*

* Statistically significant treatment effect

Impact of Genotype on Exposure to Metabolites in Subjects Receiving 500 mg and 1000 mg Ranolazine Alone under Consideration of Simultaneous Exposure to Ranolazine

Ranolazine Dose Level	Ratio of Metabolite to Ranolazine for AUC0-12 in Ranolazine Alone Treatments, LS Mean		Impact of Genotype Ratio PM/EM, %
	PM	EM	
500 mg			
CVT-2512	0.018	0.104	17 (10-28)*
CVT-2514	0.047	0.411	11 (7.7-17)*
CVT-2738	0.337	0.275	122 (93-161)
1000 mg			
CVT-2512	0.013	0.052	25 (15-42)*
CVT-2514	0.038	0.250	15 (10-23)*
CVT-2738	0.283	0.230	123 (94-161)

* Statistically significant treatment effect

The final 2 tables list the results of the statistical evaluation of the impact of co-administering DLT and RAN on the exposure to the metabolites

Impact of Diltiazem Co-Administration on Exposure to Metabolites without Considering Simultaneous Exposure to Ranolazine

Ranolazine Dose Level	Ratio of Metabolite AUC0-12 in Presence and Absence of Diltiazem LS Mean (90% CI), %	
	PM	EM
500 mg		
CVT-2512	91 (82-100)	76 (70-82)*
CVT-2514	167 (148-188)*	151 (138-167)*
CVT-2738	94 (86-102)	93 (86-100)

* Statistically significant treatment effect

Impact of Diltiazem Co-Administration on Exposure to Metabolites under Consideration of Simultaneous Exposure to Ranolazine

Ranolazine Dose Level	Metabolite to Ranolazine Ratio for AUC0-12 in Presence and Absence of Diltiazem, LS Mean (90% CI), %	
	PM	EM

500 mg		
CVT-2512	43 (35-53)*	31 (27-37)*
CVT-2514	79 (69-91)*	63 (56-70)*
CVT-2738	45 (39-51)*	38 (35-43)*

* Statistically significant treatment effect

Ranolazine

Among all subjects receiving RAN alone or together with DLT a PM subject receiving RAN 1000 mg alone displayed the highest Cmax (7240 ng/mL) and AUC0-12 (81975 ng·h/mL). Among the subjects receiving 500 mg RAN alone or together with DLT a PM subject receiving RAN + DLT displayed the highest Cmax (4680 ng/mL) and AUC0-12 (48070 ng·h/mL).

AUC0-12 and Cmax after RAN 500 mg alone are statistically significantly greater in PMs than EMs. No statistically significant difference in AUC0-12 or Cmax between PMs and EMs is found after administration of 1000 mg RAN alone. AUC0-12 and Cmax after alone administration of 1000 mg are more than 2 fold greater than after 500 mg RAN alone in EMs and PMs indicating that the PK of RAN are more than dose proportional in both genotypes. Co-administration of DLT 180 mg and RAN 500 mg increases exposure to RAN about 2.4 fold in EMs and about 2.0 fold in PMs. Co-administration of DLT 180 mg and RAN 1000 mg increases exposure to RAN about 1.7 fold in EMs and about 1.4 fold in PMs indicating that the inhibition of the CYP3A mediated metabolism by DLT is smaller at the higher dose level with both genotypes. The extent of inhibition of RAN by DLT is in agreement with the findings in previous studies.

Metabolites

After administration of RAN 500 mg and 1000 mg alone, the respective AUC 0-12 values of CVT-2512 and CVT-2514 are smaller in PMs than in EMs, whereas the exposure to CVT-2738 is greater in PMs than in EMs in agreement with the notion that CVT-2512 and CVT-2514 are metabolized by CYP 2D6 and CVT-2738 by CYP 3A. The respective AUC0-12 values for CVT-2738 normalized for AUC0-12 of the parent drug (normalized AUC0-12/exposure) are not statistically significantly different in the two genotypes. In contrast, the corresponding values for CVT-2512 and CVT-2514 are significantly smaller in PMs than in EMs indicating that the difference in the PK of RAN and metabolites between the genotypes is associated with the CYP 2D6 pathway. Similar to the parent drug, the respective AUC0-12 values for CVT-2514 and CVT-2738 after a dose of 1000 mg RAN alone are more than 2.0 fold greater than those after 500 mg RAN alone in both genotypes. In contrast, AUC0-12 for CVT-2512 at the higher dose level is less than 2.0 fold greater than AUC0-12 at the lower dose level of RAN in both genotypes suggesting that the CYP2D6 mediated pathway generating CVT-2512 is primarily responsible for the non-linearity in the PK of RAN.

Co-administration of DLT and 500 mg RAN decreases AUC0-12 of CVT-2512 in EMs and increases the AUC0-12 of CVT-2514 in both genotypes. Co-administration of DLT and RAN 500 mg does not change AUC0-12 of CVT-2738. The respective normalized AUC0-12 values of CVT-2512, CVT-2514 and CVT-2738 are decreased in both genotypes when DLT is co-administered with RAN 500 mg compared to RAN alone. This finding suggests that the contribution of CYP 2D6 to the elimination of RAN at the plasma concentrations of RAN enhanced by DLT's inhibition of CYP3A is small.

Conclusions

PK

Previous studies have shown that RAN is predominantly eliminated by metabolism. It is known to be a substrate mainly of CYP3A, but also of CYP2D6. Among the measured first generation metabolites of RAN, CVT-2738 is thought to be generated mainly by CYP3A, whereas CVT-2512 and CVT-2514 are thought to be produced in part by CYP2D6. CVT-2738 and CVT-2512 are end-products, whereas CVT-2514 is glucuronidated prior to elimination. As a consequence of the ability of RAN to inhibit CYP2D6, the kinetics of RAN are more than dose proportional at therapeutic levels. The respective contributions of CYP3A to pre-systemic and systemic elimination of RAN from the body are not known. Unknown is also the contribution of enzymes other than CYP3A and 2D6 to the metabolism of RAN.

The present study shows that the PK of RAN are more than dose proportional at therapeutic dose levels. Exposure to RAN at the 500 mg dose level in PMs is greater than in EMs. At the 1000 mg dose level the exposure to RAN is not statistically significantly different between PMs and EMs. Co-administration of DLT 180 mg and RAN 500 mg increases exposure to RAN about 2.4 fold in EMs and about 2.0 fold in PMs. Co-administration of DLT 180 mg and RAN 1000 mg increases exposure to RAN about 1.7 fold in EMs and about 1.4 fold in PMs indicating inhibition of the CYP3A mediated metabolism by DLT is smaller at the higher dose level with both genotypes. The extent of inhibition of RAN by DLT is in agreement with the findings in previous studies.
Normalized exposure to CVT-2738 is similar in PMs and EMs after administration of RAN 500 mg or 1000 mg alone, in contrast to the corresponding values of CVT-2512 and CVT-2514 which are smaller in PMs than in EMs. Co-administration of DLT and 500 mg RAN reduces not only normalized exposure to CVT-2738, but also to CVT-2512 and CVT-2514 in both genotypes. The observed reduction of the normalized exposures to CVT-2512 and CVT-2514 suggests that the increased levels of RAN resulting from inhibition of CYP3A by DLT saturate CYP 2D6 enough so that the respective rates of formation of CVT-2512 and CVT- 2514 relative to the rate of formation of CVT-2738 are not increased.

Safety

Nine subjects (2 PMs and 7 EMs) discontinued the study because of AEs and 8 others were withdrawn due to meeting a protocol-specified ECG interval stopping criterion. The incidence of dizziness, both unspecified and postural, generally correlated with the RAN plasma concentrations with higher occurrences in PMs than in EMs. Three PM subjects and 2 EM

subjects experienced episodes of severe bradycardia on one or more treatment days during the co-administration regimen with 500 mg RAN or 1000 mg + 180 mg DLT bid. Two subjects experienced asymptomatic VT runs, one of which had developed a severe bradycardia the day before and a third subjects showed an idioventricular rhythm. All of these arrhythmia events occurred during the co-administration regimen with 500 mg RAN + 180 mg DLT. The expected exposure dependent prolongations of QTcF of up to 23 msec were seen.

Comments

1. It is well known that the pH of the urine samples influences the dextrometorphan/dextrorphan ratio. The pH in the urine samples used to determine the ratio varied greatly among the individuals potentially biasing the phenotype results. Surprisingly, the genotype and phenotype determinations were in agreement.

2. It is unclear why the evaluation of Cmin was excluded from the analysis of all treatments.

3.4 Study Report CVT 3023: A Double-Blind, Randomized, Parallel-Group Dose Escalation Tolerability Study of Ranolazine ER in Patients with Chronic Angina

Primary Investigator and Study Sites

(b) (4)

Objectives

Primary

To determine the tolerability of ranolazine ER at oral doses up to 3000 mg bid in patients with chronic angina, as assessed by specific adverse events

Secondary

To characterize the adverse events and the changes in vital signs and laboratory parameters associated with ranolazine ER at oral doses up to 3000 mg bid in these patients

Investigational Drugs and Formulations

Design

This was a double-blind, randomized, parallel group, dose escalation study of ranolazine ER; in Part 1 of the study, patients with chronic angina received oral doses ranging from 750 up to 2250

mg bid. Patients were randomized (1:1:1within each center) to one of the three treatment regimens shown in the Table below:

Table 1 Treatment Regimens for Part 1 of the Study

Treatment Regimen (Part 1)	Dose (mg twice a day)		
	Treatment Period 1 Days 1–3	Treatment Period 2 Days 4–7	Treatment Period 3 Days 8–13
750/750/750	750	750	750
750/1500/1500	750	1500	1500
750/1500/2250	750	1500	2250

Each treatment regimen included three treatment periods. At the beginning of each treatment period the dose of ranolazine was potentially increased depending on the treatment regimen. During Period 1, all patients were to receive ranolazine at a dose of 750 mg bid. During the Period 2 the dose of ranolazine for patients in Group 2 and 3 was increased to 1500 mg bid, whereas the patients of Group 1 stayed on 750 mg bid. During Period 3 only the patients of Group 3 received an increased dose of 2250 mg bid, whereas the patients in Groups 1 and 2 remained on their dose of 750 and 1500 mg bid, respectively. The patients were resident in the clinic for 14 days and physical examinations, ECGs, blood pressure and heart rate, and laboratory evaluations were performed. Approximately 14 days after discharge they were contacted to assess their condition, and to record any adverse events.

Safety

The primary tolerability endpoint was the number of patients who experience at least one of the pre-specified adverse events including syncope, diplopia, somnolence, depressed level or loss of consciousness, confusion and disorientation, symptomatic hypotension, dizziness, nausea, and vomiting, experienced any severe event or terminated from the study due to an adverse event.

Pharmacokinetic Profiling

Blood samples for the determination of the plasma concentrations of ranolazine were collected at the following times:

Days 3, 7, and 13: at 4 h after the morning dose of ranolazine (steady-state peak concentrations)

Days 4 and 8: within 15 minutes before the administration of the morning dose (steady-state trough concentration)

Day 14: before discharge and within 15 minutes of the time previously established for the morning dose (steady-state trough concentration)

At the time of early withdrawal or discontinuation from the study (within 2 h from the event leading to withdrawal)

Bioassay

The plasma concentrations of ranolazine were measured by a validated LC/MS/MS method. The LLOQ and ULOQ of the method are 50 and 10000 ng/mL respectively. Precision of the assay is < 5.8% and accuracy ranges between -1.8 % and 2.4 %.

Data Analysis

Mean and standard deviations of the plasma ranolazine levels were calculated for subjects receiving the respective dose regimens.

RESULTS

A total of 37 patients enrolled in the study. Twelve patients were randomized to remain on the initial dose of 750 mg bid for all three periods, 13 patients were randomized to escalate to 1500 mg bid in Periods 2 and 3 and 12 patients were randomized to escalate to 1500 mg bid and 2250 mg bid in Periods 2 and 3, respectively. The demographics of the participating patients are shown in the table below:

Table 4 Demographic and Baseline Characteristics

TABLE 1.2 [T-1.2] (PAGE 1 OF 1)
Demographic and Baseline Characteristics

		Treatment Regimen (mg)			
	Statistics	750/750/750 (n=12)	750/1500/1500 (n=13)	750/1500/2250 (n=12)	Overall (n=37)
Age (years)	n	12	13	12	37
	Mean (SD)	57.4 (8.0)	59.5 (10.5)	56.0 (11.9)	57.7 (10.1)
	Median	57.5	56.0	51.0	54.0
	Min - Max	45.0 - 67.0	46.0 - 82.0	47.0 - 78.0	45.0 - 82.0
Gender					
Male	n (%)	7 (58%)	9 (69%)	7 (58%)	23 (62%)
Female	n (%)	5 (42%)	4 (31%)	5 (42%)	14 (38%)
Race					
Caucasian	n (%)	5 (42%)	7 (54%)	7 (58%)	19 (51%)
Black	n (%)	7 (58%)	6 (46%)	5 (42%)	18 (49%)
Height (cm)	n	12	13	12	37
	Mean (SD)	170.0 (8.4)	169.2 (8.0)	171.6 (13.7)	170.2 (10.1)
	Median	169.3	169.0	172.7	170.5
	Min - Max	154.0 - 188.0	157.0 - 180.3	153.0 - 200.7	153.0 - 200.7
Weight (kg)	n	12	13	12	37
	Mean (SD)	91.8 (8.9)	87.0 (16.4)	103.3 (33.6)	93.8 (22.5)
	Median	94.8	86.0	94.8	92.1
	Min - Max	76.2 - 102.5	63.5 - 118.8	69.3 - 196.4	63.5 - 196.4
BMI (kg/m^2)	n	12	13	12	37
	Mean (SD)	32.0 (4.5)	30.4 (5.1)	34.5 (6.7)	32.2 (5.6)
	Median	32.2	30.1	32.9	32.0
	Min - Max	25.9 - 40.2	22.9 - 38.7	25.5 - 48.8	22.9 - 48.8

Source: tdemog.sas (20DEC2005:16:27 by PSERN) tdemog.doc

Safety

Twenty three patients completed the study. A total of 14 patients withdrew early from the study as shown in the table below:

Table 2 Patient Disposition

	Treatment Regimen (mg)		
	750/750/750 (n=12)	750/1500/1500 (n=13)	750/1500/2250 (n=12)
No. of patients who completed treatment	11 (92%)	7 (54%)	5 (42%)
No. of patients who terminated early	1 (8%)	6 (46%)	7 (58%)
Primary reason for early termination			
QTc prolongation	0	1 (8%)	0
Adverse event(s)	0	1 (8%)	4 (33%)
Death	0	0	0
Protocol Violation	0	0	0
Lost to follow-up	0	0	0
Did not meet entrance criteria	0	1 (8%)	0
Other	1 (8%)	3 (23%)	3 (25%)

Source: tdispo.sas (20DEC2005:16:27 by PSERN) tdispo.doc

A listing of patient disposition information is presented in Section 13.1.

Dose levels and reason for premature termination of the study in the 14 subjects are summarized in the table below:

Table 3 Patients Who Prematurely Terminated from the Study

Patient No.	Last Ranolazine Dose prior to Termination (mg b.i.d.)	Reason for Termination	Comment
750/750/750 Regimen			
14012336	750	Other	The study-site required evacuation for an impending hurricane
750/1500/1500 Regimen			
12122301	1500	QTc prolongation	Withdrawn for QTc prolongation (Withdrawal required per protocol, with a QTc > 500 msec and a change from baseline ≥ 60 msec)
14062306	1500	Adverse event	Withdrawn for nausea, disorientation, and confusion
14012325	1500	Other	Patient withdrew consent
14012334	1500	Other	The study-site required evacuation for an impending hurricane
14012320	750[a]	Other	Patient was discharged by the sponsor when it was realized that the patient was taking a prohibited medication (Effexor)
14012329	750	Did not meet entrance criteria	Patient was discharged by the sponsor when it was realized that on Day -1 the patient had orthostatic hypotension, not satisfying study-entrance criteria
750/1500/2250 Regimen			
12122302	1500	Adverse event	Withdrawn for nausea and vomiting
12122309	1500	Adverse event	Withdrawn for severe involuntary muscle spasms (a serious adverse event [SAE])
14062303	2250	Adverse event	Withdrawn for hematuria (emerged at a ranolazine dose of 2250 mg b.i.d.) and a transient ischemic attack (emerged at a dose of 1500 mg .b.i.d.). Both events were SAEs.
14062304	2250	Adverse event	Withdrawn for nausea and orthostatic hypotension, which emerged at a ranolazine dose of 1500 mg b.i.d.
14012302	1500	Other	Patient withdrew consent
14012305	2250	Other	Patient withdrew consent
14062308	2250	Other	Patient withdrew consent

[a] Patient 14012320 terminated on the morning of the first day of treatment period 2; hence the listings reflect that this patient withdrew during period 2, corresponding to a 1500-mg ranolazine dose. However, the patient had not yet taken study medication for the day, so the last actual dose taken was 750 mg.

Source: The data in this table were obtained from the patient disposition listing in Section 13.1 of this report.

Five patients were withdrawn from the study due to one or more adverse events, and one patient was withdrawn for QTc interval prolongation as per protocol (ΔQTc msec ≥ 60 msec and QTc > 500 msec). Four patients withdrew voluntarily. Two patients were withdrawn by the sponsor (one for not meeting the entrance criteria and one for concomitant use of prohibited medication) and 2 patients were withdrawn, because the study site required evacuation (hurricane 2005)

The below table summarizes the tolerability results:

Table 6 Primary Endpoint Analysis: Tolerability

	Treatment Regimen (mg)		
	750/750/750 (n=12)	750/1500/1500 (n=13)	750/1500/2250 (n=12)
Patients Who Experienced a Primary Endpoint Event*	1 (8%)	6 (46%)	9 (75%)
Study Specific Adverse Events	1 (8%)	6 (46%)	9 (75%)
Syncope	0	0	0
Diplopia	0	0	0
Somnolence	0	1 (8%)	2 (17%)
Depressed level/Loss of consciousness	0	0	0
Confusion/Disorientation	0	1 (8%)	0
Symptomatic Hypotension	0	1 (8%)	1 (8%)
Dizziness	1 (8%)	2 (15%)	5 (42%)
Nausea	0	3 (23%)	6 (50%)
Vomiting	0	1 (8%)	3 (25%)
Severe Adverse Events	0	2 (15%)	2 (17%)
Terminated from the Study Due to an Adverse Event	0	1 (8%)	4 (33%)

Note: * Primary endpoint will be the number of patients who experience syncope, diplopia, somnolence, depressed level/loss of consciousness, confusion/disorientation, symptomatic hypotension, dizziness, nausea, vomiting, or any severe adverse event, or terminate from the study due to an adverse event.

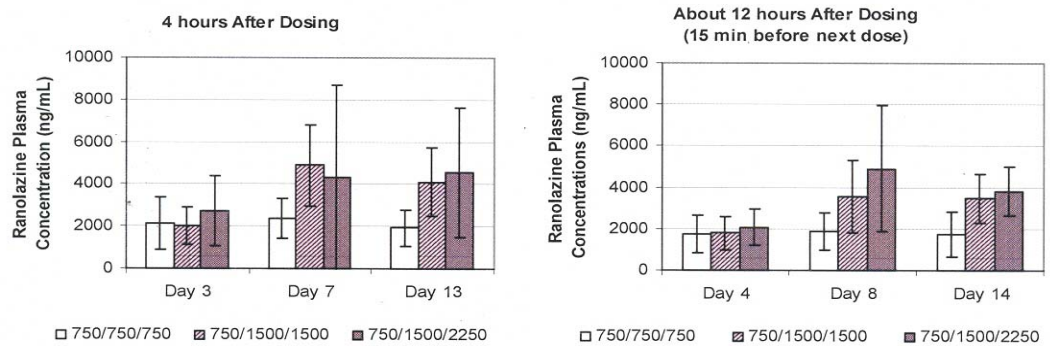
Source: tendpt.sas (20DEC2005:16:27 by PSERN) tendpt.doc

The incidence of somnolence, confusion/disorientation, symptomatic hypotension, dizziness, nausea, or vomitus increase with dose: 8% with the 750 m bid regimen, 46% with the 1500 mg bid regimen and 75% with the 2250 mg bid regimen. The number of subjects terminated from the study because of an adverse event increases also with dose: 0% with the 750 mg bid regimen, 8% with the 1500 mg bid regimen and 33% with the 2250 mg bid regimen. It can be concluded that the 750 mg bid dose regimen is tolerated and the 1500 mg bid and 2250 mg bid dose levels are not.

Pharmacokinetics

The mean peak and trough steady-state plasma concentrations of ranolazine in the patients are shown in the Figure below:

Figure 1 Ranolazine Plasma Concentrations at Scheduled Timepoints



The mean peak concentrations of ranolazine ranged between 1932 ng/mL and 2380 ng/mL and the mean trough concentrations ranged between 1743 ng/mL and 1850 ng/mL in patients receiving the 750/750/750 bid regimen. The concentrations after 750 mg bid in the patients receiving the other two regimens were consistent with those above. For patients taking 1500 mg bid in the 750/1500/1500 mg bid regimen the mean peak concentrations ranged between 4106 ng/mL and 4888 ng/mL and the trough concentrations ranged between 3467 ng/mL and 3551 ng/mL. For patients on the 750/1500/2250 mg bid regimen the peak concentrations after 1500 mg bid were in the range of the concentrations noted above. However, the mean trough concentrations were unexpectedly high, 4884 ng/mL. Finally, patients receiving the 2250 mg bid dose displayed mean peak and trough concentrations of 4540 ng/mL and 3820 ng/mL, respectively. Apart from one exception patients who had a trough concentration ≥ 6000 ng/mL discontinued the study (either being withdrawn by the Investigator or voluntarily withdrawing consent).

The results indicate that the mean plasma concentrations increase with dose, but it appears that the increase in dose from 1500 mg bid to 2250 mg bid is not associated with a proportionate increase of the mean plasma concentration. There is significant inter-subject variation as noted in earlier studies and little difference between mean peak and trough concentrations.

The plasma concentrations of the patients at the time of withdrawal from the study are listed in the table below:

Table 5 Plasma Concentrations at the Time or Following Withdrawal from the Study

Patient No.	Reason for withdrawal	Last ranolazine dose	Plasma concentration	Time since last dose
750/1500/1500 Regimen				
12122301	QTc interval prolongation[a]	1500 mg	7210 ng/mL	~7 hours
14012325	Withdrew consent	1500 mg	6840 ng/mL	~9 hours
14062306	Nausea, disorientation, and confusion	1500 mg	3520 ng/mL	~12 hours
750/1500/2250 Regimen				
12122302	Nausea and vomiting	1500 mg	2120 ng/mL	~24 hours
12122309	Involuntary muscle spasms	1500 mg	14,000 ng/mL	~9.5 hours
14012302	Withdrew consent	1500 mg	BQL	~193 hours
14012305	Withdrew consent	2250 mg	11,800 ng/mL	~12 hours
14062303	Hematuria[b] and transient ischemic attack	2250 mg	12,400 ng/mL	~11 hours
14062304	Nausea, dizziness, and orthostatic hypotension[c]	2250 mg	8800 ng/mL	~11 hours
14062308	Withdrew consent	2250 mg	BQL	~81 hours

[a] The protocol required that a patient be discontinued from the study if the QTc interval both widened to ≥ 60 msec from its baseline duration and was > 500 msec.

[b] The hematuria emerged at the 2250-mg dose, but the transient ischemic attack occurred while the patient was receiving 1500 mg b.i.d.

[c] All events emerged while the patient was receiving 1500 mg b.i.d., but the patient continued dosing and then withdrew while taking 2250 mg b.i.d.

BQL = below the quantitation limit of the assay

Source: Section 13.5

It should be noted that 14 patients withdrew from the study prematurely. Ten (10) of these 14 patients were included in the table. Four (4) patients (2 withdrawn due to study site evacuation and 2 discharged by the sponsor) are not included. Of the 10 patients considered, 7 had plasma samples taken within 12 h of the last dose and of these 7 patients, 6 had trough concentrations > 6000 (6840-14 000) ng/mL. Three (3) patients had plasma concentrations taken only 24 h -193 h after the last ranolazine dose making it difficult to relate the measured concentrations to peak or trough concentrations at steady-state. Of the 6 patients who had trough concentrations > 6000 ng/mL, 5 discontinued the study (either being withdrawn or voluntarily withdrawing consent). One (1) patient in the 750/1500/1500 regimen had trough concentrations of 6580 ng/mL (Day 8) and 4880 ng/mL (Day 14).

Conclusions

Tolerability decreases with increasing doses and plasma concentrations of ranolazine. A regimen with 750 mg ranolazine bid is tolerated. Trough plasma concentrations in excess of 6000 ng/mL were shown to be associated with intolerability. The peak and trough plasma concentrations measured in the angina patients showed considerable variability.

Comments

None.

3.5 Study Report CVT Study 3032 :" A Phase 3, Open-Label, Long Term, Safety Study of Ranolazine SR for Chronic Stable Angina Pectoris at Doses of 750 mg and 1000 mg bid

Study Investigator and Site

45 Investigators at 47 Study Centers in Canada, the Czech Republic, Poland, and the United States

Objectives

The primary objective of this follow up study of CVT study 3031 was to determine the long term safety and tolerability of ranolazine ER 750 mg bid and 1000 mg bid in patients with chronic stable angina during an open label treatment period of up to approximately 10 years duration administered with and without other anti-anginal as needed to control symptoms.

Investigational Drugs and Formulations

Ranolazine ER 375 (lot Nos. 1 H2727A, 3H3022A), 500 mg (Lot Nos. 791771, 898221, 1H2726A, 1K2754A, 3H3026A) and 750 mg (Lot Nos. 791861, 791871) tablets

Design

This was an open-label study in which patients received a treatment with an initial dose of 750 mg of ranolazine ER and may be titrated to 1000 mg ranolazine bid based on clinical response. If at the 1000 mg bid dose level symptoms were not controlled, patients may also have been taken additional anti-anginal therapy such as calcium antagonists or beta-blockers. Patients were seen at weekly intervals until their angina was controlled, then followed up at 1 month after their last titration, and every 3-6 months thereafter. A total of 143 patients enrolled in the study. The patients must have had stable angina and completed Study CVT 3031. Exclusion criteria included NYHA Class III or IV congestive heart failure, second or third degree of atrio-ventricular block, QTc > 500 msec, required medication prolonging the QTc interval, required medication significantly affecting CYP 3A, active acute myocarditis or pericarditis, hypertrophic cardiomyopathy, uncontrolled hypertension, any chronic illness likely to hinder or confuse the follow-up evaluation , or were unwilling to refrain from consumption of grapefruit/ grapefruit juice, clinically significant hepatic disease, end-stage renal disease requiring dialysis or a calculated creatinine clearance < 30 mL/min.

Overall incidences of adverse events, incidence by severity and by relationship to medication were calculated. Continuous laboratory values, vital signs (heart rate blood pressure) and ECG parameters (PR, QRS, QT and QTc) were evaluated and compared to baseline (Visit 2 of CV study 3031). Prolongation of the QTc > 500 msec and ≥ 130% of baseline were considered critical.

The inclusion and exclusion criteria are listed below:

9.3.1 Inclusion Criteria

To be eligible for enrollment, patients had to satisfy the following requirements:

- Patients had completed Study CVT 3031 according to the protocol
- For female patients only: The patient was post-menopausal or sterilized, or if she was of childbearing potential, she was not breast feeding, her pregnancy test was negative, she had no intention of becoming pregnant during the course of the study, and she was using contraceptive drugs or devices
- Patients had signed a consent form for this study approved by the investigator's IRB/IEC

9.3.2 Exclusion Criteria

If patients developed or required any of the listed exclusions below since starting Study CVT 3031, they were not eligible to be entered into Study CVT 3032:

- New York Heart Association (NYHA) Class IV congestive heart failure
- Second or third degree atrioventricular block or uncontrolled clinically significant cardiac arrhythmias
- Corrected QT interval (QTc) > 500 msec
- Required medications which are known to prolong the QTc interval, such as:
  - Class IA anti-arrhythmics and/or Class III anti-arrhythmics (quinidine, procainamide, amiodarone, sotalol, etc.)
  - Seldane (terfenadine)
  - Hismanal (astemizole)
  - Propulsid (cisapride)
- Required medications which significantly affect cytochrome P450 3A4, such as:

  Inhibitors:
  - Erythromycin, Biaxin (clarithromycin), TAO (troleandomycin)
  - Nizoral (ketoconazole), Sporanox (itraconazole)

  Inducers:
  - Dilantin (phenytoin), Tegretol (carbamazepine), phenobarbital, rifampin

  An additional list of medications which affect cytochrome P450 3A4 were listed in the protocol.

  Other medications metabolized by cytochrome P450 such as diltiazem were to be used with caution.
- Unwillingness to refrain from grapefruit/grapefruit juice consumption for the duration of the study (grapefruit juice inhibits cytochrome P450 3A4)
- Active acute myocarditis or pericarditis
- Hypertrophic cardiomyopathy
- Uncontrolled hypertension
- Any chronic illness which was likely to hinder or confuse follow-up evaluation (e.g., cancer, alcoholism, drug dependency or abuse, serious psychiatric illness, uncontrolled or labile diabetes mellitus, etc.)

Prohibited medications included the following:

9.4.5.1 Prohibited Concomitant Medications and Food

- Medications which are known to prolong the QTc interval were not allowed; they included, but were not limited to the following:
  - Class IA anti-arrhythmics (e.g., quinidine, procainamide)
  - Class III anti-arrhythmics (e.g., amiodarone, sotalol, dofetilide)
  - Phenothiazide anti-psychotics: chlorpromazine, mesoridazine, pimozide, thioridazine
  - Quinolone antibiotics: gatifloxacin, moxifloxacin, sparfloxacin
  - Others: droperidol, mefloquine, pentamidine, levomethadyl, dolasetron, systemic dosing of tacrolimus, arsenic trioxide, terfenadine, astemizole, cisapride
  - Other drugs that have a contraindication or boxed warning regarding QT prolongation in the prescribing information
- Medications that are inhibitors or inducers of cytochrome P450 3A4 were not allowed; they included, but were not limited to the following:
  - Erythromycin, clarithromycin, troleandomycin
  - Ketoconazole and itraconazole (topical agents were permissible)
  - Dilantin (phenytoin), Tegretol (carbamazepine), phenobarbital, rifampin
  - Nefazadone
  - Antiviral drugs (delavirdine)
  - Protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir)
  - Cyclosporin

Other medications metabolized by cytochrome P450 such as diltiazem were to be used with caution.

In addition to these concomitant medications, grapefruit/grapefruit juice consumption was prohibited for the duration of the study.

Allowed medications included the following:

9.4.5.2 Allowed Concomitant Medications

- Sublingual nitroglycerin was permitted for treatment of acute angina.
- Aspirin was permitted during the study.
- Any digitalis preparation (e.g., digoxin) was permitted during the study. However, if a patient received digoxin therapy, serum digoxin levels should have been monitored.
- The use of statins was permitted during the study.
- Beta blockers and calcium channel blockers may have been used as anti-hypertensives only if they had been added during the titration phase of the study for control of angina.
- Diuretics and angiotensin converting enzyme (ACE) inhibitors may have been administered as anti-hypertensive therapy.

Use of any concomitant medications should have been documented on the appropriate case report forms (CRFs).

Pharmacokinetic Profiling

Trough plasma concentrations were measured (approximately 12 h after the last dose) beginning after the first long term visit (Visit 3) and at all subsequent maintenance visits at 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69 and 72 months.

Bioassay

The plasma concentrations of ranolazine were measured by a specific LC/MS/MS method**.** The measurements were performed in the [redacted] (b) (4). The calibration curve is linear for ranolazine concentrations ranging from10 ng/mL to 12500 ng/mL. The precision of the assay measured with QC samples is <6.4% and the accuracy is ranging between-2.8% and 9.5%.

PK Data Analysis

Ranolazine plasma concentrations data at the 750 mg and 1000 mg bid dose levels were grouped into time intervals centered around time points every 3 months after start of dosing. If a patient had two plasma concentrations measured within the same time interval the values were averaged. Mean, median, 25th percentile, 75th percentile, minimum and maximum plasma concentrations of ranolazine for the patients were computed for the above time points.

PK-PD Analysis

Plots of QTc versus the ranolazine plasma concentrations were constructed.

RESULTS

Demographics of Subjects

The mean age of the patients was 64 (± 9) years, 75% were male and 92% Caucasians.

Disposition of Subjects

Table 3 Patient Disposition

	Overall n = 143
No. of patients who completed treatment	48 (33.6%)
No. of patients who terminated prematurely	95 (66.4%)
Primary reason for premature termination of the study	
Unacceptable adverse event	43 (30.1%)
Non-compliance	4 (2.8%)
Elective withdrawal	17 (11.9%)
Lost to follow-up	3 (2.1%)
Death	15 (10.5%)
Other	13 (9.1%)

Source: Section 14.1.1

Concomitant Medications

The most common co-medications were: platelet aggregation inhibitors (90%, e.g. acetyl salicylic acid), organic nitrates (73%, e.g. glyceryl trinitrate, isosorbide mono-and dinitrate), HMO Co-A reductase inhibitors (68%, e..g. atorvastatin, simvastatin), α- and β-blocking agents (49%, e..g. atenolol), ACE inhibitors(41%, eg.g lisinopril), diuretics (41%, e.g. furosemide) and calcium channel blockers (32% , 13 % diltiazem, 1.4 % verapamil)

Safety

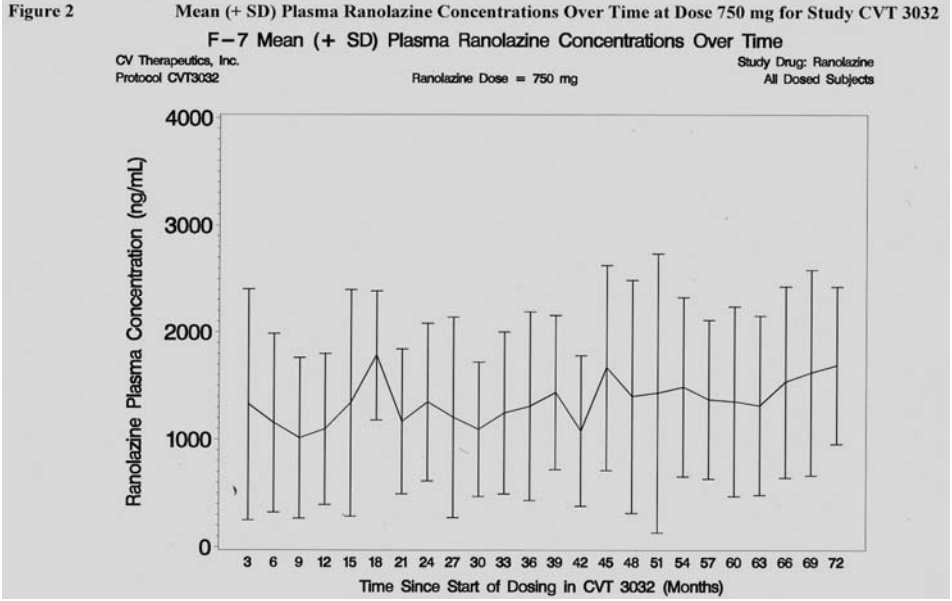
Table 5 Summary of Adverse Events

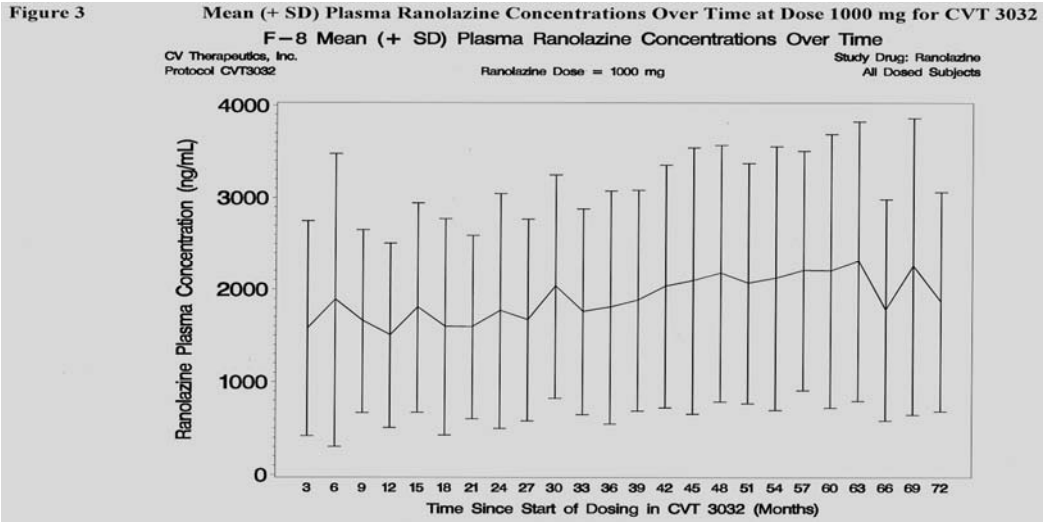
Number of Patients:	Total (n = 143)
Any adverse event	122 (85.3%)
Any potentially study drug related adverse event	51 (35.7%)
Discontinued the study due to an adverse event	53 (37.1%)
Any serious adverse event	87 (60.8%)
Death	17 (11.9%)

Pharmacokinetics

Plots of the mean (SD) trough plasma concentrations of ranolazine over time for the 750 mg bid and 1000 mg bid regimens are shown in the below 2 figures and the corresponding median and individual maximum ranolazine concentrations at each time point are listed in the below 2 tables:

Figure 2 Mean (+ SD) Plasma Ranolazine Concentrations Over Time at Dose 750 mg for Study CVT 3032





The mean trough concentrations and standard deviations show no time dependency even though the number of subjects with information on the plasma concentration of ranolazine decreased over time substantially resulting in a constantly changing population. The large values of the standard deviation point to the known significant inter-subject variation of the exposure to ranolazine. With the 750 mg bid regimen the median trough plasma concentrations over time range between 833 ng/mL and 1705 ng/mL and the individual maximum trough plasma concentrations vary between 2510 ng/mL and 5925 ng/mL. With the 1000 mg bid regimen the trough plasma concentrations over time range between 1350 ng/mL and 2000 ng/mL and the individual maximum trough plasma concentrations vary between 4230 ng/mL and 10800 ng/mL. The median trough plasma concentrations at the 1000 mg dose levels are higher than at the 750 mg dose level. Not surprisingly the plasma concentrations at the 750 and 1000 mg dose level overlap.

Median Trough and Individual Maximum Trough Plasma Concentrations of Ranolazine During a Regimen with 750 mg bid

Month	n Subjects	Median Trough Concentration ng/mL	Maximum Trough Concentration ng/mL
3	41	1090	4240
6	31	927	3540
9	33	833	2840
12	31	1150	2930
15	29	1210	5380
18	30	913	5925
21	26	1143	2510
24	24	1350	2720
27	27	1070	4660
30	23	1000	2545

33	25	1125	3330
36	20	1138	3170
39	21	1470	3510
42	17	1020	2415
45	14	1478	4555
48	13	1315	4420
51	13	1120	4250
54	13	1480	3005
57	11	1500	2605
60	13	1440	3160
63	11	999	2900
66	9	1560	2920
69	8	1705	2860
72	4	1520	2730

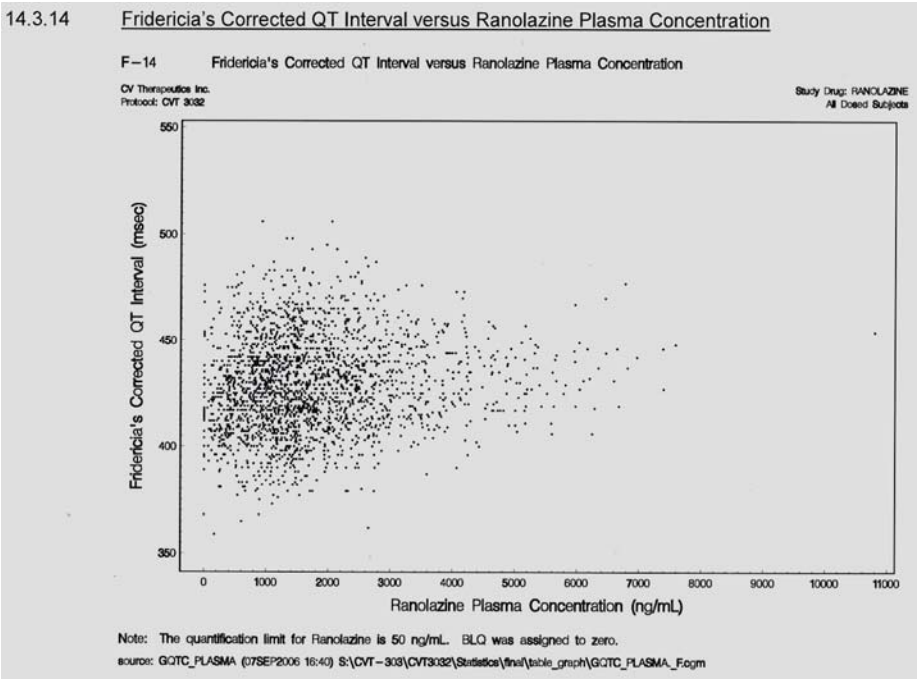
Median Trough and Individual Maximum Trough Plasma Concentrations of Ranolazine During a Regimen with 1000 mg bid

Month	n Subjects	Median Trough Concentration ng/mL	Maximum Trough Concentration ng/mL
3	82	1398	6780
6	74	1450	10800
9	76	1543	5575
12	69	1350	6290
15	70	1558	6350
18	64	1385	5650
21	67	1420	4870
24	63	1560	7590
27	66	1433	5160
30	57	1750	5190
33	62	1528	4710
36	62	1615	5320
39	56	1583	5160
42	60	1700	6070
45	53	1795	6470
48	48	1910	5795
51	43	2000	6135
54	44	1903	6210
57	44	1868	6330
60	42	1903	5370
63	40	1765	6780
66	35	1440	5625
69	27	1920	7400

72	16	1705	4230

Pharmacodynamics

A plot of the QT corrected for heart rate according to Fridericia, QTcF, versus the plasma concentrations of ranolazine is shown below:



The scatter of the data confirms the significant inter-subject variation in QTc ranolazine noted in earlier studies.

Conclusions

PK

The results confirm the significant variation of the exposure to ranolazine in subjects receiving the same dose. There is no evidence for an important time dependence of the pharmacokinetics of and exposure to ranolazine when the drug is administered at a dose of 750 mg or 1000 mg bid for a period of 6 years.

PD

The relationship between QTcF and the plasma concentrations of ranolazine shows the same high variation seen in earlier studies.

Comments

None

3.6 Report of Study CVT 3034 ”A Phase 3, Open-Label, Long-Term, Safety Study of Ranolazine SR for Chronic Stable Angina Pe4ctoris at Doses of 500 mg, 750 mg and 1000 mg Twice a Day Administered in Combination with Antianginal Therapy“

Investigator and Study Sites

This international multi-center study was conducted by 128 Investigators at 128 study centers in Australia, Bulgaria, Canada, the Czech Republic, Georgia, Greece, Israel, New Zealand, Poland Romania, Russia, Spain, the UK and the US.

Objectives

The primary objective of this study was to determine the long-term safety and tolerability of ranolazine ER 500 mg bid, 750 mg bid and 1000 mg bid administered in combination with other anti-anginal therapy(ies) in patients with chronic stable angina during an open-label treatment period of up to 8 years duration.

A secondary objective was to assess the long-term safety and tolerability of ranolazine ER 500 mg bid, 750 mg bid, and 1000 mg bid in patients who had reduced or discontinued concomitant anti-anginal medication(s).

Formulations

Ranolazine ER 375 mg (Lot Nos. 8H2750A, 8H2751A, 9G2715A, 0H2760A, 0H2761A, 1G2704A, 1H2727A, 1I2730A, 2A2760A, 2A2761A, 2D2769A, 1K2756A, 1K2758A, 3H3022A, 3K3051A and Ranolazine 500 mg tablets (Lot Nos. 8H2747A, 8H2749A, 0H2762A, 0H2763A, 1F2701A,1F2702A, 1H2725A, 1I2737A, 1I2738A, 1I2739A, 2D2770A, 1K2755A, 1K2753A, 3H3025A, 3H3027A, A02034A, A02038A.

Design

This was a long-term, open-label safety study of ranolazine ER administered with and without concomitant anti-anginal therapy in patients who had completed either 12 weeks of double-blind therapy in Study CVT 3033 or 6 weeks of double-blind therapy in study CVT 3037. Patients were initially administered the same anti-anginal therapy they received in study CVT 3033 or 3037. The background anti-anginal medications included diltiazem, atenolol, amlodipine with or with long acting nitrates. Once enrolled in study CVT-3034, investigators were permitted to adjust or discontinue background anti-anginals or add other anti-anginals based on the patient’s clinical condition. Patients were seen at weekly intervals for dose titration until their angina was controlled, then followed for 1 month after their last titration, and every 3-6 months thereafter.

The doses of ranolazine could be titrated up and down over a dose range of 500 mg bid, 750 mg bid and 1000 mg bid, based on clinical response.

The inclusion and exclusion criteria are listed below:

9.3.1 Inclusion Criteria

To be eligible for enrollment, patients had to satisfy the following requirements:

- Patients who had completed either Study CVT 3033 (through Visit 6) or Study CVT 3037 (through Visit 5) according to the respective protocol
- For female patients only: The patient was post-menopausal or sterilized, or if she was of childbearing potential, she was not breast feeding, her pregnancy test was negative, she had no intention of becoming pregnant during the course of the study, and she was using contraceptive drugs or devices
- Patients who reviewed the patient information sheet and signed an informed consent form for this study approved by the investigator's IRB or IEC
- Patients who were willing to comply with requirements of the protocol
- Patients who provided HIPAA authorization (U.S. residents only)

9.3.2 Exclusion Criteria

If patients had developed any of the listed exclusions since starting either Study CVT 3033 or Study CVT 3037 they were not be eligible to be entered into Study CVT 3034:

- New York Heart Association (NYHA) Class IV congestive heart failure
- Active acute myocarditis or pericarditis
- Hypertrophic cardiomyopathy
- Uncontrolled hypertension
- Clinically significant hepatic disease
- End-stage renal disease requiring dialysis or a calculated creatinine clearance (CLcr) < 30 mL/min
- Hypersensitivity to ranolazine
- Second or third degree atrioventricular block in the absence of a functioning ventricular pacemaker or uncontrolled clinically significant cardiac arrhythmias or a history of life-threatening ventricular arrhythmias unassociated with acute myocardial infarction (MI)
- Had a QTc interval measurement > 500 msec at Visit 5 of either Study CVT 3033 or Study CVT 3037 as determined by the investigator. Repeat ECGs were allowed to confirm the measurement if required.
- Had a need (or anticipated need) for treatment during the study period with any of the following agents which might interfere with the evaluation of the therapeutic response or safety of the study drug:
  - Agents known to prolong the QT interval, including, but not limited to:
    - Class IA anti-arrhythmics (e.g., quinidine, procainamide)
    - Class III anti-arrhythmics (e.g., amiodarone, sotalol, and dofetilide)
    - Phenothiazide anti-psychotics: chlorpromazine, mesoridazine, pimozide, and thioridazine
    - Quinolone antibiotics: gatifloxacin, moxifloxacin, and sparfloxacin
    - Others: droperidol, mefloquine, pentamidine, levomethadyl, dolasetron, systemic dosing of tacrolimus, arsenic trioxide, terfenadine, astemizole, and cisapride
    - Other drugs that have a contraindication or boxed warning regarding QT prolongation in the prescribing information
  - Agents that were inhibitors or inducers of the cytochrome P450 pathway isoform 3A4, including, but not limited to:
    - Erythromycin, clarithromycin, and troleandomycin
    - Ketoconazole and itraconazole (topical agents were permissible)
    - Phenytoin, carbamezepine, phenobarbital, and rifampin

- Nefazadone
- Antiviral drugs (e.g., delavirdine)
- Protease inhibitors (indinavir, nelfinavir, ritonavir, and saquinavir)
- Cyclosporin

An additional list of medications which affect cytochrome P450 3A4 was presented in the protocol.

- Unwillingness to refrain from grapefruit/grapefruit juice consumption for the duration of the study (grapefruit juice inhibits cytochrome P450 3A4)
- Any chronic illness likely to hinder or confuse compliance with the protocol (e.g., cancer, alcoholism, drug dependency or abuse, serious psychiatric illness, uncontrolled or labile diabetes mellitus, etc.)
- Any condition which might increase the risk to the patient
- Any condition which might decrease the chance of obtaining satisfactory data to achieve the objectives of the study

Prohibited Concomitant Medications included the following:

9.4.5.1 Prohibited Concomitant Medications

Medications which are known to prolong the QTc interval were not allowed to be taken by patients in this study. Prohibited medications included (but were not limited to) the following:

- Class IA anti-arrhythmics (e.g., quinidine, procainamide)
- Class III anti-arrhythmics (e.g., amiodarone, sotalol, dofetilide)
- Phenothiazide anti-psychotics: chlorpromazine, mesoridazine, pimozide, thioridazine
- Quinolone antibiotics: gatifloxacin, moxifloxacin, sparfloxacin
- Others: droperidol, mefloquine, pentamidine, levomethadyl, dolasetron, systemic dosing of tacrolimus, arsenic trioxide, terfenadine, astemizole, cisapride
- Other drugs that have a contraindication or boxed warning regarding QT prolongation in the prescribing information

Medications that are inhibitors or inducers of cytochrome P450 3A4 were not allowed; they included, but were not limited to the following:

- Erythromycin, clarithromycin, and troleandomycin
- Ketoconazole and itraconazole (topical agents were permissible)
- Phenytoin, carbamazepine, phenobarbital, rifampin
- Nefazadone
- Antiviral drugs (delavirdine)
- Protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir)
- Cyclosporin

An additional list of medications that affect cytochrome P450 3A4, was presented in the protocol.

Other medications metabolized by cytochrome P450 such as diltiazem should have been used with caution.

In addition to these concomitant medications, grapefruit/grapefruit juice consumption was prohibited for the duration of the study.

Allowed medications included the following:

9.4.5.2 Allowed Concomitant Medications

- Sublingual nitroglycerin was permitted for treatment of acute angina.
- Aspirin was permitted during the study.
- Any digitalis preparation (e.g., digoxin) was permitted during the study. However, if a patient received digoxin therapy, serum digoxin levels should have been monitored.
- The use of statins was permitted during the study.
- Background antianginal therapy from either Study CVT 3033 (atenolol, amlodipine, or diltiazem), or Study CVT 3037 (amlodipine [and a long-acting nitrate patch or isosorbide mononitrate if applicable]), at the same dose(s) used in Studies CVT 3033/3037, should have been continued initially in Study CVT 3034. Doses of the background antianginal therapy(ies) may have been increased to maximize the therapeutic effect . At the investigator's discretion, if the angina symptoms were controlled on ranolazine ER plus background antianginal medication(s), and/or if the patient experienced AEs which the investigator felt were attributable to the background antianginal medication(s), the background antianginal medication(s) may have been discontinued in Study CVT 3034 according to the titration dose adjustment scheme outlined previously.

Notes:

- Calcium channel blockers and/or beta-blockers should not have been administered solely as anti-hypertensive therapy
- Calcium channel blockers and/or beta blockers may have been used to treat hypertension ONLY if they were being used as concomitant antianginal medications and were being administered to the patient strictly as outlined in the protocol for concomitant antianginal therapy. Diuretics and angiotensin converting enzyme (ACE) inhibitors may have been administered as anti-hypertensive therapy

Use or changes of any/all concomitant medications were to be documented on the appropriate CRF.

Pharmacokinetic Profiling

Blood samples for the determination of ranolazine trough concentrations were collected approximately 12 h after the last study medication beginning at the first long-term maintenance visit (Visit 3) and at all subsequent maintenance visits (i.e. 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69 and 72 months) after start of the long term Maintenance Phase.

Pharmacokinetic Analysis

The ranolazine trough plasma concentrations data were grouped into time intervals centered around time points every 3 months after start of dosing. Mean, median, 25th percentile, 75th percentile, minimum and maximum trough plasma concentrations of ranolazine for the patients were computed for the above time points.

RESULTS

Demographics of Subjects

The mean age of the patients is 63.1 (±9) years, 76% are males and 99% Caucasians.

Disposition of Subjects

Table 2 Patient Disposition

	Overall n = 1,108
No. of patients who completed treatment	814 (73.5%)
No. of patients who terminated prematurely	294 (26.5%)
Primary reason for premature termination of the study	
Unacceptable adverse event	65 (5.9%)
Non-compliance	5 (0.5%)
Elective withdrawal	122 (11.0%)
Lost to follow-up	13 (1.2%)
Death	65 (5.9%)
Other	24 (2.2%)

Source: Section 14.1.1

Concomitant Medications

The most frequently used concomitant medications were platelet aggregation inhibitors (90 % (e.g. acetylsalicylic acid), organic nitrates (90%, e.g. glyceryl trinitrate and isosorbide mono- and dinitrate), calcium channel blockers (81%, e.g. diltiazem 16%, verapamil 1%), ACE inhibitors (53%, e.g. enalapril) HMG CoA reductase inhibitors (50%, e.g. simvastatin and atorvastatin) and α- and β- blocking agents (47%, e.g. atenolol)

Safety

A summary of the adverse events is given in the below table:

Table 4 Summary of Adverse Events (Includes Ongoing Adverse Events Originating in Studies CVT 3033/3037)

Number of Patients:	Total (n = 1,108)
Any adverse event	678 (61.2%)
Any potentially study drug related adverse event	166 (15.0%)
Discontinued the study due to an adverse event	90 (8.1%)
Any serious adverse event	290 (26.2%)
Death	74 (6.7%)

Source: Section 14.3.1

There were no reports of Torsades de Pointes. No patient met the protocol defined criteria for QTc prolongation (QTc > 500 ms and widening of >130 ms from baseline). Four patients experienced QTc prolongations of > 500 ms at one or more time points.

Pharmacokinetics

Plots of the mean (SD) trough plasma concentrations of ranolazine over time for the 500 mg bid, 750 mg bid and 1000 mg bid regimens are shown in the below 3 figures and the corresponding median and individual maximum ranolazine concentrations at each time point are listed in the below 3 tables:

Figure 5 Mean (+SD) Plasma Ranolazine Concentrations Over Time at Dose 500 mg for CVT 3034

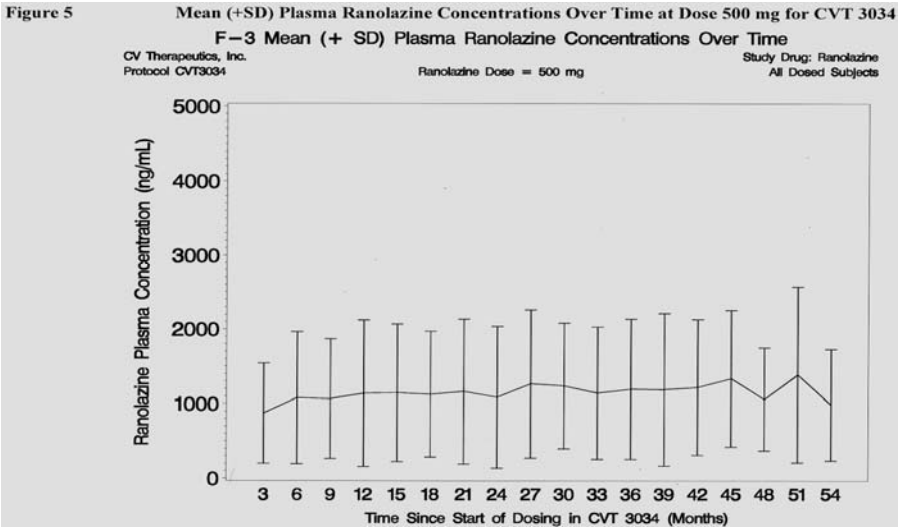


Figure 6 Mean (+SD) Plasma Ranolazine Concentrations Over Time at Dose 750 mg for CVT 3034

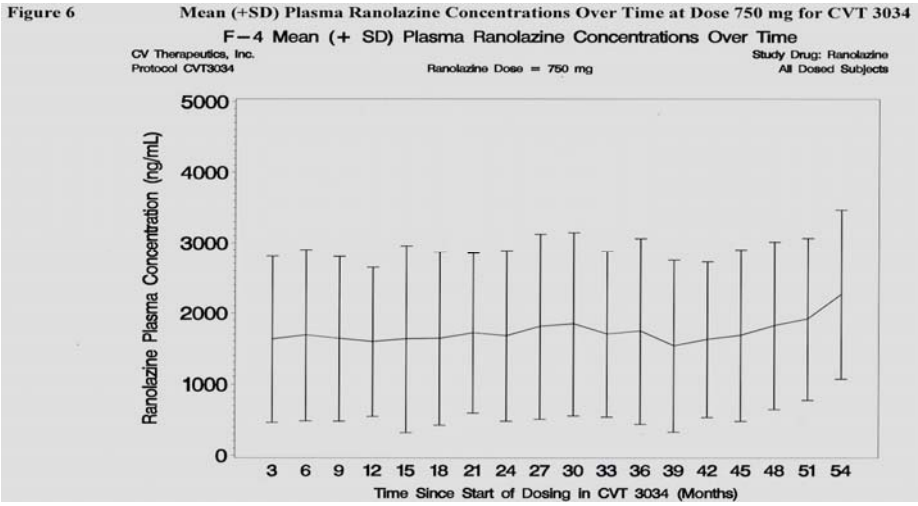
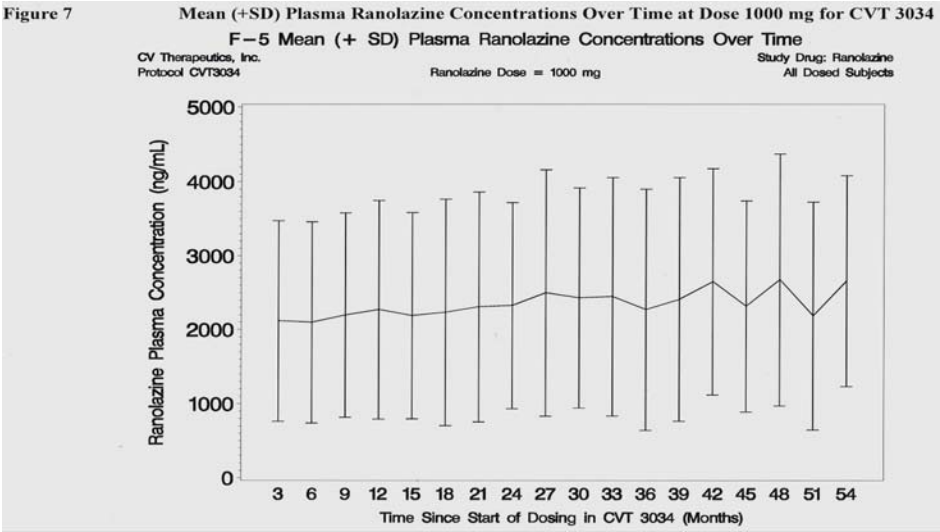


Figure 7 Mean (+SD) Plasma Ranolazine Concentrations Over Time at Dose 1000 mg for CVT 3034



Median Trough and Individual Maximum Trough Plasma Concentrations of Ranolazine During a Regimen with 500 mg bid

Month	n Subjects	Median Trough Concentration ng/mL	Individual Maximum Trough Concentration ng/mL
3	122	805	3900
6	104	948	4340
9	108	800	3690
12	107	952	6340
15	98	941	4730
18	92	1100	5140
21	97	905	4810
24	97	884	5130
27	90	1080	5240
30	89	1110	3740
33	84	996	3740
36	72	988	4150
39	68	1040	5470
42	57	963	4730
45	47	1140	3980
48	36	865	3005
51	13	1290	4560
54	7	965	1930

Median Trough and Individual Maximum Trough Plasma Concentrations of Ranolazine During a Regimen with 750 mg bid

Month	n Subjects	Median Trough Concentration ng/mL	Individual Maximum Trough Concentration ng/mL
3	211	1370	6720
6	222	1450	7200
9	239	1400	6540
12	211	1430	6460
15	208	1320	7210
18	198	1410	6505
21	180	1565	5330
24	163	1470	5750
27	164	1610	8620

30	141	1730	6930
33	128	1445	6380
36	112	1495	6810
39	97	1460	5840
42	87	1450	4450
45	79	1390	6050
48	48	1588	5050
51	30	1890	4540
54	11	2190	4230

Median Trough and Individual Maximum trough Plasma Concentrations of Ranolazine During a Regimen with 1000 mg bid

Month	n Subjects	Median Trough Concentration ng/mL	Individual Maximum Trough Concentration ng/mL
3	202	1930	6590
6	168	1935	6050
9	159	2000	7350
12	170	2265	8430
15	175	2020	7160
18	170	1840	7060
21	180	2170	7870
24	170	2080	5490
27	176	2275	9520
30	167	2230	7530
33	109	2165	7800
36	79	2070	7240
39	73	2390	9580
42	58	2560	6290
45	40	2100	5280
48	23	2650	5660
51	17	2340	4900
54	11	2810	4780

The median and mean trough concentrations as well as the standard deviations show no time dependency, even tough the number of subjects decreased over time. The large values of the standard deviation point to the known significant inter-subject variation of the exposure to ranolazine.

Conclusions

The median trough plasma concentrations measured over a period of 72 months at the 500 mg bid, 750 mg bid and 1000 mg bid levels of ranolazine varied between 800 ng/mL and 1290 ng/mL, 1370 ng/mL and 2190 ng/mL and 1840 ng/mL and 2810 ng/mL, respectively.

Comments

None

4. PARMACOMETRICS REVIEW

NDA	21526
Submission Date(s)	23 September 2007
PDUFA Due Date	23 July 2008
Brand Name	Ranexa®
Generic Name	Ranolazine
Dosage Form	Extended release tablet
Dosage Regimen	500 mg bid increased to 1000 mg bid if needed based on clinical symptoms
Pharmacometrics Reviewer	Nitin Mehrotra, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Clinical Pharmacology Reviewer	Peter Hinderling, M.D.
Clinical Pharmacology Team Leader	Patrick J Marroum, Ph. D.
Sponsor	CV Therapeutics Inc.
Submission Type	NDA Supplement
Proposed indication	Chronic Angina

Executive Summary

The aim of the document is to evaluate if the transition from intravenous infusion to oral dosing in study CVT 3036 resulted in similar exposure of ranolazine in the two dosing periods.

The key question of the present review is:

Did the transition from intravenous infusion to oral extended release formulation resulted in comparable ranolazine plasma levels?

A reasonable population PK model was developed and simulations were conducted both at population and individual level to predict the steady state concentrations after i.v. infusion and compared with observed oral concentrations at steady state. It was seen based on population simulations that the average oral steady state concentrations (calculated based on observed oral data and prior information) were randomly distributed around the mean predicted steady state concentration after i.v. infusion. Similar results were observed after individual level simulations. Thus, it could be concluded that the transition from infusion to oral dosing resulted in comparable exposures.

Recommendation

None

Signatures:

Nitin Mehrotra, Ph.D.	Yaning Wang, Ph.D.
Pharmacometrics Reviewer	Pharmacometrics Team Leader
Office of Clinical Pharmacology	Office of Clinical Pharmacology

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Labeling Statements

There are no relevant statements directly referring to the present population pharmacokinetic analysis and simulations or its implication in the label.

Introduction

Ranolazine (Ranexa®) is approved by the US FDA for the treatment of chronic angina pectoris in combination with amlodipine, β-adrenoceptor antagonists or nitrates in patients who do not respond to other anti-anginals.

Sponsor's Analysis

Study CVT 3036 was conducted to support:

• The use of Ranexa for first-line treatment of chronic angina;

• Reduction of the cautionary language in the Ranexa labeling regarding the observation of QT prolongation; and

(b) (4)

(b) (4)

As part of study CVT 3036 which involved the treatment of ranolazine initiated as a continuous intravenous infusion followed by long term oral administration of the extended release formulation, sponsor developed a population pharmacokinetic model and using simulations showed that the transition from intravenous infusion to oral dosing resulted in comparable exposures of ranolazine.

Population Pharmacokinetics of Ranolazine

Objectives

To evaluate using simulation that the transition from intravenous infusion to oral extended release formulation resulted in similar ranolazine plasma concentrations.

Study Design and Available Data

An i.v. infusion of study drug (ranolazine/placebo) was initiated with 200 mg administered over 1 hour, followed immediately by an 80 mg/h i.v. infusion. The infusion was to be continued for a minimum of 12 hours and up to 96 hours.

The first dose of oral study medication was to be administered prior to termination of the infusion (optimally 1 hour prior to termination); the first dose of oral ranolazine (or matching placebo) was based on the infusion rate at the time of transition, as follows:

Intravenous Dose at Transition	Oral Dose	Preparation
80 mg/h	1000 mg, bid	2 x 500 mg tablet
60 mg/h	750 mg, bid	2 x 375 mg tablet
40 mg/h	500 mg, bid	1 x 500 mg tablet
30 mg/h	375 mg, bid	1 x 375 mg tablet

At selected centers in North America, blood samples were obtained at the following time points for determination of plasma ranolazine levels: 12–16 hours and 24–36 hours after randomization, at the end of the iv infusion, and at trough after oral administration (12 hours after the previous dose) on Day 14 and Month 4.

Of the patients providing pharmacokinetic data, the great majority received the loading infusion of 200 mg over one hour followed by a maintenance infusion of 80 mg/h for approximately 24 hours. Oral doses of 1000 mg bid were thereafter administered throughout the study. A few patients received i.v. infusions of 60 mg/h or 40 mg/h during the maintenance infusion period due to reduced renal function; after the i.v. phase, these patients received oral doses of 750 mg or 500 mg ranolazine bid, respectively.

A total of 220 plasma samples from 112 patients were available for the analysis. In 4 samples, the ranolazine plasma concentration was significantly higher than the rest; these samples were deemed to be outliers and were excluded from the modeling analysis. In addition, 15 samples had duplicate values; the mean data at each time-point were used for the analysis. The final data file included 201 data points from 111 individuals. During the oral dosing period, 273 plasma samples were collected from 132 patients. Of these samples, 22 had no detectable ranolazine concentration, and 1 was deemed as an outlier due to an inordinately high concentration. Six of

the patients were receiving lower ranolazine doses relative to the rest of the group because of low creatinine clearance values; data from these patients were excluded when comparing oral data with the population simulation

Bioanalytical Method

The samples were analyzed using LC/MS/MS validated method (PCB-00-B-M004 amendment 1). The amendment was done to enable use of 96 well plates for extraction and injection as apposed to culture tubes used for sample preparation and HPLC vials for sample injection in the original method. The quantitation limit of the assay was 50 ng/ml with a calibration range of 50-1000 ng/ml. The mean accuracy, expressed as percent relative error ranged between -4.8 and 6% while the precision ranged from 0.7 to 13% across concentrations. The complete details of amendment and the original validated method can be found at \\cdsesub1\evsprod\NDA021526\\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-pcd-00-b-m004\study-pcd-00-b-m004.pdf

Analysis Methods

A mixed effect modeling approach, using NONMEM, version VI ((b) (4) , was used in modeling the i.v. data. During the modeling process, 1- and 2-compartment models were tested. Model selection was based on a drop of 10.8 in the objective function value provided by NONMEM, graphical analysis (using Xpose software), and a predictive check of the model.

The estimated individual i.v. pharmacokinetic parameters were used to simulate an i.v. infusion over the entire study period, which was used to determine the steady-state concentration for each patient. The predicted steady state level during the iv infusion was compared with the observed plasma concentrations after oral dosing at a population and an individual level. In the population simulation, mean population estimates of the iv pharmacokinetic parameters were used to predict the typical concentration-time profile for an iv dosing regimen of 200 mg/h for 1 hour followed by 80 mg/h for over 460 days. This concentration profile was compared with the observed oral administration concentration data from all individuals who received this standard dosing regimen. Results are presented where the predicted steady-state ranolazine plasma concentration levels (with 5th and 95th percentiles) have been extended beyond the actual duration of the i.v.

infusion to facilitate the comparison with the observed concentrations during the oral dosing period. For individual simulations, the empirical bayesian estimates of volume of distribution and clearance were used to simulate the concentration at various time points for which the oral data was available. The difference between simulated infusion concentrations and observed oral concentrations was plotted against individual simulated concentrations.

Results (Sponsor's Analysis)

Population Pharmacokinetics

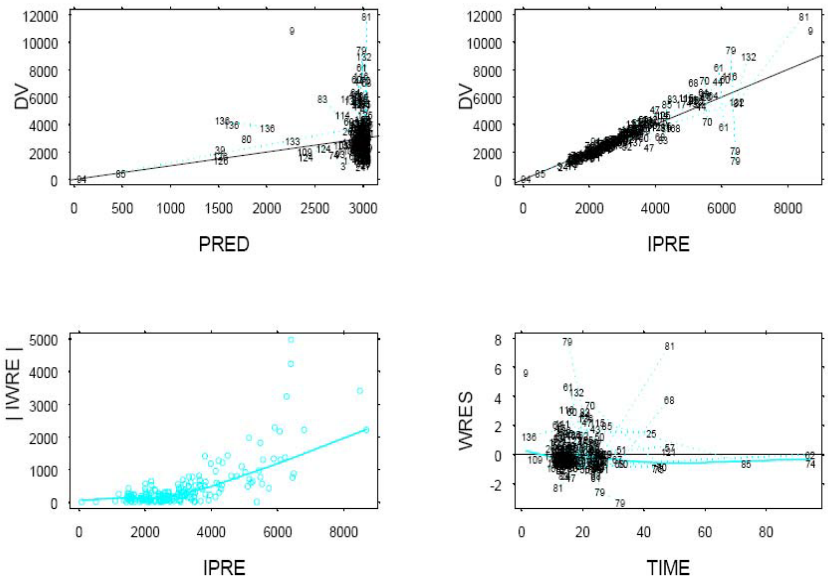
Final Model

The final model was a 1-compartment system with interindividual variability (IIV) in both clearance and volume of distribution parameters, and an exponential error term, using untransformed data. Model parameters are shown in Table 1, and a few diagnostic plots are shown in (Figure 1). A visual predictive check was performed to evaluate the performance of the model (Figure 2).

Table 1: Parameter estimates for the final model.

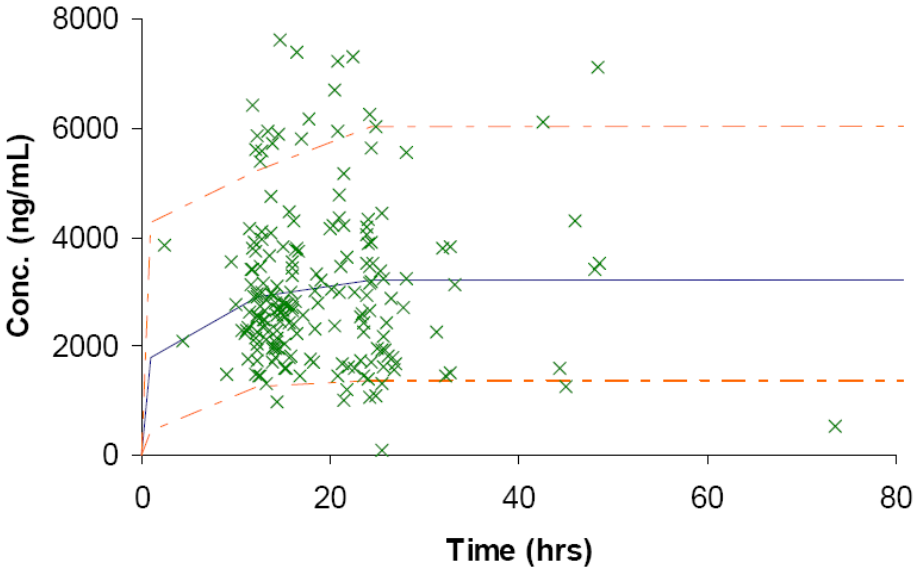
Parameter	Estimate (%RSE)	%Between Subject Variability (%RSE)
Clearance (L/h)	26.3 (5.3)	46 (17)
Volume of distribution (L)	113 (29)	74 (41)
Residual Variability (Proportional Error)	22 (33)	--

Figure 1: Basic goodness of fit diagnostic plots for the Final pharmacokinetic model.



DV = dependent variable (observations), PRED = population prediction, IPRE = individual prediction, IWRE = individual weighted residuals, WRES = weighted residuals

Figure 2: Visual predictive check.



The solid line represents the population prediction, the dashed lines represent the 5th and 95th percentiles. The X's are the observations.

Covariate assessment

No covariate analysis was performed by the sponsor.

Model evaluation

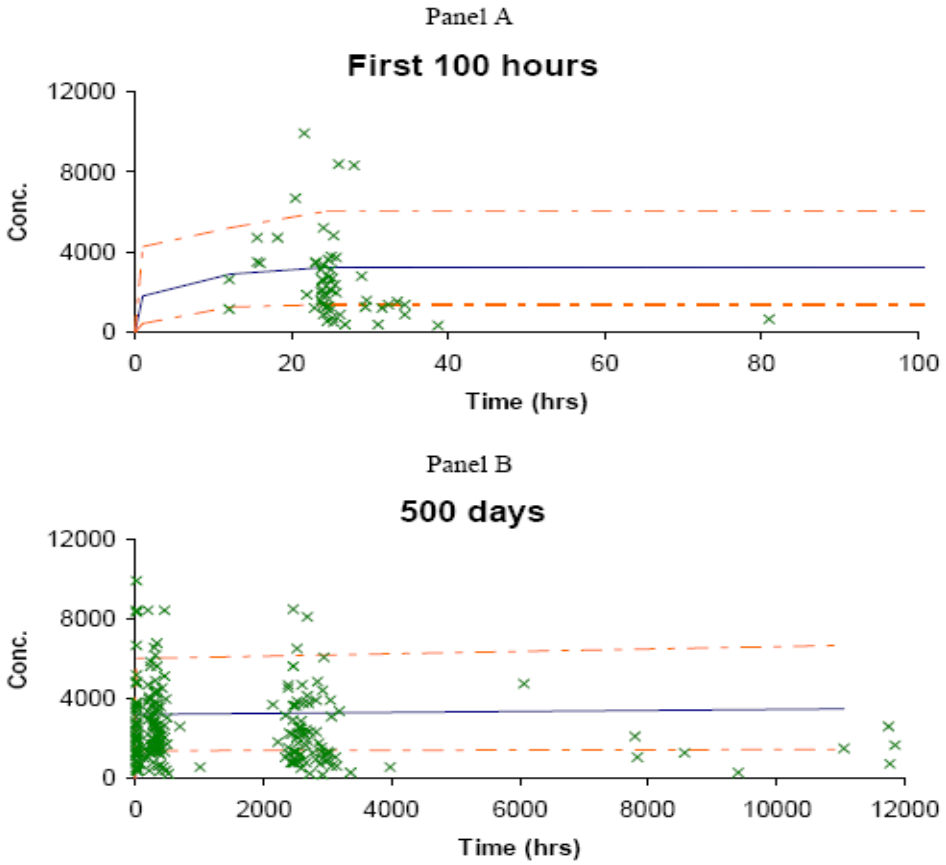
A visual predictive check was performed to evaluate the performance of the model (Figure 2).

Simulation

The simulation results suggest a successful transition from iv infusion dosing to oral dosing, with a majority of the predominantly trough observations during oral dosing falling slightly below the estimated steady state concentrations during the iv phase (Figure 3). The population prediction of the ranolazine concentration at steady-state was 3448 ng/mL, and the arithmetic mean value of all observed concentrations during oral dosing was 2492 ng/mL.

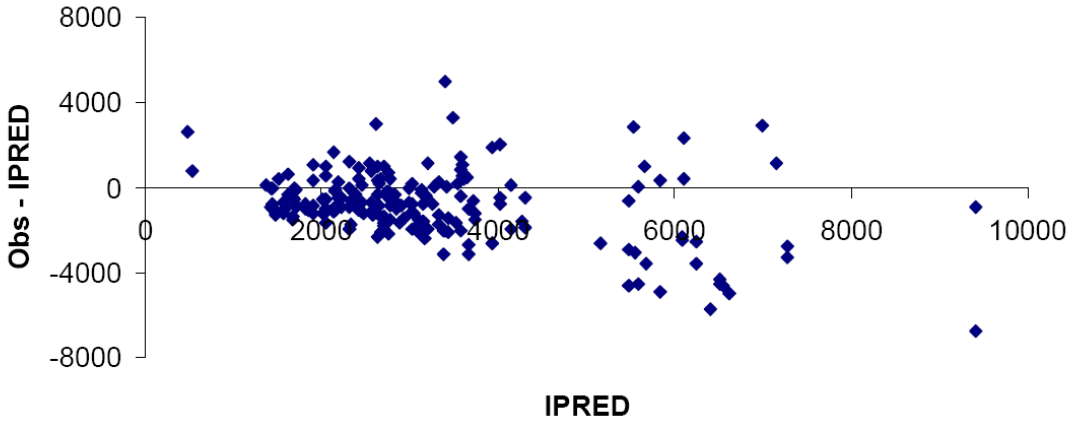
Figure 4 shows individual residuals, i.e. the difference between the actual concentration following oral dosing (oral observation) and the concentration from the simulation of the extended iv infusion (simulated infusion) vs the individual predictions from the simulation. Of the total 201 data points, 151 (75%) are less than 0, while 50 (25%) are greater than 0. The mean deviation between the individually predicted iv steady-state concentration and the observed concentration during the oral phase was −882.

Figure 3: Population Simulation of Intravenous infusion.



Population simulation of iv infusions (200 mg/h for 1 hour followed by 80 mg/h for an extended period of time).
The solid line represents the population prediction, the dashed lines represent the 5th and 95th percentiles. The X's are the observations.
Panel A shows the first 100 hours, and **Panel B** represents a simulated infusion for 500 days.

Figure 4: Individual Residuals (Oral Observation - Simulated Infusion) vs Individual Predictions.



Conclusion

In conclusion, despite a limited number of samples and a rather complex underlying pharmacokinetics of ranolazine, a reasonable i.v. model was developed. The predicted steady state levels were compared with the observed data after oral administration of ranolazine. Study results suggest an adequate transition from the initial i.v. infusion to the long-term oral administration of ranolazine.

Reviewer's comments

The approach of the Sponsor in evaluating the transition from i.v. infusion to oral dosing seems to be reasonable. However, the dataset utilized by the sponsor to build the population PK model was inappropriate. The sponsor had planned to use only intravenous data to build the population model while the dataset (the i.v. infusion dataset) used to develop this model actually includes observations after administration of oral dose. Thus, the reviewer trimmed the dataset to include only those observations after intravenous infusion. The population PK model was re-built with minor modifications, evaluated and population and individual simulations performed again. Furthermore, sponsor compared the predicted intravenous infusion steady state exposures to observed oral trough concentrations which is not a reasonable comparison as trough concentrations would always be lower than the average steady state exposures. Therefore reviewer calculated the average steady state concentrations after oral administration using observed data and prior information, and used these to compare to predicted steady state exposures after i.v. infusion (see simulation for details).

Reviewer's Analysis

Data

Data from 93 patients (114 observations) was used to develop the population PK model such that 80% of patients had only one observation. Considering the sparse nature of the data, it was decided to fix the volume of distribution and it's between subject variability to 110 L (mean population estimate) and 67% respectively which is reported earlier in a population pharmacokinetic analysis.

Analysis Methods

NONMEM VI using FOCE with interaction was utilized to estimate the parameters. One compartment model with interindividual variability in clearance modeled using exponential structure reasonably described the data. Residual variability was also described using exponential error model.

Covariate assessment

Visual inspection of the plots of interindivdual variability in CL (ETA1) vs weight (WT) depicted a clear pattern. Thus, CL was allometrically scaled for weight using power model of 0.75 with weight centered around its median (91.0 kg).

Final Model

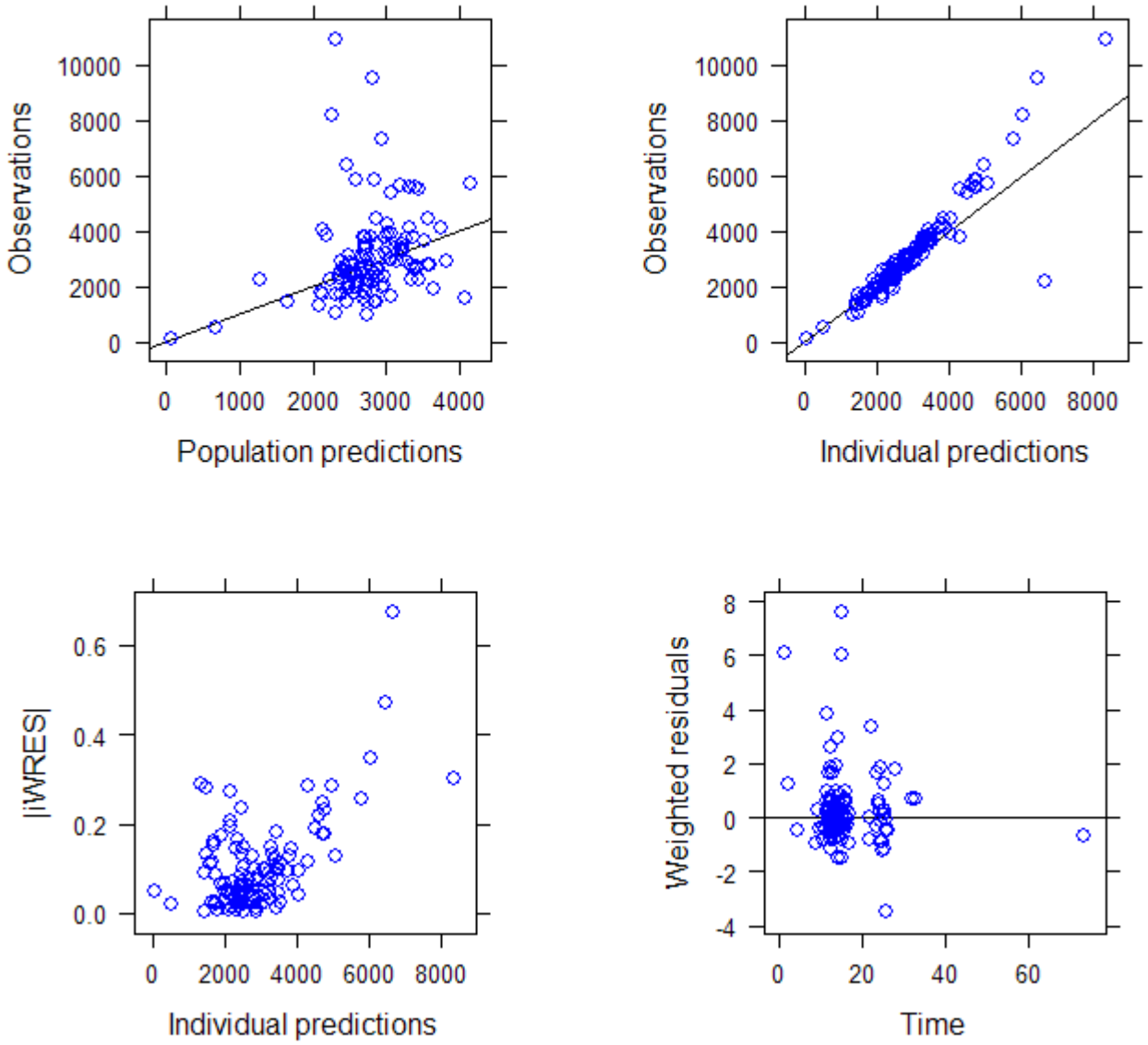
Inclusion of WT as a covariate on CL decreased the objective function by 5.7 and also improved goodness of fit diagnostics (Figure 5).

Moreover, weight was a covariate in the population pharmacokinetic model developed for oral extended release formulation earlier and thus was included in the final model. The final parameter estimates are presented in Table 2 which are similar to sponsor's results (Table 1).

Table 2: Parameter estimates for the Reviewer's final model.

Parameter	Estimate (%RSE)	% Between subject variability (%RSE)
Clearance (L/h)	27.5 (4.4)	37.5 (23.4)
Volume of distribution (L)	110 FIXED	67 FIXED
Residual variability (%) (Exponential Error)	22.4 (48.2)	-

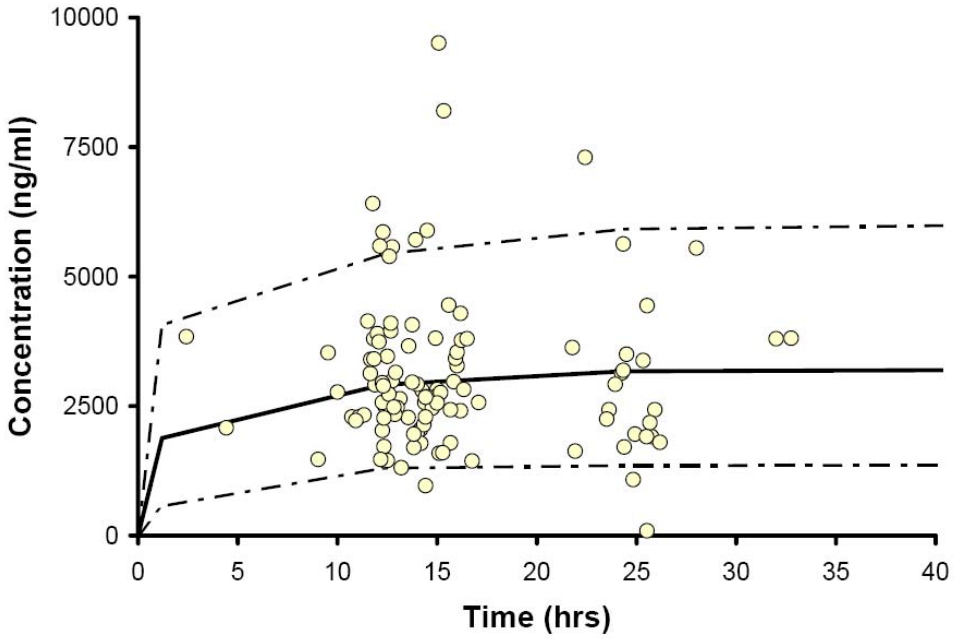
Figure 5: Basic goodness of fit diagnostic plots for the Reviewer's Final pharmacokinetic model. (Solid lines in top two plots represent lines of identity)



Model evaluation

Visual predictive check was performed to evaluate the model which showed that the model provided a reasonable summary of the data in hand (Figure 6).

Figure 6: Visual predictive check (Reviewer's model); Solid line represents the population prediction while dashed lines represent 90% confidence interval; open circles are the observed data available after i.v. infusion.



Simulation

Population and individual simulations were performed in the similar method as described above under Sponsor's Analysis. A factor was calculated as the ratio of the average steady state concentration of ranolazine after 1000 mg bid (obtained from an earlier pharmacokinetic study (RAN0114) to the average (geometric mean) of the observed oral concentrations. All the observed oral concentrations were multiplied by this factor (1.45) to calculate the average steady state concentrations and were used for comparison with predicted steady state exposures after i.v. infusion (Figure 7 and 8).

Figure 7: Population simulation (Reviewer's model); Solid lines represent the population prediction while dashed lines represent 90% confidence interval; open circles are the calculated average steady state concentrations after oral administration based on observed oral data.

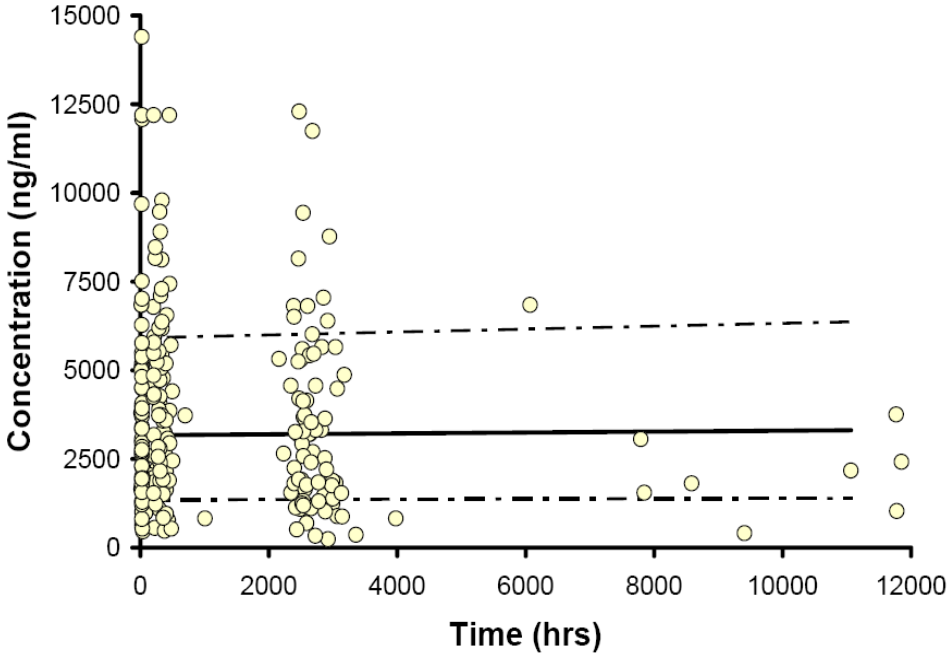
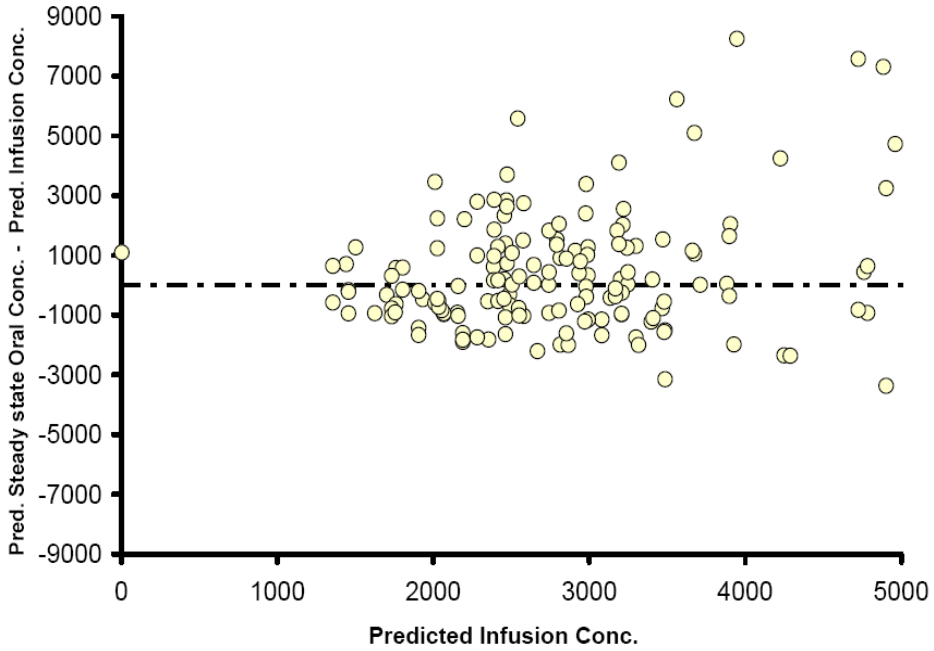


Figure 8: Individual simulation (Reviewer's model); Individual residuals vs predicted concentration after intravenous infusion.



Conclusions

The calculated average steady state concentrations were randomly scattered around mean population predicted steady state concentration after i.v. infusion which is in accordance with individual simulations where approximately 52% of the residuals (Oral-infusion) were more than zero (Figure 7 and 8). Thus, based on these simulation results and also considering higher variability after oral dosing when compared to i.v. infusion, it could be concluded that the transition from i.v. infusion to oral administration resulted in comparable exposures.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	SE 21526	Brand Name	Ranexa
OCPB Division (I, II, III)	I	Generic Name	Ranolazine
Medical Division	DCRP	Drug Class	Antianginal
OCPB Reviewer	Hinderling	Indication(s)	Angina pectoris
OCPB Team Leader	Marroum	Dosage Form	Extended release Tablets
		Dosing Regimen	bid
Date of Submission	September 27, 2007	Route of Administration	oral
Estimated Due Date of OCPB Review	May 1, 2008	Sponsor	CV Therapeutics
PDUFA Due Date	July 27, 2008	Priority Classification	S
Division Due Date	April 20, 2008		

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				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	x	1		

Patients-				
single dose:	x	1		
multiple dose:	x	4		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	1		
In-vivo effects of primary drug:				
In-vitro:	x	1		
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	X	1		
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:		**1**		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:		**1**		
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**5**	**7**		
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 ?	**None**	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**NA**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Peter Hinderling 5-20-08**	
Secondary reviewer Signature and Date	**Patrick Marroum 5-20-08**	

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

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
5/23/2008 01:36:32 PM
BIOPHARMACEUTICS

Patrick Marroum
5/23/2008 01:39:23 PM
BIOPHARMACEUTICS

NDA #21526 NDA supplement (S-004)
Name of Sponsor: CV Therapeutics, Inc.
Name of Finished Product: Ranexa®
Name of Active Ingredient: Ranolazine

Introduction

Chronic stable angina

This efficacy supplement proposes to change the use of Ranexa® from second-line to first-line of treatment for patients with chronic stable angina. The sponsor submitted the results of protocol CVT 3036 in the defense of this application.

Protocol CVT 3036 was reviewed as a special clinical protocol assessment (May 7, 2004, request, serial number 232). The study was designed to investigate the possible association of QT prolongation provoked by ranolazine and excess mortality. The Agency stated that

> [a well controlled, well conducted, adequately sized trial showing] "no adverse trend in death and arrhythmia would be assuring and could support approval of ranolazine as first-line therapy for long-term treatment of chronic angina. The interpretability of the safety results in this regard does not depend on the primary endpoint reaching statistical significance."

There were additional safety data submitted from six clinical trials (1 interaction trial with diltiazem, 1 trial in subjects with congenital long QTc[1], 1 trial with higher doses of ranolazine, 3 trials with uncontrolled long term safety information). There is little new information obtained from the results of these trials.

Decrease of clinically significant arrhythmias

There was a decrease in the incidence of clinically significant arrhythmias[2] found during the 7-day Holter monitoring period (83% and 74% for placebo and ranolazine, respectively; table 24 clinical study report). However, the analysis showing statistical significance is invalid because:

1. the original objective was not met so additional analyses are inappropriate;
2. the endpoint was not an efficacy endpoint but rather part of a long list of safety objectives[3].

In addition, this "finding" seems to occur in a vacuum: the incidence rates for sudden death were similar for the two treatment groups, there were no differences between placebo and ranolazine regarding other types of non fatal arrhythmias including those that were

[1] CVT 3114 was previous evaluated and is not discussed in this review.
[2] Defined as ventricular tachycardia ($\geq$ 3 beat), supraventricular tachycardia with ventricular rate of $\geq$ 120 bpm, new-onset atrial fibrillation, and bradyarrhythmia with ventricular rate of < 40 bpm or 3rd degree AV block.
[3] 1.1.4 of statistical analysis plan dated 8-25-2006.

symptomatic (table 23 of study report), and there were only minor differences between the treatment groups in the reporting of various arrhythmias as adverse events (14.3.1.4.1).

Currently, there is insufficient evidence that ranolazine decreases arrhythmias of any kind. A prospectively defined, placebo controlled study with the occurrence of symptomatic arrhythmias as the primary endpoint is, therefore, required.

Conclusions

Protocol CVT 3036 enrolled a total of 6556 subjects who were hospitalized for non-ST elevation acute coronary syndrome (ACS) with the qualifying event being at least one episode of ischemic symptoms at rest. Subjects were randomized to either ranolazine or placebo and followed for at least 8 months.

The primary efficacy endpoint was a composite of cardiovascular (CV) death, MI, and recurrent ischemia. The primary efficacy analysis was time from randomization to first occurrence of CV death, myocardial infarction (MI), or recurrent ischemia. The null hypothesis was that there is no difference between the study treatments with respect to the time to first occurrence of any element of the primary efficacy endpoint.

Key results: There were 1448 subjects who experience a primary efficacy event. The null hypothesis was not rejected. There was no statistical difference between the treatment groups for the composite endpoint (p=0.11).

The incidence of death from any cause was approximately 5.3% for both treatment groups. The relative risk of mortality (ranolazine: placebo) was 0.988 (95% CI 0.80, 1.21). Therefore, a 21% or greater increase in mortality resulting from ranolazine use can be excluded with 95% confidence. The percents of those deaths deemed to be sudden were also similar for the two treatment groups (2% for placebo and 1.7% for ranolazine).

Based on the findings of this medium sized study, ranolazine, compared to placebo and within certain limits, does not increase mortality, the occurrence of MIs, or recurrent ischemia in subjects with non-ST elevation ACS. It is reasonable to allow the promotion of ranolazine as a first-line treatment for chronic stable angina.

Conclusions from the 6 additional trials are:
-The addition of diltiazem 180 mg bid increases ranolazine AUC_{0-12} by more than 2 fold (CVT 301-19);
-many subjects are unable to tolerate doses 1500 mg bid and above. Dose limiting adverse events include syncope, nausea, dizziness, and vomiting (CVT 3023);
-no unexpected adverse events were reported in the uncontrolled safety trials (CVT 3024, 3032, 3034).

Study CVT 3036, the clinical outcome trial, is discussed in detail in this review. The other studies are briefly presented.

Background

A total of seven studies were submitted to support the efficacy supplement. These are briefly outlined below.

Study ID	Design	No. of subjects dosed	Doses used	Duration of rx	Major objective
CVT 3036 (MERLIN)	Double blind, randomized	6541	RAN IV infusion RAN 375/500 mg ER bid	8 months	Clinical outcome trial (including survival)
CVT 301-19	Open label, cross over	31	RAN 500 and 1000 mg Diltiazem 90 mg	2 weeks	Diltiazem interaction
CVT-3023	Double blind, randomized	37	RAN 375 mg ER	2 weeks	Tolerability of extended release
CVT 3024	Open label follow up to CVT 3023	9	RAN 500 mg ER bid	14 months	Safety
CVT 3032	Open label follow up to CVT 3031	143	RAN ER 375, 500,750 mg bid	Mean exposure 3.8 years	Safety
CVT 3034	Open label follow up to CVT 3033 and 3037	1108	RAN 500,750, 1000 mg ER bid	Mean exposure 2.25 years	Safety

Study CVT 3036

Title: Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes (MERLIN)-TIMI 36

The study was conducted by 457 investigators at 442 sites in 17 countries.

Study Period: October 8, 2004 (first patient enrolled) to February 14, 2007 (last patient completed)

Objectives: The primary efficacy objective was to determine if ranolazine compared to placebo is effective in reducing the rate of cardiovascular (CV) death, myocardial infarction (MI), or recurrent ischemia during long-term treatment of patients with non-ST elevation acute coronary syndrome (ACS) receiving standard therapy.

Secondary efficacy objectives were to determine whether ranolazine was superior to placebo:
(1) for reducing the rate of major cardiovascular events (CV death, MI, or severe recurrent ischemia) during long-term treatment;

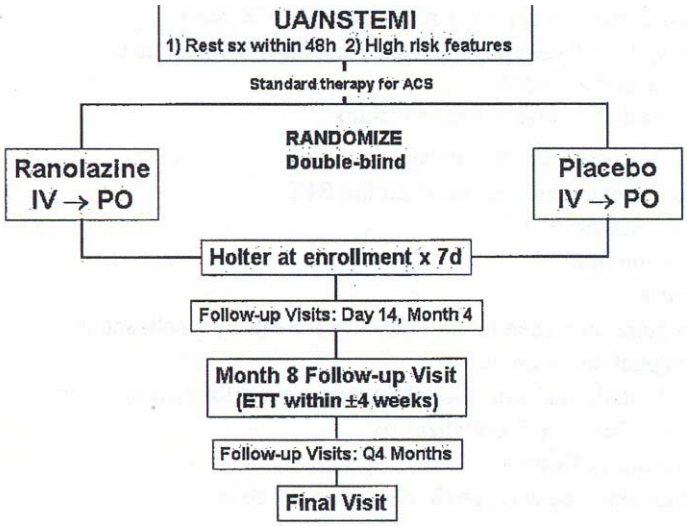
(2) for reducing the rate of failure of therapy (CV death, MI, recurrent ischemia, positive Holter for ischemia, hospitalization for new/worsening heart failure, or early positive exercise tolerance test [ETT]) during long-term treatment;
(3) for reducing the rate of CV death, MI, severe recurrent ischemia, or positive Holter for ischemia during acute treatment (30 days);
(4) for improving quality of life (QOL) as assessed using the anginal frequency scale and the physical limitation scale of the Seattle Angina Questionnaire (SAQ) at 4 months;
(5) with respect to the duration of exercise on ETT at 8 months (or Final Visit if earlier); and
(6) with respect to the total duration of ischemia on Holter monitoring early after presentation with ACS (between randomization and 72 hours).

Methodology: This was a randomized, double-blind, parallel-group, placebo-controlled, multinational clinical trial. Eligible patients were randomized no later than 48 hours after the most recent rest symptoms in a 1:1 ratio to receive either ranolazine or placebo, stratified by the physicians intended initial management strategy (early invasive vs. conservative) as declared at the time of randomization.

Ranolazine (or matched placebo) was administered initially as a 200 mg intravenous (iv) infusion over 1 hour, followed by an 80 mg/h infusion (or 40 mg/h for patients with severe renal insufficiency), adjusted downward for patients experiencing adverse events deemed treatment related. The infusion was to be continued for a minimum of 12 hours and up to a maximum of 96 hours.

Patients to be managed with an early invasive evaluation were to have received iv ranolazine/placebo for at least 6 hours prior to angiography, and for a minimum of 6 hours after percutaneous coronary intervention. Following infusion, patients were transitioned to oral ranolazine (or matched placebo) at a dose of 1000, 750, 500, or 375 mg bid, based upon the final infusion rate. Oral dose adjustments were to be made for patients with renal insufficiency, and those experiencing adverse events deemed to be treatment related. Patients were to be treated with ranolazine or placebo until the end of follow-up. However, patients who discontinued therapy continued to be followed for efficacy endpoints and survival until the end of the study.

Patients were to receive other therapies that were commensurate with contemporary local treatment guidelines and practices. A digital continuous ECG (Holter) monitor for ischemia was applied at the time of randomization and remained in place for 7 days. After discharge, patients returned for study visits at Day 14, Month 4, and every 4 months thereafter, until the end of the study, at which time a final visit occurred. Fourteen days after the final study visit, a follow-up telephone call was conducted to assess adverse events for the purpose of safety reporting. The trial was designed to continue until at least 730 major CV events (CV death, MI, severe recurrent ischemia) and 310 deaths from any cause were recorded. When both of these minimums were met, sites scheduled final visits for all patients.



Assignment to Treatment Groups
Subjects were randomized centrally in a 1: 1 ratio to receive either ranolazine or placebo; randomization was stratified by the physician's intent to manage the patient with an early invasive strategy (angiography within 48 hours and revascularization if appropriate).

Diagnosis and Main Criteria for Inclusion:
(1) > 18 years;
(2) hospitalized with non-ST elevation ACS defined as chest discomfort or anginal equivalent occurring at rest, lasting ≥ 10 minutes, and consistent with myocardial ischemia;
(3) at least one episode of ischemic symptoms (≥ 5 minutes) at rest within 48 hours of enrollment (may include the index episode);
(4) at least one of the following indicators of moderate to high risk:
- -elevated cardiac troponin or CK-MB (> the upper limit of normal);
- -ST depression (horizontal or down-sloping) ≥ 0.1 mV;
- -diabetes mellitus (requiring insulin or oral therapy);
- -TIMI Risk Score for unstable angina/non-ST elevation MI ≥ 3;

(5) willing and able to provide written informed consent.

Exclusion Criteria
1) Persistent (>20 min) acute ST -segment elevation > 0.1 mV in 2 or more contiguous leads
2) Successful revascularization of the culprit stenosis during the qualifying hospitalization, prior to randomization
3) Acute pulmonary edema requiring endotracheal intubation, sustained systolic blood pressure < 90 mm Hg, or evidence of cardiogenic shock
4) Left bundle branch block, electronic pacemaker, or left ventricular hypertrophy (LVH) with severe repolarization abnormality (baseline> 0.1 mV ST depression) that would interfere with interpretation of the Holter
5) Pregnant or lactating women, or women of child bearing potential not using an acceptable

form of birth control (negative pregnancy test also required)
6) Use at randomization of agents that are strong inhibitors of the cytochrome P450 pathway isoform 3A4
7) Need for ongoing or anticipated need for chronic treatment during the study period with any of the following agents which might interfere with the evaluation of the therapeutic response or safety of the study drug:
-Agents known to prolong the QT interval
-Any digitalis preparation (e.g. digoxin)
8) Clinically significant hepatic disease
9) End stage renal disease requiring dialysis
10) Participation in another trial of an investigational drug or device within 30 days (or longer as per local requirements), or treatment with ranolazine, (concomitantly or within 14 days of enrollment), or previous participation in MERLIN
11) Inability to comply with the protocol and follow-up visits
12) Any serious medical co-morbidity such that the patient's life expectancy is less than 12 months
13) Any condition which might increase the risk to the patient or decrease the chance of obtaining satisfactory data to achieve the objectives of the study.

Recommended Concomitant Therapy
All study subjects were to be treated with standard therapy consistent with local guidelines for the acute management of unstable angina and non-ST elevation MI, as well as secondary prevention.

It was recommended that concomitant antianginal medication (beta-blockers, calcium channel blockers, long-acting nitrates, and/or drugs in other classes indicated for the treatment of chronic angina outside the United States (e.g., nicorandil) were to be instituted or titrated upwards for angina (ischemia) only for clear evidence of recurrent ischemia. Similarly, to the extent possible, hypertension was to be treated with alternatives to adding or increasing the doses of calcium channel blockers, nitrates, or beta blockers.

Prohibited Concomitant Therapy
Any agent known to prolong the QT interval was prohibited during treatment with study medication. Study medication was to be temporarily withheld if treatment of limited duration with such an agent was required.

Subjects receiving or anticipated to require chronic treatment with preparations of digitalis at the time of randomization were excluded from participation in the trial. Digoxin (or other preparations of digitalis) could have been initiated after enrollment, if clinically necessary; however, alternative medications were to be administered whenever possible.

Number of Patients: A total of 6,560 patients (3,281 placebo; 3,279 ranolazine) were randomized into the study and included in the intent-to-treat (ITT) analysis population; of these, 6,541 (> 99%) patients (3,273 placebo; 3,268 ranolazine) received at least one dose of study drug and were included in the safety analysis population. The goal was to enroll

subjects until at least 730 major cardiovascular events (CV death, MI, severe recurrent ischemia) and 310 deaths occurred.

Study drug:
1) iv infusion of study drug (ranolazine/placebo) started within 30 minutes after randomization. Patients received an iv loading dose of ranolazine/placebo at a rate of 200 mg over 1 hour, followed immediately by a maintenance infusion at a rate of 80 mg/h between 12 and 96 hours, inclusive. (Patients with severe renal insufficiency (creatinine clearance < 30 mL/min) had a starting maintenance infusion rate limited to 40 mg/h.) During administration of the maintenance infusion, the infusion rate was to be titrated downward or temporarily discontinued in the event of profound and persistent QTc prolongation or other specific adverse events. Subjects who were stratified to the early invasive evaluation were to receive IV study drug for at least 6 hours prior to angiography, and for a minimum of 6 hours after PCI.

2) Approximately one hour prior to completion of the maintenance infusion, patients were to receive their first oral dose of ranolazine extended release (ER)/placebo at a dose that was based on the infusion dose at the time of transition; patients receiving an infusion rate of 80, 60, 40, or 30 mg/h were to receive ranolazine ER at a dose of 1000, 750, 500, or 375 mg bid, respectively.

The oral dose administered following the maintenance infusion was to be maintained through the end of the study unless the patient had newly developed severe renal insufficiency, profound or persistent QTc prolongation or other specific adverse events, in which case, the oral dose was to be down-titrated.

Table 1 Schedule of Procedures

Procedures	Screening	Day 1	Day 2 – Hospital D/C	Day 14[a]	M4[b]	M8[b]	4 Month Visits[b] (M12, M16, etc)	Final Visit[c]
Informed consent	X							
Medical history	X							
Full Physical exam[d]	X							X
Targeted Physical exam (w/orthostatic vital signs)			X	X	X	X	X	
12-lead ECG	X[e]		X[f]	X		X	Q8 months	X
Serum Chemistries, Hematology (Local)	X		X[k]	X[l]	X	X	Q8 months	X
CK-MB and/or cardiac troponin (Local)[f]	X	X[f]	X[f]					
Pregnancy test (women of child-bearing potential)	X			X	X	X	X	
Blood for Cardiac Biomarkers (Central Lab)	X	X[h]	X[h]	X				X
Blood for Genetic Analysis	X							
HgbA1c, Lipids (Local)	X				X	X	Q8 months	X
Blood sample for ranolazine levels		X[m]	X[m]	X[m]	X[m]			
Oral glucose tolerance test (OGTT)								X[l]
Randomization		X						
Dispense Study Drug		X	X		X	X	X	
Holter Monitor[g]		X	X					
Transthoracic echo (selected sites only)	X[n]	X[n]			X			
Exercise Tolerance Testing						X		X[l]
Assess for Adverse Events		X	X	X	X	X	X	X
Assess for Endpoints		X	X	X	X	X	X	X
QOL Questionnaires	X				X	X	X (M12)	X
Monitor Concomitant Medications		X	X	X	X	X	X	X
Monitor Compliance with Study Drug				X	X	X	X	X
Study Status/Discharge								X

[a] The Day 14 visit was to occur between day 10 and day 21 following randomization (inclusive).
[b] The Month 4 visit was to occur at 4 months after randomization (± 14 days), Month 8 at 8 months after randomization (± 14 days), etc.
[c] The Final Visit procedures were to be conducted upon completion of the study or permanent cessation of study medication.
[d] Including orthostatic vital signs and waist circumference.
[e] Retain ECG from qualifying event, as well as immediately prior to randomization.
[f] Local serial CK-MB and/or cardiac troponin for evaluation of qualifying event was to be performed; this testing was to be repeated for any episodes of chest symptoms consistent with ischemia lasting ≥ 10 min (During 24 hours post-PCI or CABG, serial local measurement of CK-MB x 2 were also to be repeated).
[g] Holter monitor for ischemia was to be placed within 15 min of starting study drug and worn by patient for 7 days after enrollment.
[h] Blood samples for central laboratory cardiac biomarkers were to be drawn pre-randomization, at 12–16 h and 24–36 h post-randomization (North America and selected centers in Europe).
[i] 12-lead ECG was to be obtained on Day 3 or discharge (whichever was sooner), and after any adjustment of study drug for prolonged QTc interval.
[j] Only serum creatinine was to be analyzed.
[k] Measurement of platelet density was to be recorded from local CBC pre-randomization and then QD x 5 days or until discharge (Selected centers).
[l] If not already performed. The OGTT was to be performed upon notification by the Operations Committee that this end-of-study procedure could occur.
[m] Selected centers only: A blood sample for ranolazine levels was to be drawn at 12–16 h, 24–36 h, and at the end of the iv infusion, Day 14, Month 4 and at the time of specific adverse events, or profound and persistent QTc prolongation (whenever possible).
[n] Patients enrolled in echo substudy: echo at 1–3 h after start of study drug. Baseline echo performed in selected patients.

Criteria for Efficacy: Efficacy was measured through evaluation of the time from randomization to CV death, MI, or recurrent ischemia (primary endpoint), time to severe recurrent ischemia, time to CV re-hospitalization, SAQ scores, duration of exercise on ETT, cardiac biomarkers, and antianginal medications.

Efficacy Endpoints
All elements of the primary composite and major secondary endpoint were to be reviewed by members of a Clinical Events Committee blinded to treatment allocation, or a central laboratory (Holter and ETT) blinded to treatment allocation and clinical outcomes.

Primary Endpoint
The primary efficacy endpoint was the time to first occurrence of any element of the composite of CV death, MI, or recurrent ischemia. The definitions of the elements of the composite primary endpoint are as follows:

1) CV Death: Any death for which there was no clearly documented noncardiovascular cause. Cardiovascular death was to be sub-categorized into sudden vs. nonsudden cardiac death as described in the separate Clinical Events Committee Charter.

2) Myocardial infarction must be distinct from the index event, and was defined by symptoms suggestive of ischemia/infarction in association with either electrocardiographic, cardiac biomarker or pathologic evidence of infarction.

Recurrent ischemia was defined by ischemia meeting any of the criteria below:
1) Recurrent ischemia with ECG changes: Recurrent ischemic discomfort or equivalent at rest lasting > 10 minutes associated with new ST or T -wave changes consistent with ischemia or
2) Recurrent ischemia leading to hospitalization: Recurrent ischemic discomfort or equivalent at rest lasting >10 minutes, repeated episodes at rest lasting >5 minutes, or an accelerating pattern of ischemic discomfort (episodes that are more frequent, severe, longer in duration and/or precipitated by less exertion) prompting re-hospitalization and considered to be myocardial ischemia upon final diagnosis (not meeting criteria for recurrent ischemia with ECG changes) or
3) Recurrent ischemia prompting revascularization, defined as:
a) During the index hospitalization: PCI or CABG prompted by recurrent ischemia with ECG changes (In countries where waiting lists exist, the revascularization must be scheduled during the hospitalization and carried out within 30 days) or
b) After hospital discharge from index hospitalization: PCI or CABG prompted by
1. Increase in angina to a higher Canadian Cardiovascular Society Class, or
2. Evidence for ischemia on provocative testing* or
4) Worsening angina/ischemia requiring additional therapy occurring after the Day 14 visit**, defined as:
a) An increase in angina to a higher Canadian Cardiovascular Society Class and

b) Requiring intensification of anti-anginal therapy with new or increasing doses of anti-anginal medications

*Evidence for ischemia on provocative testing must be manifest by ischemic symptoms and/or ECG criteria, or ischemic symptoms in conjunction with reversible perfusion defects or wall motion abnormalities on nuclear or echocardiographic imaging. Reversible perfusion deficits in the absence of symptoms or diagnostic ST changes are not sufficient to meet this criterion. Moreover, this criterion may not be met by adenosine or persantine stress imaging.

**This definition of recurrent ischemia may be applied only after baseline Canadian Cardiovascular Society Class is established at the Day 14 Visit.

Statistical Methods: All efficacy analyses were based on the analysis set of all patients randomized with intention to treat. Patients were assigned to treatment groups based on randomized treatment, regardless of treatment actually received. Hypotheses of no treatment difference were tested for the primary and secondary efficacy endpoints in the following pre-specified order using a closed testing procedure in order to control the family-wise error rate at 0.05:

1. Primary efficacy endpoint (CV death, MI, or recurrent ischemia).

2. Major secondary composite endpoint (CV death, MI, or severe recurrent ischemia).
3. Failure of therapy (CV death, MI, recurrent ischemia, positive Holter for ischemia, hospitalization for new/worsening heart failure, or early positive ETT).
4. CV death, MI, severe recurrent ischemia, or positive Holter for ischemia at or before 30 days.
5. The angina frequency scale of the Seattle Angina Questionnaire.
6. The physical limitation scale of the Seattle Angina Questionnaire.
7. Duration of exercise on ETT at 8 months (or Final Visit, if earlier).
8. Total duration of ischemia on Holter between randomization and 72 hours.

Time to event variables were analyzed using a Cox proportional hazards model with effect for treatment, stratifying by the intention for early invasive management. Relative risk estimates were calculated along with 95% confidence intervals and times to event were described using Kaplan-Meier curves and Nelson-Aalen cumulative hazard curves. Safety analyses were performed using the analysis set of all patients who received study medication. The relative risk of all-cause mortality was estimated along with a 95% confidence interval using a Cox proportional hazards model with effect for treatment, stratifying by intention for early invasive management. The composite of death from any cause or cardiovascular hospitalization was analyzed using the same methods. The incidence of symptomatic documented arrhythmia, based on the events adjudicated by the clinical events committee, was compared between treatment groups using the Cochran-Mantel-Haenszel test, stratifying by intention for early invasive management. The incidence of clinically significant arrhythmias observed during the 7-day Holter was compared between treatment groups using the same method.

All components of the primary and major secondary endpoints, as well as hospitalization for new or worsening heart failure and the safety endpoint of symptomatic documented arrhythmias were adjudicated by a blinded, independent Clinical Events Committee.

There was a planned efficacy interim analysis of the endpoint CV death conducted by an independent DSMB, with a significance level of 0.001. The reference significance level in the final analysis was adjusted to 0.0497 using the method of Fleming, Harrington and O'Brien.

The protocol required the study to continue until 730 major cardiovascular events and 310 deaths were observed. The projected power for the major secondary endpoint to detect a 20% reduction in relative risk was 90%, assuming a placebo incidence of 18% at one year. Assuming a 22% one-year incidence for the primary efficacy endpoint in the placebo group, the projected power to detect a 20% reduction in the primary efficacy analysis was 95%. A sample size of 5,500 patients was planned with a resizing calculation when 1,000 patients had 4 months of follow-up that permitted an increase up to 6,500 patients in order that the duration of the study not be unduly extended if the rates of major cardiovascular events and mortality differed substantially from pre-study predictions.

Results

Subject disposition.

The numbers of subjects enrolled and the numbers dropping out or completing the study are shown below.

Table 2 Patient Disposition: ITT Analysis Set

	Treatment		
	Placebo (n=3281)	Ranolazine (n=3279)	All (n=6560)
Number of patients taking at least one dose of study drug	3273 (>99%)	3268 (>99%)	6541 (>99%)
Total Follow-up (Days)			
n	3281	3279	6560
Mean (SEM)	347 (2.6)	346 (2.6)	346 (1.9)
Median	348	347	348
25th Percentile - 75th Percentile	238 - 458	234 - 460	236 - 460
Min - Max	1 - 759	1 - 784	1 - 784
Number of patients who prematurely and permanently ceased taking study drug	745 (23%)	925 (28%)	1670 (25%)
Primary reason for prematurely and permanently ceasing to take study drug			
Adverse event	154 (5%)	286 (9%)	440 (7%)
Protocol violation	13 (<1%)	8 (<1%)	21 (<1%)
Lost to follow-up	18 (<1%)	21 (<1%)	39 (<1%)
Does not meet entrance criteria	6 (<1%)	3 (<1%)	9 (<1%)
Patient withdrew consent to treatment	408 (12%)	455 (14%)	863 (13%)
Non-compliance	44 (1%)	44 (1%)	88 (1%)
Other	94 (3%)	96 (3%)	190 (3%)
Missing	8 (<1%)	12 (<1%)	20 (<1%)
All Reasons reported for prematurely and permanently ceasing to take study drug			
Adverse event	267 (8%)	449 (14%)	716 (11%)
Protocol violation	14 (<1%)	12 (<1%)	26 (<1%)
Lost to follow-up	22 (<1%)	24 (<1%)	46 (<1%)
Does not meet entrance criteria	7 (<1%)	7 (<1%)	14 (<1%)
Patient withdrew consent to treatment	462 (14%)	532 (16%)	994 (15%)
Non-compliance	82 (2%)	76 (2%)	158 (2%)
Other	124 (4%)	130 (4%)	254 (4%)
End of study status			
Alive	2940 (90%)	2931 (89%)	5871 (89%)
Withdrew consent to follow-up in writing	165 (5%)	170 (5%)	335 (5%)
Lost to follow-up	2 (<1%)	7 (<1%)	9 (<1%)
Dead	174 (5%)	171 (5%)	345 (5%)

Note: Patients may have more than 1 reason for permanently ceasing taking drug although only one is considered the primary reason. The end of study status is collected at the final visit for all patients.

A total of 6560 subjects were randomized: 3281 to placebo and 3279 to ranolazine. Nearly all randomized subjects took at least one dose of study drug. The numbers of subjects who prematurely discontinued study drug for any reason were greater in the ranolazine group (925, 28%) compared to placebo (745, (23%). Mean follow up days were similar for both treatment groups (placebo: 347 days, ranolazine: 346 days).

There were more ranolazine subjects who withdrew primarily because of adverse event (s) (286, 9%) compared to placebo subjects 154 (5%).

At the end of study, there were slightly more placebo subjects known to be alive (2940, 90%) compared to ranolazine subjects (2931, 89%). The percents of subjects who either withdrew consent to follow up or were lost to follow up were the same (5%) for both treatment groups. The percents of subjects who were known to have died were also the same (5%) for both treatment groups.

The primary reason for the largest number of subjects who prematurely discontinued was "patient withdrew consent to treatment." As of February 29, 2008[4], status unknown or no response from study site includes 39 ranolazine subjects and 27 placebo subjects. Therefore, follow up on vital status was unobtainable for 1% of the study population.

Baseline demographics

Baseline characteristics of the study population by treatment groups are shown below.

[4] Email sent 2-29-2008 from Carol Karp

Table 5 Demographics and Baseline Characteristics

	Treatment			
	Placebo (n=3281)	Ranolazine (n=3279)	P-value	All (n=6560)
Age (yrs)				
n	3281	3279	.32 (ANOVA)	6560
Mean (SD)	63.6 (11.0)	63.3 (11.0)		63.5 (11.0)
Median	64	64		64
25th - 75th Percentile	56 - 72	55 - 72		55 - 72
Min - Max	24 - 97	26 - 99		24 - 99
< 65	1647 (50%)	1703 (52%)	.35 (CMH)	3350 (51%)
65 - 74	1042 (32%)	1014 (31%)		2056 (31%)
>= 75	592 (18%)	562 (17%)		1154 (18%)
Sex				
Male	2096 (64%)	2173 (66%)	.042 (CMH)	4269 (65%)
Female	1185 (36%)	1106 (34%)		2291 (35%)
Race				
Asian	39 (1%)	49 (1%)	.73 (CMH)	88 (1%)
Black	53 (2%)	50 (2%)		103 (2%)
Caucasian	3129 (95%)	3112 (95%)		6241 (95%)
Hispanic	23 (<1%)	23 (<1%)		46 (<1%)
Other	37 (1%)	45 (1%)		82 (1%)
Body mass index (kg/m^2)				
n	3235	3235	.45 (ANOVA)	6470
Mean (SD)	28.9 (5.3)	28.8 (4.9)		28.8 (5.1)
Median	28.3	28.2		28.3
25th - 75th Percentile	25.5 - 31.6	25.4 - 31.4		25.5 - 31.5
Min - Max	15.4 - 145.5	15.0 - 68.9		15.0 - 145.5

Note: ANOVA = Analysis of variance model with effects for treatment and intention for early invasive management; CMH = Cochran-Mantel-Haenszel general association test stratifying by the intention for early invasive management.
Source: 14.1.2

The average subject was 63 years old, male (65%) and white (95%). Elderly subjects comprised 18% of the population. The treatment groups were well balanced.

Renal function
The majority of subjects (77%) had creatinine clearance above 60 mL/min; 2% had a rate of ≤ 30 mL/min. The percent of subjects per creatinine clearance rates were similar between the two treatment groups.

Region of origin
Patients were enrolled at 442 study centers in 17 countries; 1,102 patients (17%) enrolled in North America; 2,485 (38%) enrolled in Eastern Europe; and 2,973 (45%) enrolled in Western Europe, Israel, and South Africa.

Stratification
At randomization, patients were stratified by whether early invasive management (angiography within 48 hours and revascularization, if appropriate) was the intended therapeutic strategy or not. Approximately 41 % of patients in each group (1334/3281 placebo, 1333/3279 ranolazine) had a management plan that included an early invasive strategy.

Medical history and risk factors by treatment group are shown below.

Table 6 Medical History and Risk Factors (ITT Analysis Set)

Parameter	Treatment			
	Placebo (n = 3281)	Ranolazine (n = 3279)	p value	All (n = 6560)
Cardiovascular History[a]				
Previous MI	1095 (33%)	1119 (34%)	0.52	2214 (34%)
Angina pectoris	1776 (54%)	1789 (55%)	0.72	3565 (54%)
Hypertension	2409 (73%)	2395 (73%)	0.73	4804 (73%)
Previous PCI	636 (19%)	684 (21%)	0.13	1320 (20%)
Previous CABG	380 (12%)	389 (12%)	0.72	769 (12%)
CHF	557 (17%)	538 (16%)	0.52	1095 (17%)
TIMI risk score				
0–2	884 (27%)	882 (27%)	0.99	1766 (27%)
3–4	1730 (53%)	1727 (53%)		3457 (53%)
5–7	667 (20%)	670 (20%)		1337 (20%)
Risk Factors[b]				
Dyslipidemia	2022 (62%)	2028 (62%)	0.85	4050 (62%)
Diabetes mellitus	1116 (34%)	1104 (34%)	0.77	2220 (34%)
Current or former smoker	1862 (57%)	1911 (58%)		3773 (58%)
ST Depression (Qualifying Event)[d]				
0.5–0.9 mm	585 (18%)	599 (18%)		1184 (18%)
≥ 1 mm	1162 (35%)	1142 (35%)		2304 (35%)
Non-cardiac History[c]				
Asthma	132 (4%)	153 (5%)	0.20	285 (4%)
COPD	266 (8%)	280 (9%)	0.53	546 (8%)

The majority of subjects had either one or more of the following medical conditions: hypertension, angina, or dyslipidemia. Regarding cardiovascular status, about 33% had had a previous MI, more than half complained of angina, about 20% had had PCI, 12% a previous CABG and 17% had CHF. The majority of subjects were TIMI risk score 3-4 and ST depression for the qualifying event was ≥ 1 mm for the majority of subjects. The treatment groups were well balanced.

The qualifying event was non-STEMI for 51% of subjects and unstable angina in 47%. There were no differences between groups regarding time from onset of qualifying event to randomization, time from hospitalization for qualifying event to randomization, and duration of qualifying episode. The groups were well balanced (14.1.7).

There were 51 subjects randomized to ranolazine who had severe renal impairment (defined as creatinine clearance rate of < 30 mL/min). Of these, 18 received the initial maintenance infusion rate of 80 mg/h, 32 received 40 mg/h and 1 received <40 mg/h (14.3.1.1.1).

Subjects whose dose of study drug was down titrated at least once included 22 (9 placebo and 13 ranolazine) because of impaired creatinine clearance and 44 (13 placebo and 31 ranolazine) for QT prolongation (14.3.1.1.1, 16.2.7.4).

Concomitant medications
The most commonly used medications included ACE inhibitors, anticoagulants, beta-blockers, calcium channel blockers, diuretics, lipid lowering agents, nitrates/coronary vasodilators, and platelet inhibitors.

The percentages of subjects using one or more of concomitant medications either before admission, during hospitalization, and/or after hospitalization were similar for the treatment groups.

Table 8 Summary of Commonly Used Concomitant Medications

Medication Type	Placebo			Ranolazine		
	2 Weeks Before Admission[a] n = 3273	During Hospitalization[a] n = 3273	After Hospitalization[b] n = 3273	2 Weeks Before Admission[a] n = 3268	During Hospitalization[a] n = 3268	After Hospitalization[b] n = 3268
ACE Inhibitors	1403 (43%)	2164 (66%)	2367 (72%)	1343 (41%)	2119 (65%)	2331 (71%)
Anticoagulants	247 (8%)	2977 (91%)	427 (13%)	254 (8%)	3015 (92%)	392 (12%)
Beta-blockers	1505 (46%)	2747 (84%)	2887 (88%)	1495 (46%)	2712 (83%)	2862 (88%)
Calcium Channel Blockers	755 (23%)	998 (30%)	1200 (37%)	780 (24%)	971 (30%)	1119 (34%)
Diuretics	797 (24%)	1236 (38%)	1547 (47%)	812 (25%)	1148 (35%)	1411 (43%)
Lipid Lowering Agents	1354 (41%)	2462 (75%)	2828 (86%)	1348 (41%)	2474 (76%)	2863 (88%)
Nitrates/Coronary Vasodilators	1540 (47%)	2772 (85%)	2032 (62%)	1522 (47%)	2749 (84%)	2020 (62%)
Platelet Inhibitors	2011 (61%)	3094 (95%)	3170 (97%)	2001 (61%)	3093 (95%)	3181 (97%)

Source: [a]Section 14.1.10.1, [b]Section 14.1.10.2

Despite the exclusion criterion[5] prohibiting the use of these agents during the trial, 8 percent of subjects per treatment group were receiving a CYP3A4 inhibitor (diltiazem being the most frequent). Table 118.adhoc

Efficacy
The primary endpoint was a composite of CV death, MI, and recurrent ischemia.

[5] Any agent known to prolong the QT interval was prohibited during treatment with study medication. Study medication was to be temporarily withheld if treatment of limited duration with such an agent was required.

Table 10 Primary Efficacy Analysis: Time from Randomization to First Occurrence of CV Death, MI, or Recurrent Ischemia

	Placebo (n=3281)	Ranolazine (n=3279)
Number of Patients with Events	753	695
Endpoint-defining events		
CV Death	78 (10.4%)	87 (12.5%)
MI	210 (27.9%)	208 (29.9%)
Recurrent Ischemia	465 (61.8%)	400 (57.6%)
Severe Recurrent Ischemia	332 (44.1%)	302 (43.5%)
Worsening angina/ischemia requiring additional therapy	133 (17.7%)	98 (14.1%)
Relative Risk Ranolazine:Placebo	0.919	
95% Confidence Interval	(0.83, 1.02)	
P-value	.11	
Proportion of patients experiencing an event (KM estimates)		
30 days	8.3%	7.7%
60 days	10.9%	9.9%
90 days	12.5%	11.8%
180 days	17.0%	16.2%
270 days	20.5%	19.7%
360 days	23.5%	21.8%
450 days	25.7%	23.6%
540 days	30.1%	26.3%

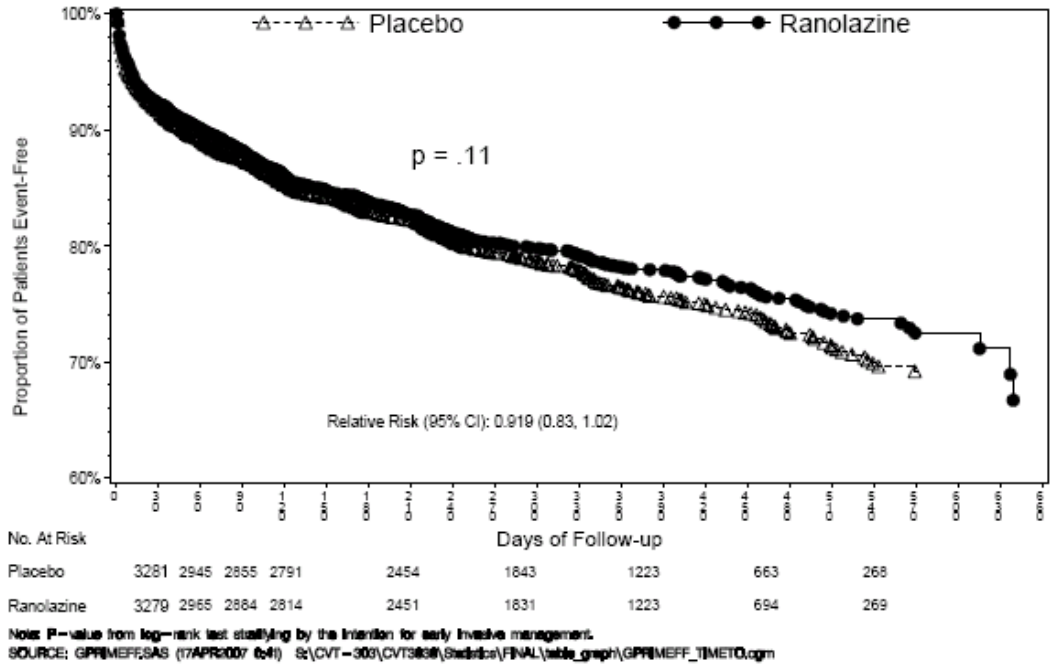
Note: P-value from log-rank test stratifying by the intention for early invasive management. Relative risk estimates from Cox regression model stratifying by the intention for early invasive management. KM = Kaplan Meier.

There were 753 (23%) placebo subjects who experienced a primary efficacy event compared to 695 (21.2%) ranolazine subjects. There was no statistical difference between the treatment groups (p=0.11). Relative risk (ranolazine: placebo) was 0.919 with 95% CI=(0.83,1.02).

There were slightly higher percentages of CV deaths and MI in the ranolazine group (12.5% and 29.9%) compared to the placebo group (10.4% and 27.9%). As expected, there were slightly higher percentages of recurrent ischemia in the placebo group (61.8%) compared to the ranolazine group (57.6%).

The composite endpoint evaluated $\leq$ 30 days and $\geq$ 30 days after randomization were similar for the 2 treatment groups.

Figure 2 **Time from Randomization to First Occurrence of CV Death, MI, or Recurrent Ischemia**



Secondary endpoints

The primary analysis was not met, therefore the review of the secondary endpoints is only exploratory.

1. There was no difference between treatment groups regarding the time to first occurrence of CV death, MI, or severe recurrent ischemia during long term treatment. The relative risk (ranolazine to placebo) was 0.962 (95% CI =(0.86, 1.08); p=0.50).

2. Time to Failure of Therapy During Long-term Treatment (failure of therapy was defined as CV death, MI, recurrent ischemia, positive Holter for ischemia, hospitalization for new or worsening heart failure, or early positive ETT). The relative risk (ranolazine to placebo) was 0.943 (95% CI =(0.87, 1.02); p= 0.15).

3. Incidence of CV Death, MI, Severe Recurrent Ischemia, or Positive Holter for Ischemia During Acute Treatment (at 30 Days). The relative risk (ranolazine to placebo) was 0.92 (95% CI = (0.84, 1.00)).

4. Quality of Life at 4 Months after Randomization. At 4 months following randomization, Seattle Angina Questionnaire results showed that subjects randomized to ranolazine had less perceived angina compared to subjects randomized to placebo ($p < 0.001$). However, there was no difference in the physical limitation scale between the two treatment groups ($p = 0.91$).

5. Duration of Exercise on ETT at 8 Months or Final Visit (combining treadmill with bicycle data) was not significantly different between the two treatment groups (542.8 ± 5.5 seconds for the placebo group vs. 550.0 ±5.5 seconds for the ranolazine group, $p = 0.35$).

6. Total Duration of Ischemia on Holter between Randomization and 72 Hours. The mean duration of ischemia showed no significant difference between the two treatment groups: 28.1 ± 2.3 minutes for placebo patients and 31.8± 2.5 minutes for ranolazine patients (p = 0.26).

Safety

The safety data base includes a total of 6541 subjects (3273 received placebo and 3268 received ranolazine. This represents a total of 99.7% of the randomized population.

The majority of subjects received iv infusion of study drug at 80 mg/h for the entire infusion period. There were 51 subjects in the ranolazine group with creatinine clearance rate < 30 mL/min and, therefore, received a lower infusion rate. There were 4% of placebo subjects and 5% of ranolazine subjects who were down titrated because of adverse events, QTc prolongation, and/or decreased creatinine clearance.

Most subjects began the oral doses of 1000 mg bid. The last oral dose being 1000 mg bid was true for 89% of placebo subjects and 83% of ranolazine subjects. There were 6% of placebo subjects and 11% of ranolazine subjects who had their dose down titrated. The mean duration for oral placebo treatment was 302 days and 284 days for oral ranolazine treatment.

Serious safety

Percent of death from any cause was 5.3% for both treatment groups. The relative risk of mortality (ranolazine: placebo) was 0.988 (95% CI=(0.80, 1.22)). The percents of those deaths deemed to be sudden were also similar (2% for placebo and 1.7% for ranolazine[6]).

Combined deaths from any cause or cardiovascular hospitalization were similar for the treatment groups. Estimated relative risk (ranolazine:placebo) was 0.975 (95% CI=(0.90, 1.06)).

The incidences of symptomatic documented arrhythmias leading to or prolonging hospitalization or deemed to be medically important were similar for the two treatment groups (3.1% and 3.0% for placebo and ranolazine, respectively).

The number of reported different types of arrhythmias are shown below.

[6] 14.3.1.8.1

Table 23 Incidence and Frequency of Symptomatic Documented Arrhythmias

	Placebo (n=3273)	Ranolazine (n=3268)	P-value
Incidence of Symptomatic Documented Arrhythmias	102 (3.1%)	99 (3.0%)	.84 (CMH)
Incidence of Symptomatic Documented Arrhythmia by Category			
Ventricular arrhythmia	29 (0.9%)	22 (0.7%)	
Supraventricular arrhythmia	41 (1.3%)	38 (1.2%)	
Bradyarrhythmia	29 (0.9%)	34 (1.0%)	
Cardiac arrest NOS	9 (0.3%)	10 (0.3%)	
Frequency of Symptomatic Documented Arrhythmias per Patient by Category			
Ventricular arrhythmia			
1	29	20	
2	0	1	
5	0	1	
Supraventricular arrhythmia			
1	39	34	
2	1	4	
3	1	0	
Bradyarrhythmia			
1	29	32	
2	0	2	
Cardiac arrest NOS			
1	9	10	

Note: P-value from Cochran-Mantel-Haenszel general association (CMH) test stratifying by the intention for early invasive management.

The results for the two treatment groups are similar.

Subjects underwent 7-day Holter monitoring starting a 0-15 minutes after initiation of study drug. The data card was sent to the (b) (4)
The significant arrhythmias and their occurrence by treatment group are shown below.

Table 24 **Incidence and Frequency of Clinically Significant Arrhythmias During the 7-Day Continuous ECG (Holter) Monitoring**

	Placebo (n=3273)	Ranolazine (n=3268)	P-value
Number of Patients with Holter Data	3189	3162	
Incidence of Clinically Significant Arrhythmias	2650 (83.1%)	2330 (73.7%)	<.001 (CMH)
Incidence of Any Clinically Significant Arrhythmias			
Any VT>=100 bpm >= 3 beats	1211 (38.0%)	948 (30.0%)	
Any SVT>=120 bpm	1752 (54.9%)	1413 (44.7%)	
New-onset Atrial fibrillation	75 (2.4%)	55 (1.7%)	
Any Bradycardic episode	1485 (46.6%)	1257 (39.8%)	
Frequency of Triplets			
0	1502 (47.1%)	1737 (54.9%)	
1 to 5	912 (28.6%)	765 (24.2%)	
6 to 10	174 (5.5%)	174 (5.5%)	
11 to 25	212 (6.6%)	183 (5.8%)	
26 to 50	105 (3.3%)	92 (2.9%)	
51 to 100	106 (3.3%)	80 (2.5%)	
> 100	172 (5.4%)	127 (4.0%)	
Frequency of VT >= 100 bpm lasting >= 4 beats			
0	2242 (70.3%)	2496 (78.9%)	
1 to 5	834 (26.2%)	595 (18.8%)	
6 to 10	58 (1.8%)	34 (1.1%)	
11 to 25	31 (1.0%)	21 (0.7%)	
26 to 50	12 (0.4%)	9 (0.3%)	
51 to 100	3 (<0.1%)	0 (0.0%)	
> 100	3 (<0.1%)	3 (<0.1%)	
Frequency of bradycardia			
0	1813 (56.9%)	2033 (64.3%)	
1 to 5	376 (11.8%)	335 (10.6%)	
6 to 10	107 (3.4%)	92 (2.9%)	
11 to 25	150 (4.7%)	127 (4.0%)	
26 to 50	104 (3.3%)	85 (2.7%)	
51 to 100	114 (3.6%)	92 (2.9%)	
> 100	519 (16.3%)	394 (12.5%)	
Frequency of ventricular pauses >= 2.5sec			
0	2806 (88.0%)	2839 (89.8%)	
1 to 5	254 (8.0%)	220 (7.0%)	
6 to 10	32 (1.0%)	35 (1.4%)	
11 to 25	36 (1.1%)	30 (0.9%)	
26 to 50	31 (1.0%)	18 (0.6%)	
51 to 100	7 (0.2%)	12 (0.4%)	
> 100	17 (0.5%)	4 (0.1%)	

Note: P-value from Cochran-Mantel-Haenszel general association (CMH) test stratifying by the intention for early invasive management. Frequencies are based on actual number of events reported for each patient. No adjustment has been made for patients who wore Holter device longer or shorter than the protocol specified 7 days.

Nearly all subjects (97%) had Holter monitoring data. A somewhat higher percentage of placebo subjects (83%) had clinically significant arrhythmias compared to ranolazine subjects (74%). A post hoc examination of the data by the sponsor revealed more subjects with ventricular tachycardia (>100 bmp) $\geq$ 8 bpm in the placebo group (8.3%) compared to ranolazine subjects (5.2%). The differences between groups could be the result of chance.

Renal impairment

There were similar reported adverse renal events in the 2 treatment groups (5% placebo and 7% ranolazine). The incidence rates for renal failure (acute, chronic and not otherwise specified), and renal impairment were 1% or less for both treatment groups.

There were 102 subjects (50 placebo and 52 ranolazine) with creatinine clearance $\leq$ 30 ml/min at enrollment. The blood pressure measurements for these 2 groups at baseline and endpoint are shown below.

SBP/DBP mmHg

	supine		standing	
	placebo	ranolazine	placebo	ranolazine
baseline	133/69 (50)+	135/72 (52)	126/66 (34)	130/70 (32)
final visit	132/72 (24)	143/73 (24)	127/75 (21)	136/74 (24)

+numbers in parentheses are sample sizes.

Compared to placebo, there appears to be negligible effect of ranolazine on the renal impaired subgroup (with possible exception of supine systolic blood pressure). However, half the subject did not have final visit blood pressure measurements. This result does not override the finding of elevated diastolic blood pressure in subjects with severe renal impairment (CVT 3016).

Concomitant diltiazem[7]
Of the 234 patients in the ranolazine treatment group who received diltiazem at any time during the course of the study, 12 patients died while receiving ranolazine, and an additional 7 patients died after having discontinued ranolazine treatment for a period ranging from 10 to 450 days. Of the 219 patients in the placebo group who received diltiazem at any time during the course of the study, 11 died.

A total of 69 of the 234 patients in the ranolazine treatment group who received diltiazem at any time during the course of the study discontinued ranolazine treatment, and 63 out of the 219 placebo patients who received diltiazem discontinued placebo treatment at any time during the study. A total of 41 out of the 234 patients in the ranolazine treatment group who received diltiazem and 18 out of the 219 patients who received placebo and diltiazem had their oral dose down titrated.

QTc prolongation
The trial did not have an exclusion criterion for subjects with prolonged QTc at baseline.

There were 615 subjects randomized to ranolazine and 618 subjects randomized to placebo group with a baseline QTc value $\geq$ 450 msec. There were 68 subjects randomized to ranolazine and 79 subjects randomized to placebo with a baseline QTc value $\geq$ 500 msec[4].

Of the 62 subjects needing reduction of the dose of study drug because of prolonged QTc, 40 had been randomized to ranolazine and 22 to placebo. 16.2.7.4

All adverse events
The overall adverse event reporting rates were similar for the treatment groups (73% placebo and 76% ranolazine). Events reported more frequently by at least 3% of subjects in either treatment group and reported more often in the ranolazine group compared to placebo are shown below.

Percents

Adverse event	Placebo N=3273	Ranolazine N=3268	Placebo subtracted
Dizziness	7	13	6
Constipation	3	9	6
Nausea	6	9	3
Asthenia	3	5	2
Hypotension	3	5	2

14.3.1.4

This is consistent with the safety summary supporting the original NDA.

[7]Data received in email sent from sponsor dated 2-25-08

Laboratory abnormalities
Differences between ranolazine and placebo at final visit compared to baseline for selected laboratory values were largest for hemoglobin, creatinine, and total bilirubin (see table below).

Change from baseline

Lab value	Month 4		Month 8		Last visit	
	Pla	Ran	Pla	Ran	Pla	Ran
Creatinine mcmol/L	1.6	6.4	2.3	8.4	2.7	6.5
Hemoglobin G/L	0.5	-2.2	1.2	-0.8	1.3	-1.0
Total bilirubin mcmol/L	-0.9	-0.5	-0.2	-0.2	-0.1	3.3

14.3.5.1

There was a greater persistent rise in creatinine in the ranolazine group compared to placebo. A total of 50 subjects (2%) reported increased blood creatinine in the ranolazine group compared to 34 subjects (1%) in the placebo group. The percents of subjects reporting renal dysfunction (defined as renal failure, renal failure acute, renal impairment, renal failure chronic) were slightly higher in the ranolazine group (3.0%) compared to placebo (2.0%).

Compared to placebo, there was a small decline in hemoglobin throughout the study in the ranolazine group and there was a small and inconsistent increase in total bilirubin.

<u>CVT 301-19</u>

Conclusion
The addition of diltiazem 180 mg bid increases ranolazine AUC_{0-12} by more than 2 fold.

Title
Phase 1, Multiple Dose, Fixed Sequence, Cross Over, Open Label Study to Evaluate the Effect of Diltiazem 180 mg bid on the Pharmacokinetics, Safety and Tolerability of Ranolazine ER in Healthy Male and Female Subjects with Poor (PM) and Extensive (EM) Metabolizer Genotype for CYP2D6

Primary Objective
To evaluate the effect of diltiazem hydrochloride (DILT) 180 mg bid at steady state on the pharmacokinetic parameters of ranolazine (RAN) extended-release (ER) at the 500 mg bid dose level at steady state in subjects with PM and EM genotypes for CYP2D6.

Methodology
This study was an open-label, multiple dose, cross-over study in healthy volunteers in which dosing was to last for 15 days. Subjects were to receive oral ranolazine ER at the following doses and times: 500 mg bid starting on Day 1 until the morning of Day 4; 1000 mg bid starting the evening of Day 4 through the morning of Day 8; and 500 mg bid starting the evening of Day 8 through the morning of Day 15. Subjects were also to receive an oral dose of diltiazem at the following doses and times: 90 mg the evening of Day 8 and the morning of Day 9; 180 mg bid the evening of Day 9 through the morning of Day 15. The study included an additional treatment period lasting from the evening of Day 15 to the

morning of Day 22, during which subjects received RAN 1000 mg bid concomitantly with DILT 180 mg bid.

Number of subjects
52 healthy male and female volunteers were planned, 33 subjects were enrolled, and 31 subjects were dosed in the study.

Study design
Plasma samples for the measurement of ranolazine and metabolite concentrations were to be obtained on Days 1, 2, and 3 at 0 h and 12 h (predose); on Days 4, 8, and 15 at 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 h (full PK profile); and on Days 5, 6, 7, 9, 10, 11, 12, 13, and 14 (trough sample taken prior to evening dose at 12 h). For subjects enrolled in the original protocol, blood was also to be drawn for a full ranolazine PK profile on Day 22 and for analysis of trough samples on Days 16-21.

Pharmacokinetic Results
Ranolazine AUC0-12 at steady state increased by around 2.11-fold in poor metabolizers (PM) and 2.42-fold in extensive metabolizers (EM) when diltiazem 180 mg bid was added. The corresponding increases for Cmax were 1.86-fold in PMs and 2.20-fold in EMs.

Safety Results
Reported adverse events included dizziness, postural dizziness, application site erythema (at Holter electrode sites), chest pain, nausea, and paresthesia. There were 9 subjects (2 PMs and 7 EMs) who discontinued the study because of an adverse event and eight others (3 PMs and 5 EMs) were withdrawn because of the protocol-specified ECG interval stopping rule (PR interval exceeding 0.22 sec or QTc interval exceeding 500 msec). There were no serious safety events reported in this study.

Two subjects (1 PM and 1 EM) had an asymptomatic episode of ventricular tachycardia (up to 6 beats) captured on Holter recording during treatment with RAN 500 mg bid + diltiazem180 mg bid.

<u>CVT 3023</u>

Conclusions
This high dose tolerability study showed that many subjects were unable to tolerate doses 1500 mg bid and above. Dose limiting adverse events included syncope, nausea, dizziness, and vomiting (25%). The ten subjects who withdrew because of QTc prolongation or adverse events had been taking the 1500 mg bid dose.

Three patients reported at least one serious adverse event including one report of involuntary muscle contractions by subject 12122309 who had been receiving the 750 mg dose. There was a positive rechallenge with the 1500 mg dose. The episode resolved when he was discontinued from study drug. Blood concentration of ranolazine 9.5 hours after the last dose taken by this subject was 14,000 ng/mL[8].

Title of Study
A Double-Blind, Randomized, Parallel-Group Dose Escalation Tolerability Study of Ranolazine ER in Patients with Chronic Angina.

[8] Mean steady state Cmax with the 1000 mg dose bid is less than 2600 ng/mL.

Objectives
The primary objective of this study was to determine the tolerability of ranolazine ER at oral doses up to 3000 mg bid in subjects with chronic angina, as assessed by specific adverse events. The secondary objective was to characterize the adverse events and the changes in vital signs and laboratory parameters associated with ranolazine ER at oral doses up to 3000 mg bid in these subjects.

Study design
This was a double-blind, randomized, parallel-group, dose escalation study of ranolazine ER at oral doses ranging from 750 mg bid up to a maximum of 3000 mg bid in patients with chronic angina.

The maximum dose of ranolazine given was 2250 mg bid. Subjects were in the clinic for 14 days and started with 750 mg bid. They were titrated to the highest level. The plan to titrate to the 3000 mg bid dose was dropped.

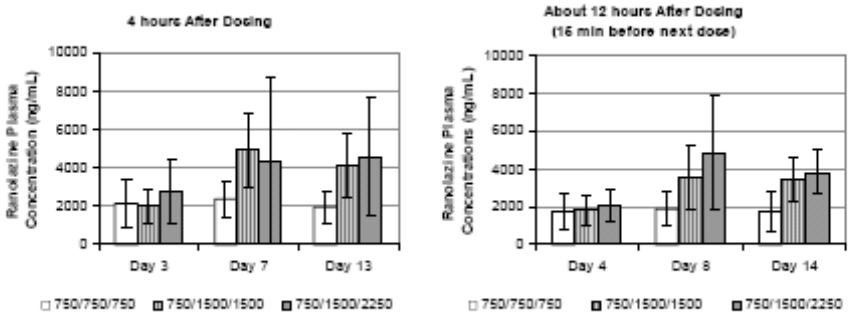
Number of Patients
A total of 37 patients were enrolled and dosed. Of these, 12 received the highest dose (2250 mg). There were 14 subjects who prematurely discontinued from the study (5 were withdrawn for an adverse event and 1 for a QTc interval prolongation, 4 withdrew consent, 2 were withdrawn by the sponsor, and 2 were withdrawn for evacuation of the study site).

Main inclusion criteria
Subjects had to have at least a 3-month history of chronic angina pectoris that was triggered by physical effort and was relieved by rest and/or sublingual nitroglycerin; had a diagnosis of coronary artery disease (as documented by angiographic evidence of > 60% stenosis of one or more major arteries; or had a history of myocardial infarction with positive MB-CPK enzymes, troponin, or EGG changes; or had a cardiac imaging scan indicating coronary artery disease); had or will have a minimum of 2 weeks treatment with daily chronic anti-anginal medications prior to admission.

Intolerability was defined as the number of subjects who (1) experienced syncope, diplopia, somnolence, depressed level/loss of consciousness, confusion/disorientation, symptomatic hypotension, dizziness, nausea, vomiting, or (2) had any severe adverse event, or (3) terminated from the study due to an adverse event.

PK results

Figure 1 Ranolazine Plasma Concentrations at Scheduled Timepoints



Note: The figures show mean ranolazine plasma concentration on each of the days; the error bars reflect the standard deviation.

The number and percent of patients who experienced one or more of the tolerability endpoint events were as follows: 1 (8%) patient in the 750 mg bid regimen, 6 (46%) patients in the 750 mg bid followed by 1500 mg bid regimen, and 9 (75%) patients in the 750 mg bid followed by 1500 mg bid followed by 2250 mg bid regimen.

Table 6 Primary Endpoint Analysis: Tolerability

	Treatment Regimen (mg)		
	750/750/750 (n=12)	750/1500/1500 (n=13)	750/1500/2250 (n=12)
Patients Who Experienced a Primary Endpoint Event*	1 (8%)	6 (46%)	9 (75%)
Study Specific Adverse Events	1 (8%)	6 (46%)	9 (75%)
Syncope	0	0	0
Diplopia	0	0	0
Somnolence	0	1 (8%)	2 (17%)
Depressed level/Loss of consciousness	0	0	0
Confusion/Disorientation	0	1 (8%)	0
Symptomatic Hypotension	0	1 (8%)	1 (8%)
Dizziness	1 (8%)	2 (15%)	5 (42%)
Nausea	0	3 (23%)	6 (50%)
Vomiting	0	1 (8%)	3 (25%)
Severe Adverse Events	0	2 (15%)	2 (17%)
Terminated from the Study Due to an Adverse Event	0	1 (8%)	4 (33%)

Note: * Primary endpoint will be the number of patients who experience syncope, diplopia, somnolence, depressed level/loss of consciousness, confusion/disorientation, symptomatic hypotension, dizziness, nausea, vomiting, or any severe adverse event, or terminate from the study due to an adverse event.

Safety

There were no deaths. Subjects in highest dose group reported the highest incidence of nausea (50%), dizziness (42%), and vomiting (25%).

The most frequently reported adverse events included orthostatic hypotension (51%), headache (41%), constipation (32%), nausea (24%), and dizziness (22%). Dose dependent adverse events included nausea, vomiting, and dizziness. Three patients reported at least one serious adverse event including one report of involuntary muscle contractions by a subject randomized to the 750/1500/2250 regimen. Subjects receiving the higher ranolazine dose reported more laboratory abnormalities (increased creatinine or creatinine phosphokinase).

There were 6 subjects who withdrew from the study for either an adverse event (5 patients) or QTc interval prolongation (1 patient). Most of the adverse events that led to withdrawal occurred while the

patients were taking the 1500-mg dose of ranolazine; at the time of withdrawal, 4 of 6 patients had ranolazine plasma concentrations that were high relative to their cohorts.

Table 5 Plasma Concentrations at the Time or Following Withdrawal from the Study

Patient No.	Reason for withdrawal	Last ranolazine dose	Plasma concentration	Time since last dose
750/1500/1500 Regimen				
12122301	QTc interval prolongation[a]	1500 mg	7210 ng/mL	~7 hours
14012325	Withdrew consent	1500 mg	6840 ng/mL	~9 hours
14062306	Nausea, disorientation, and confusion	1500 mg	3520 ng/mL	~12 hours
750/1500/2250 Regimen				
12122302	Nausea and vomiting	1500 mg	2120 ng/mL	~24 hours
12122309	Involuntary muscle spasms	1500 mg	14,000 ng/mL	~9.5 hours
14012302	Withdrew consent	1500 mg	BQL	~193 hours
14012305	Withdrew consent	2250 mg	11,800 ng/mL	~12 hours
14062303	Hematuria[b] and transient ischemic attack	2250 mg	12,400 ng/mL	~11 hours
14062304	Nausea, dizziness, and orthostatic hypotension[c]	2250 mg	8800 ng/mL	~11 hours
14062308	Withdrew consent	2250 mg	BQL	~81 hours

[a] The protocol required that a patient be discontinued from the study if the QTc interval both widened to ≥ 60 msec from its baseline duration and was > 500 msec.

[b] The hematuria emerged at the 2250-mg dose, but the transient ischemic attack occurred while the patient was receiving 1500 mg b.i.d.

[c] All events emerged while the patient was receiving 1500 mg b.i.d., but the patient continued dosing and then withdrew while taking 2250 mg b.i.d.

BQL = below the quantitation limit of the assay

<u>CVT 3024</u>

Conclusions
The data from this is truncated, open label safety study are difficult to interpret. Of a total of 150 subjects planned only 9 were enrolled. There was 1 death (pancreatic cancer) and 1 discontinuation for adverse events (hospitalized for unstable angina).

Title of Study
An open-label, long-term safety and tolerability study of ranolazine ER at doses up to 1000 mg twice daily in patients with chronic angina.

Investigators and Study Centers
The study was conducted at 2 sites in the United States:
Study Period: August 29, 2005 (first patient enrolled) to November 29, 2006 (last patient completed)

Objectives

The objective of this study was to determine the safety and tolerability of ranolazine extended- release (ER) at oral doses up to 1000 mg twice daily (bid) in patients with chronic angina who had previously completed study 3023.

Study design
This study was a 1-year open-label, uncontrolled follow up to base study 3023. All subjects started on a ranolazine ER dose of 500 mg bid. If this dose was not tolerated, the patient was discontinued from the study. If it was well-tolerated, the dose was escalated to 1000 mg bid. If the 1000 mg bid dose was not tolerated, the dose was reduced back to 500 mg bid, where the subject was maintained for the duration of the study. If the 1000 mg bid dose was well-tolerated, the subject remained at this higher dose for the duration of the study.

Number of Patients
The study planned to enroll up to 150 subjects. However, since study 3023 was terminated early, enrollment in CVT 3024 was only 9.

Serious Safety
Of the 9 subjects studied, 5 were prematurely discontinued (3 withdrew consent, 1 was hospitalized because of chest pain, and 1 died from metastatic pancreatic cancer).

CVT 3032

Conclusions
The results of this small, open label, uncontrolled, long term study with doses up to 1000 mg bid are difficult to interpret. There were numerous reports of death (12%), reports of serious adverse events and withdrawals for adverse events (37%, mostly for angina). However, nothing unexpected was reported during the study.

Title of Study
A Phase 3, Open-label, Long-term, Safety Study of Ranolazine SR for Chronic Stable Angina Pectoris at Doses of 750 mg and 1000 mg bid

Objectives
The primary objective of this study was to determine the long-term safety and tolerability of ranolazine ER 750 mg bid and 1000 mg bid in patients with chronic stable angina during an open-label treatment period of up to approximately 10 years duration administered with or without other antianginal medications as needed to control symptoms.

Study design
Long-term open-label safety study of ranolazine ER administered with or without other antianginal therapy in patients with chronic stable angina who had completed Study CVT 3031. Subjects received open-label treatment with ranolazine ER at an initial dose of 750 mg bid which may have been titrated to 1000 mg bid based on clinical response. If at a ranolazine ER dose of 1000 mg bid symptoms were not controlled, subjects may also have taken additional antianginal therapy (calcium channel blockers or beta-blockers) as necessary.

Number of Patients

A total of 143 patients enrolled in this follow-on study to CVT 3031.

Main Criteria for Inclusion
The study population consisted of patients with stable angina pectoris who completed Study CVT 3031. Subjects were not eligible to enter Study CVT 3032 if they had NYHA Class IV congestive heart failure, second or third degree atrioventricular block or uncontrolled clinically significant cardiac arrhythmias, QTc > 500 msec, required medications known to prolong the QTc interval, required medications significantly affecting cytochrome P450 3A4, active acute myocarditis or pericarditis, hypertrophic cardiomyopathy, uncontrolled hypertension, any chronic illness likely to hinder or confuse the follow-up evaluation, or were unwilling to refrain from consumption of grapefruit/grapefruit juice.

Continued eligibility criteria
If a patient developed any of the following criteria during this study they were not eligible to continue: clinically significant hepatic disease, end-stage renal disease requiring dialysis or a calculated creatinine clearance (CLcr) < 30 mLlmin.

Duration of Treatment
This study was intended to last up to approximately 10 years. The actual duration of the study was approximately 8 years.

Results
The mean duration of exposure was 3.8 years (range: 12 days to 8 years).

There were 17 deaths and 87 serious adverse events: 53 subjects withdrew for an adverse event (most common were for angina (5), MI (4), dizziness (3), coronary artery surgery(3)).

The causes of death included myocardial infarction (4%), cancer (3%), sudden death (1%). Other rarely reported events included cerebrovascular event, ventricular fibrillation/tachycardia, acute respiratory failure, multi-system failure, congestive heart failure, and cardiovascular insufficiency.

The serious adverse events included angina, MI, unstable angina, CHF, and CAD. Cerebrovascular accident and syncope were reported by 4% and 2% of the study population, respectively. Torsade de Pointes was not reported.

The most frequently reported adverse events were angina pectoris (29%), dizziness (22%), constipation (16%), chest pain (15%) peripheral edema (14%), and fatigue (13%).

There was one report of "a prolonged QTc" in a subject who had been started on amiodarone 7 days previously for atrial fibrillation and the second was an "arrhythmia" in a subject with a history of atrial fibrillation and supraventricular tachycardia.

<u>CVT 3034</u>

Conclusions
There were no unusual findings in this large open label, uncontrolled study.

Title of Study

A Phase 3, Open-label, Long-term, Safety Study of Ranolazine SR for Chronic Stable Angina Pectoris at Doses of 500, 750 mg and 1000 mg bid Administered in Combination with Background Antianginal Therapy

Objectives
The primary objective of this study was to determine the long-term safety and tolerability of ranolazine ER 500 mg bid, 750 mg bid and 1000 mg bid in patients with chronic stable angina during an open-label treatment period of up to 8 years.

Study design
Long-term open-label safety study of ranolazine ER administered with or without other antianginal therapy in patients with chronic stable angina who had completed Study CVT 3033 or CVT 3037. Subjects received open-label treatment with ranolazine ER at an initial dose of 750 mg bid which may have been titrated to 1000 mg bid based on clinical response. If at a ranolazine ER dose of 1000 mg bid symptoms were not controlled, subjects may also have taken additional antianginal therapy (calcium channel blockers or beta-blockers) as necessary.

Number of Patients
A total of 1108 subjects were enrolled for up to 6 years.

Results
A total of 814 (74%) subjects completed the trial. The mean duration of exposure was 2.25 years (range: 6 days to 6.27 years).

There were 74 deaths and 87 serious adverse events: 90 subjects (8%) withdrew for an adverse event (most common were cardiac disorders including MI, and one subject was discontinued because of abnormal BUN, serum creatinine and serum uric acid). Torsade de Pointes was not reported.

The causes of death included myocardial infarction (3%), sudden death (1%), and cancer (1%). Other reported events in 3 or few subjects included accident/trauma, ventricular fibrillation/ tachycardia, and pulmonary embolism. There were 2 subjects who died of unknown causes.

There were 290 (26%) subjects who reported a serious adverse event.

The most commonly reported adverse events included constipation (9%), angina (7%), dizziness (7%), peripheral edema (6%), unstable angina (5%), and hypertension (4%).

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/s/

Maryann Gordon
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