CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-526

Medical Review(s)

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DATE: December 20, 2005

FROM: Shari L. Targum, M.D.
TO: NDA 21-526 ranolazine

SUBJECT: Safety Update
SPONSOR: CV Therapeutics
DATE OF SUBMISSION: November 21, 2005

Proposed Indication: Treatment of chronic angina in patients who have not achieved an adequate response with other anti-anginal drugs.

1.0 Safety Update:

Executive Summary: The information from this safety update does not change the conclusions in the July 26, 2005 submission.

1.1 Introduction
The addendum includes a review of a November 21, 2005 safety update, as well as additional analyses provided by the sponsor.

1.2. Materials Used in this Review:
The materials in this review were provided by the sponsor.

1.3. Overview:
The November 21, 2005 Safety Update provided updated serious adverse events, deaths, and adverse events that led to discontinuation of study medication obtained during the period October

1, 2004 through April 1, 2005 in two long-term open-label, ranolazine ER studies CVT 3032 and CVT 3034.

1.4. Deaths:

Eight patients died during the reporting period, and updated information was provided for one additional patient (CVT 3033_4939680) whose death was previously reported as "lung tumor" in the July 26, 2005 submission; in the safety update, this patient's term was changed to "lung cancer." These are listed below. All deaths were noted to occur in the long-term open-label study CVT 3034.

Table 1. Deaths by Study Number and Patient (October 1, 2004-April 1, 2005; deaths prior to October 1, 2004 received updated coding).

Protocol/Site/Patient number	Age/Sex	Fatal AE	Last Treatment	Days on Ranolazine	Days since last study medication	Date of Death
CVT 3033_4939680*	63/M	Cancer	Ran 1000 BID	679	5	[redacted]
CVT 3033_1887009*	69/M	Post-procedural hemorrhage, acute coronary syndrome	Ran 1000 BID	1223		
CVT 3033_7067575*	62/M	Acute Cardiac Failure	Ran 1000 BID	607		
CVT 3033_5078116	73/M	Sudden Death	Ran 750 BID	1674	1	
CVT 3033_6428507	67/M	Myocardial Infarction (MI)	Ran 1000 BID	1358	6	
CVT 3033_7048732	65/M	Acute Cardiopulmonary Failure	Ran 1000 BID	1051	23	
CVT 3033_7117610	63/M	MI	Ran 1000 BID	1117	1	
CVT 3037_57017006	56/M	Accident/Trauma	Ran 1000 BID	85	1	
CVT 3037_61017005	43/M	Sudden Death	Ran 500 BID	83	1	
CVT 3037_86057010	54/M	MI	Ran 1000 BID	70	1	
CVT 3037_86097004	65/M	Congestive Heart Failure	Ran 1000 BID	35	0	[redacted]

*These deaths were noted in the July 26, 2005 submission. Patient CVT 3033_1887009 was noted as post-surgical (left kidney cancer) hemorrhage. Patient CVT 3033_7067575 was listed in the review as "sudden death."

Narratives and case report forms for the eight new deaths were not submitted for review. From the above summary, it appears that most of the deaths were cardiovascular in nature.

1.5 Serious Adverse Events

Serious adverse events are listed in Table 2. Many, but not all, are cardiovascular in nature.

Table 2. Serious adverse events (excluding deaths)

Protocol/Site/Patient	Age/Sex/Race	AE preferred term	Days on (off) treatment at onset	Treatment dose at (prior to) onset	Action/Outcome
CVT 3031_1282008	70/M/W	Syncope	1967	Ran 1000 BID	Rx interrupted/Recovered
CVT 3031_1331022	78/M/W	Angina pectoris	2320	Ran 1000 BID	None/Controlled
CVT 3031_1401139	72/M/W	MI, myelopathy	2106	Ran 1000 BID	None/Recovered
CVT_1411162	53/M/W	Constipation	?	Ran 1000 BID	Rx interrupted/Recovered
CVT 3031_1711294	56/F/W	Post-laminectomy syndrome	?	Ran 1000 BID	Rx interrupted/recovered
CVT 3031_1771468	56/M/W	Unstable angina, Coronary artery disease, Pelvic/peritoneal abscess	1977, 1994, 1702	Ran 1000 BID	None/Recovered
CVT 3031_5271337	61/M/W	Coronary artery disease	?	Placebo	None/Recovered
CVT 3033_1418123	74/M/W	Congestive heart failure	1069	Ran 1000 BID	None/Recovered
CVT 3033_1748031	79/M/W	Ankle fracture, Fall, Syncope	432	Ran 1000 BID	None/Recovered
CVT 3033_1818226	48/M/W	Shoulder pain	581	Ran 750 BID	None/Recovered
CVT 3033_1827418	70/M/W	Colon cancer	278	Ran 750 BID	None/Recovered
CVT 3033_1857288	78/M/W	Benign prostatic hyperplasia	?	Ran 750 BID	None/Recovered
CVT 3033_1858358	65/F/W	Food intolerance, anti-infective therapy	906	Ran 750 BID	Rx discontinued/Recovered
CVT 3033_1858373	79/M/W	Unstable angina	1520	Ran 750 BID	None/Recovered
CVT 3033_2169346	43/F/W	Bronchitis	1325	Ran 750 BID	None/Recovered
CVT 3033_2188381	75/M/W	Congestive heart failure, MI, prostatitis	45	Ran 500 BID	Rx interrupted/Recovered
CVT 3033_2189303	59/M/W	Angina pectoris	1535	Ran 750 BID	Dose reduced/Recovered
CVT 3033_2189303	59/M/W	Ischemia	1381	Ran 750 BID	None/Recovered
CVT 3033_5088099	63/F/W	Acute pancreatitis	1506	Ran 750 BID	None/Recovered
CVT 3033_5537111	69/M/W	Metastatic prostate cancer	?	Ran 750 BID	Rx discontinued/Ongoing
CVT 3033_5538174	65/M/W	Angina pectoris, MI	?, 1618	Ran 750 BID	None/Recovered
CVT 3033_5637056	63/M/W	Unstable angina	1411	Ran 750 BID	None/Recovered
CVT 3033_5638062	62/F/W	Cerebrovascular accident	1424	Ran 750 BID	Rx discontinued/Recovered

CVT 3033_6227267	57/F/W	Uterine perforation	1015	Ran 1000 BID	None/Recovered
CVT 3033_7037668	60/M/W	MI	1005	Ran 1000 BID	None/Recovered
CVT 3033_7187642	60/M/W	MI	725	Ran 1000 BID	None/Recovered
CVT 3037_13017001	75/M/W	Bronchitis/Pneumonia	(9)	Ran 1000 BID	None/Recovered
CVT 3037_13017006	71/M/W	Arthropod bite	?	Ran 500 BID	None
CVT 3037_13017008	55/M/W	Chest pain	2	Ran 750 BID	None/Recovered
CVT 3037_86077014	68/M/W	MI	54	Ran 1000 BID	None/Recovered
CVT 3037_86117012	64/F/W	Cardiac failure	?	Ran 500 BID	None/Recovered
CVT 3037_86117019	60/M/W	Pulmonary embolism	31	Ran 500 BID	None/Recovered
CVT 3037_ 86187007	70/M/W	Bladder neoplasm	11	Ran 750 BID	None/Recovered
CVT 3037_86247002	52/M/W	MI	3	Ran 1000 BID	None/Recovered
CVT 3037_86267006	54/M/W	Pulmonary edema	5	Ran 1000 BID	None/Recovered
CVT 3037_86287003	51/M/W	Hypotension	77	Ran 1000 BID	None/Recovered
CVT 3037_86287005	52/M/W	Osteoarthritis	36	Placebo	None/Ongoing

? = data not listed in submission. According to the sponsor, if the onset date was not complete in the CRF, the days on treatment at onset of AE were left blank. Two placebo patients are noted; according to the sponsor, these were related to a change in data management.

1.6 Withdrawals due to adverse events:

Under treatment-emergent adverse events leading to discontinuation of study medication, four patients(#4939680, 6428507, 7067575, 86057010) have already been noted in Table 1. Three others (#1858358, 5537111, 5638062) are noted in Table 2. Two other patients (#1311041, 2277294) discontinued due to angina, one patient (#86097027) discontinued due to hepatitis B, and one (#86157014) discontinued due to pruritis and urticaria.

1.7 IND Safety Reports (Active Cases) in Ongoing Studies CVT 3036 and 3023

Unblinded IND safety reports have been submitted for CVT 3036 (8 cases) and CVT 3023 (1 case). In addition, 7 IND safety reports for CVT 3036 placebo patients were submitted. In CVT 3036, two cases of renal failure (chronic renal failure, renal insufficiency) are noted with active ranolazine treatment and two cases of renal failure (one with acute renal failure) are noted in the placebo group. Three cases of confusion or hallucinations are noted with active treatment (none in the placebo group). In CVT 3023, a case of involuntary muscle contractions was noted.

2.0 Review of cancer cases from the safety database

This reviewer searched the updated Integrated Summary of Safety database for patients with cancer, suspected cancer, other malignancy, precancerous lesion, or polyps (with the exception of basal cell skin cancer). Forty patients were found that met this criteria (39 ranolazine and 1 placebo patient). Thirty-seven out of 39 ranolazine patients were first reported with

cancer/precancerous lesion/polyp during long-term open-label studies; there are no concurrent matched long-term control groups to ascertain background rates. Therefore, no conclusion can be made from these results.

3.0 Further subgroup analysis from CVT 3037

In response to a request from this review, the sponsor provided further subgroup analyses for study CVT 3037. In the next figure, the mean effect is smaller in females however, the mean value trends in a direction favorable toward ranolazine (albeit with confidence intervals that cross zero). With the exception of the diabetes subgroup, the other subgroups show means favorable toward ranolazine.

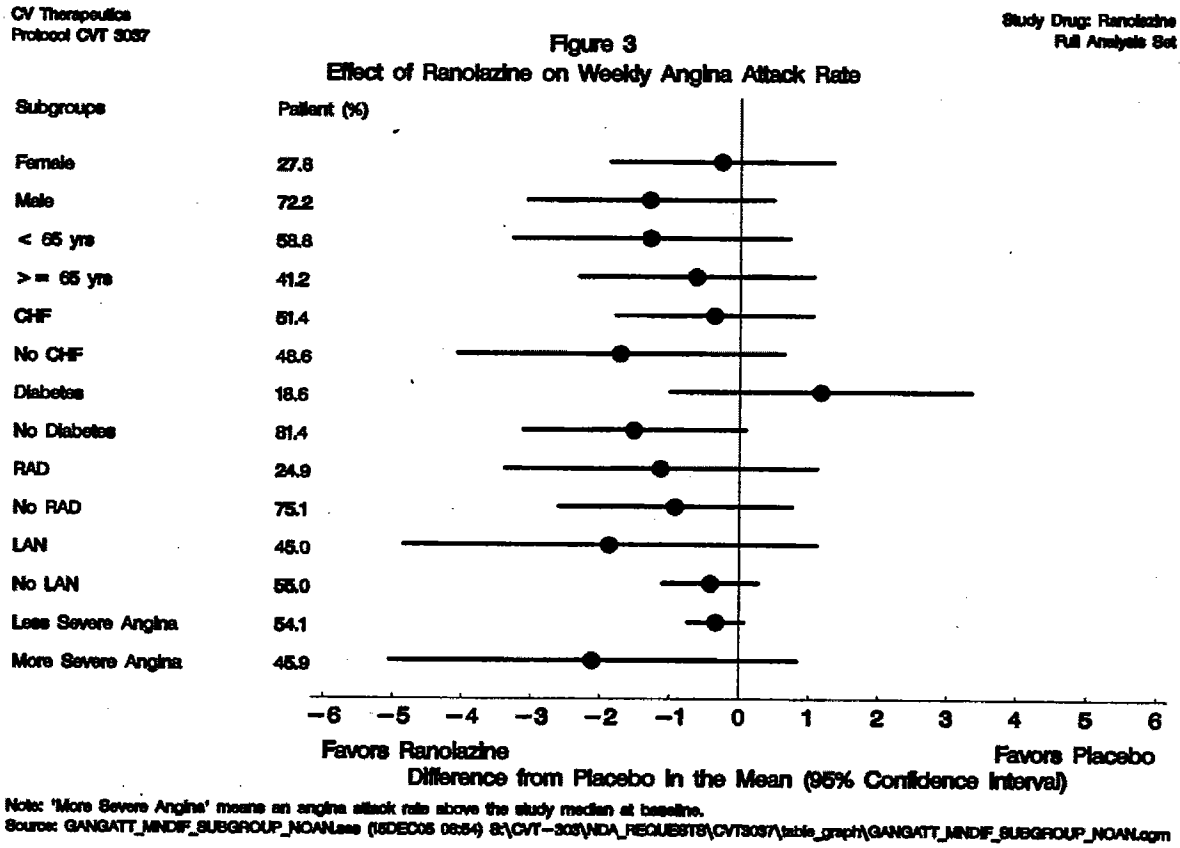

Figure 1. CVT 3037: Primary efficacy variable by subgroup: difference from placebo in mean value (95% CI)

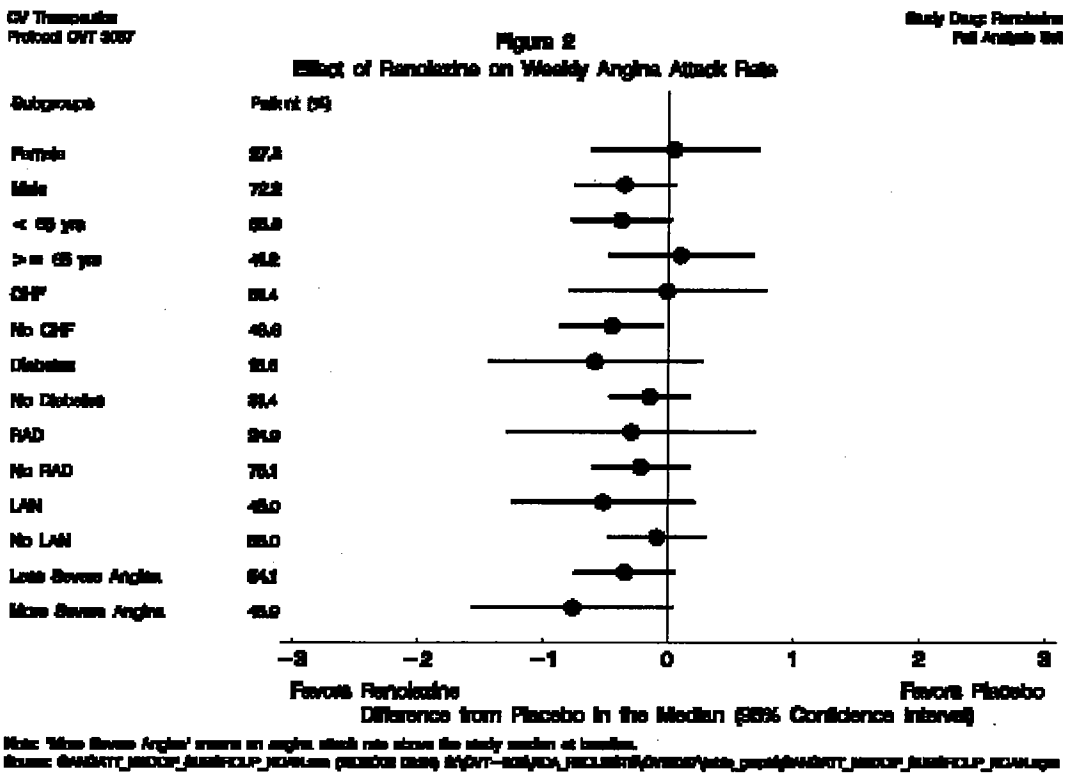

Figure 2. Primary efficacy variable: difference from placebo in the median value (95% CI)

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/s/

Shari Targum
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MEDICAL OFFICER

Clinical Review Cover Sheet

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Clinical Review for NDA 21-526

Executive Summary

I. Recommendations

A. Recommendation on Approvability

1. Ranolazine appears to have an anti-anginal effect, as evidenced by improvement in exercise tolerance at peak in the two pivotal trials. Also supportive, although demonstrated in only one trial, is a decrease in anginal attacks and nitroglycerin consumption. There have been no studies related to outcomes and it is not known whether or not ranolazine affects survival.
2. A major safety issue is ranolazine's effect on repolarization. In addition, since ranolazine is metabolized via the cytochrome pathway, the potential arises for drug interactions leading to increased ranolazine concentration (and increased risk).
3. Remaining issues include: exploration of dosing and dose-response, establishment of benefit in women, and benefit-risk (see Conclusions).
4. It is therefore recommended that ranolazine be granted "approvable" status, with further studies/data needed prior to approval (see Conclusions).

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

If ranolazine were to be approved, it would be recommended that some risk management steps be undertaken in order to minimize the risk of torsade de pointes. These risk management steps can include labeling recommendations and education programs for physicians, patients, and pharmacies.

In addition, the Division of Clinical Pharmacology and Biopharmaceutics has offered the following recommendations to the sponsor:

1. As a Phase 4 committment perform a drug interaction study in healthy volunteers of both genders investigating the potential of ranolazine to inhibit the metabolism of a probe substrate mainly metabolized by CYP 2D6.
2. Change the proposed dissolution specifications according to FDA recommendations (as noted in their review).

II. Summary of Clinical Findings

Executive Summary Section

A. Brief Overview of Clinical Program

According to the sponsor, ranolazine is a novel compound proposed for the treatment of angina. The proposed mechanism of action is pFOX (partial fatty acid oxidation) inhibition, which would then prevent or reduce ischemia by improving the efficiency of myocardial oxygen use. The sponsor claims that this unique metabolic mechanism of action can be useful in symptomatic chronic angina patients who cannot tolerate reductions in blood pressure, heart rate, contractile performance or AV conduction from the use/upward titration of beta-blockers, calcium channel blockers or nitrates. While both oral and intravenous formulations were used in clinical studies, the proposed dose form consists of tablets (375 and 500 mg) which are intended for oral, chronic use.

The number of patients who were included in the database and received ranolazine is around 2700; approximately 280 subjects received the drug for at least 1 year. Several formulations were studied: immediate release (IR) with nearly 1300 subjects, sustained release (SR) with nearly 1360 subjects, and intravenous (IV) with less than 80 subjects. There were 3 placebo controlled SR angina clinical trials (designated as Phase 2/3 controlled angina) with a total of 749 ranolazine and 455 placebo subjects. One of these trials (CVT 3031) was a crossover with doses up to 1500 mg bid. The other trial (CVT 3033) was a parallel group, 12 weeks duration with the highest dose being 1000 mg bid. The third trial (RAN 2240) enrolled only 11 patients. Targeted SR dose range was 500 mg- 1500 mg bid.

Two studies in intermittent claudication were included in this submission but were not used to support efficacy claims.

B. Efficacy

Efficacy studies, included in the ISE analysis, consisted of two Phase 3 studies (CVT 3033 and CVT 3031) which used the SR formulation and 3 controlled clinical trials (RAN 072, RAN 080, RAN 1514) which used the IR formulation. These five studies randomized a total of 1596 angina patients. In addition, six studies (total 157 patients randomized) supporting mechanism of action (CVT 3021, RAN 003, RAN 004, RAN 011, RAN 014, RAN 070) were used by the sponsor to support the sponsor's proposed mechanism of action.

Efficacy results: Efficacy at peak was demonstrated in the two Phase 3 studies. A modest statistically significant treatment effect was seen at trough in one study (CVT 3033). Due to interpretability issues in CVT 3031, the reviewers could not conclude a statistically significant treatment effect at trough using first period data. In addition, a statistically significant decrease in anginal attacks and nitroglycerin consumption was seen in one study (CVT 3033). Taken together, these findings support an anti-anginal effect, with uncertainty about inter-dosing interval and appropriateness of bid dosing. There appeared to be no increase in treatment effect with ranolazine SR 1000 mg bid compared to 750 mg bid; these results do not support a benefit with up-titration. The lowest effective dose with the SR formulation is unknown.

A statistically significant treatment effect was seen after 2 weeks of dosing in one study (CVT 3033). Despite adequate serum concentrations, a significant treatment effect after one week was

not seen in Study RAN 1514 and a marginal effect at peak was seen in CVT 3031; it may be that a treatment period of one week is too short (despite adequate serum levels as claimed by the sponsor) and a longer treatment period may be necessary.

Unresolved efficacy issues include: 1. Efficacy of ranolazine when added to maximal doses of anti-anginal (s); 2. Comparisons to other anti-anginals; 3. Efficacy in a refractory population; 4. Complete exploration of the dose-response relationship such that efficacy of lower doses/ onset of significant treatment effect/ appropriate dosing interval are identified. In addition, efficacy in women should be explored.

C. Safety

QT interval prolongation and T wave morphology changes

The sponsor found out early in development that ranolazine increases the QT interval on ECG and changes the morphology of the T wave. The drug effect at peak concentration is greater than at trough. The mean changes by dose are shown below.

Mean change from baseline in QT[1]/QTc interval (msec) at peak

	Placebo N=432	Ranol 500 N=177	Ranol 750 N=269	Ranol 1000 N=428	Ranol 1500 N=170
Mean change from baseline	-3.7/-2.0	-1.0/3.3	7.3/3.5	6.7/5.0	8.5/11.0
Max mean change from baseline	0.9/1.1	-1.0/3.3	16.3/8.9	11.5/8.1	8.5/11.0

Table N-1.3.2.1vol 1.0376

The table below shows the number and percent of patients, by dose, who had selected QTc interval changes from baseline at endpoint at peak drug concentration.

No. and (percent) of patients

Change from baseline	Placebo N=433	Ranol 500 N=177	Ranol 750 N=271	Ranol 1000 N=433	Ranol 1500 N=170
0-30 msec	167 (38.6)	67 (37.9)	160 (59.0)	242 (55.9)	71 (41.8)
31-60 msec	21 (4.8)	20 (11.3)	6 (2.2)	29 (6.7)	28 (16.5)
≥61 msec	4 (0.9)	6 (3.4)	1 (0.4)	1 (0.2)	10 (5.9)

Table N-15.3.1 vol 1.0377

There also were changes in the morphology of the T-wave during ranolazine use. The frequencies of notched T waves are shown below by treatment group at peak and trough concentrations (study CVT 3031).

[1] From fax dated 6-27-03

% of subjects with notched T waves

	Placebo	Ranol 500	Ranol 1000	Ranol 1500
peak	2	1	3	6
trough	<1	<1	5	5

There were more notched T waves reported in the Ranolazine 1000 mg and 1500 mg doses than in the placebo and ranolazine 500 mg dose groups.

The number and percent of patients in CVT 3033 with notched T waves at weeks 2 and 12 by drug group are shown below.

% of subjects with notched T waves (at peak)

Placebo		Ranolazine SR 750 mg		Ranolazine SR 1000 mg	
Week 2	Week 12	Week 2	Week 12	Week 2	Week 12
0.4	0	4.1	1.2	2.0	3.4

Genetic studies have shown that long-QT syndrome (LQTS) is a primary electrical disease caused by mutations in specific ion channels.[2] LQTS patients exhibit QT prolongation on the ECG and are at risk of arrhythmogenic syncope and sudden death. In addition to duration, T-wave morphology is often abnormal, and notched T waves have been included in diagnostic criteria.[3] This pattern has been associated with a poor prognosis.[4]

Drug interactions

CYP3A4 is a major determinant for ranolazine clearance. There was an average increase of plasma concentration of 3- to 4-fold in the presence of the potent CYP3A4 inhibitor ketoconazole (200 mg bid)[5]. The effect on QTc is shown below.

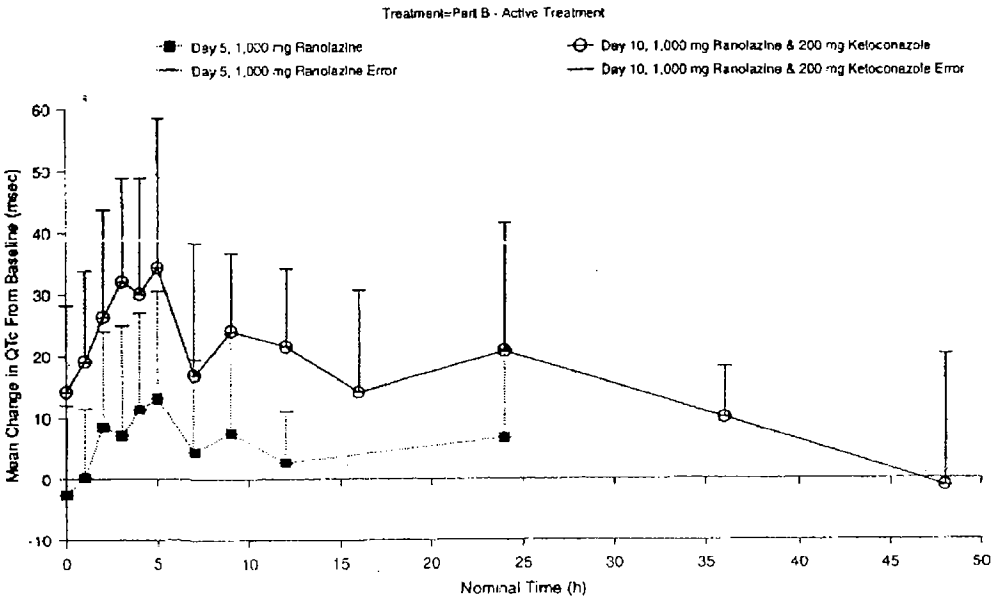
[2] Roden DM, Spooner PM. Inherited long QT syndromes: a paradigm for understanding arrhythmogenesis. J Cardiovasc Electrophysiol. 1999;
10: 1664-1683.

[3] Schwartz P1, Moss AJ, Vincent GM, and et al. Diagnostic criteria for the long QT syndrome: an update. Circulation. 1993; 88: 78-784.

[4] Malfatto G, Beria B, Sala S, et al. Quantitative analysis of T wave abnormalities and their prognostic implications in the idiopathic long QT syndrome. J Am Coll Cardiol. 1994; 23: 296-301.

[5] Study CVT 301-10

Figure 14.4.3.2 Mean Plots of Changes in QTc Interval From Baseline in Part A Following Twice Daily Administration of 1,000 mg Ranolazine/Placebo Alone (Day 5) and Co-administration of 200 mg Ketoconazole (Day 10)



Concomitant use with diltiazem resulted in increases in ranolazine plasma concentrations of 1.5- to 2.4-fold over the diltiazem total daily dose range (180-360 mg)[6]. Ranolazine 1,000 mg bid at steady-state caused a less than two-fold increase simvastatin exposure dosed at 80 mg qd[7].

Hepatic impairment:
Subjects with moderate hepatic impairment had increases in AUC and Cmax. This resulted in increases in QTc. The pharmacometric review suggests that patients with hepatic impairment were more sensitive to ranolazine than patients without hepatic impairment. In other words, the same concentration resulted in more QTc prolongation in hepatic impaired patients.

Renal impairment:
Subjects with creatinine clearance decreasing from 100 mL/min to 30 mL/min had increases in AUC and Cmax.

Adverse events:
Commonly reported events in the SR controlled angina studies were dizziness (6.8% placebo subtracted

[6] Studies CVT 3012, RANO121, and RANO6S
[7] Study CVT 3017

D. Dosing

There appears to be a linear relationship between ranolazine plasma concentrations and change in QTc (please see the Clinical Pharmacology and Biopharmaceutics review). There appears to be no increase in treatment effect when the ranolazine SR dose is increased from 750 to 1000 mg bid. These two factors suggest that the benefit-risk ratio for ranolazine would favor lower doses. Results of the clinical studies do not support the proposed labeling, which gives a starting dose of 500 mg bid with upward titration through 750 mg bid to 1000 mg bid, as needed, based on clinical response.

Dose modifications are recommended in patients on concomitant diltiazem, CYP 3A4 inhibitors, renal impairment/hepatic impairment (please see safety review);

E. Special Populations

Gender Differences:

According to the clinical pharmacology reviewer, a population analysis of the relationship between ranolazine plasma concentrations and exercise duration in patients with angina showed that the exercise duration at identical plasma concentrations in women is reduced to between about 28% and 42% of that in men, indicating a significantly smaller extent and time duration of the exercise performance improving effect of ranolazine in women. The reduced exercise improving effects of ranolazine in women have not been shown to be statistically significantly different from placebo.

From the efficacy review, subgroup analyses by gender focused on one study (CVT 3033); finding showed statistically significant effects in males but not females. This was the only subgroup analysis where results at peak were favorable toward placebo.

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

The safety reviewer concluded that gender differences in the safety database are undeterminable.

Ethnic/Racial Studies: The study population in studies CVT 3033 and 3031 was over 90% Caucasian. There were insufficient numbers of non-Caucasians studied to provide for a meaningful analysis of racial/ethnic differences.

Hepatic/renal impairment: Patients with hepatic impairment are more sensitive to the QTc prolonging effects of ranolazine than patients without hepatic impairment and use of ranolazine in this population is not recommended. The slope of the concentration QTc prolongation is steeper in patients with hepatic impairment. Thus, the same concentration produces more QTc prolongation in patients with hepatic impairment compared to patients without hepatic impairment. The exposure to ranolazine at peak is increased in patients with renal impairment and thus the initial dose of ranolazine should be reduced to 375 mg in patients with renal impairment and the maximum dose should be restricted to 500 mg in this population.

Pediatric studies: A pediatric waiver was granted and no pediatric program is planned for ranolazine.

Use in pregnancy: There are no data concerning use in pregnancy.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Drug Name: Ranolazine (RS 43285)
Proposed Trade Name: Ranexa™
Proposed Indication: According to proposed labeling, ranolazine will be indicated for the treatment of chronic angina in patients with severe coronary artery disease, and should be reserved for use in patients in whom other anti-anginals are inadequate or not tolerated.
Drug Class: Ranolazine is pharmacologically unrelated to other calcium channel blockers, beta-blockers and nitrates. According to the sponsor, its mechanism of action is believed to result from partial inhibition of fatty acid oxidation, via inhibition of enoyl-CoA hydratase and carnitine acyl carnitine translocase. In theory, the shift in fatty acid oxidation and increase in glucose oxidation results in more oxygen-efficient production of adenosine triphosphate (ATP), improved cardiac efficiency and reduced ischemia-induced increases in lactic acid and cellular acidosis.
Dose/Regimens: The proposed usual starting dose for ranolazine is 500 mg bid, with upward titration through 750 mg bid to 1000 mg bid, as needed, based on clinical response. A dose range of 375 to 750 mg bid is proposed in patients with severe renal impairment, and in patients treated with diltiazem $\geq$ 240 mg/day or verapamil $\geq$360 mg/day.
Age Groups: Ranolazine has not been studied in the pediatric population. The total number of angina patients in ranolazine studies included 521 patients (51%) $\geq$ 65 years old and 116 (11%) $\geq$ 75 years old.

B. State of Armamentarium for Indication(s)

Current U.S.-approved therapeutic options for angina include beta-blockers, calcium channel-blockers and nitrates. In addition, non-pharmacologic options exist for certain patient populations with angina pectoris: percutaneous coronary intervention (PCI) including angioplasty/stent placement and coronary artery bypass grafting (CABG) including internal mammary artery grafting.

**In 1990, bepridil (NDA 19,002), a calcium channel blocker associated with QT prolongation and torsades de pointes was approved for the treatment of angina. The approval of bepridil as a second-line agent appears to have based on: 1. One well-controlled study showing superiority to diltiazem in a diltiazem-resistant population; 2. Two other studies suggesting superiority to two other agents.

C. Important Milestones in Product Development

1. In 1987, Syntex filed an IND (30,205) to conduct studies of an immediate release formulation of ranolazine in patients with chronic angina. In 1993, Syntex filed IND 43,735 for ranolazine SR (sustained release). An End-of-Phase 2 meeting between the Agency and Syntex was held in April, 1994; however, in September, 1994, Roche Holding, Ltd. acquired Syntex and the development program for ranolazine SR was terminated.
2. In March, 1996, CVT (CV Therapeutics) acquired the license for ranolazine from Syntex, a subsidiary of Roche. CVT then initiated a development program with ranolazine SR for the treatment of angina pectoris under IND 43,735.
3. An End-of-Phase 2 meeting between CVT and the Agency was held on December 12, 1997. *According to the sponsor*, it was agreed that the design of studies CVT 3031 and 3033 would support the intended claim. It was further agreed that the primary efficacy variable should be symptom-limited ETT duration at trough. Evaluation of the mortality effect of ranolazine would probably not be required before approval. In addition, the ranolazine safety database, including patients receiving the IR formulation, appeared to be adequate. It was agreed that the sponsor would monitor metabolites in its PK studies and assess the pharmacologic activity of the most abundant metabolites. It was recommended that CVT explore the plasma level-QTc relationship in healthy volunteers. *According to Agency minutes*, the sponsor was cautioned about the problems encountered with crossover design trials (3031), including 1. presence of treadmill learning effects and 2. treatment by period effects being greater than drug effects. Evaluation of the mortality effect was advised but probably not required before approval. The sponsor was asked to consider a simple long-term outcome trial (but probably not needed pre-approval).
4. In addition, four pre-NDA meetings were held on July 25, 2000, December 20, 2001, August 13, 2002, and October 10, 2002, respectively. According to Agency minutes, concerns raised by the Agency in July, 2000 included: dose-related tumors noted in animal carcinogenicity studies; relative potency of mice vs. humans indicating a narrow therapeutic margin; three metabolites whose activity is unknown (that may be associated with carcinogenicity); Ikr blockade and QTc prolongation. It was suggested that, without a mortality outcome trial, the sponsor should demonstrate ranolazine superiority (vs.other antianginal agent) in patients refractory to anti-anginal agents used at maximally tolerated doses. It was concluded that the two pivotal trials, if successful, would serve as a basis for approval on efficacy; however, QT prolongation remained a major concern and the company would have to prove that the clinical benefit outweighed the safety risks. On August 13, 2002, the Agency noted that, in CVT 3033, patients did not receive an adequate dose of amlodipine, atenolol and diltiazem and therefore interpretation of ranolazine's effect as add-on therapy was difficult. Additional data were needed to verify the efficacy of the drug; the sponsor could conduct another study with ranolazine as add-on to adequate doses of a calcium channel blocker or beta blocker or submit analyses of data already collected to show efficacy when added to patients on adequate/maximal therapy. QT prolongation was a concern, and the Agency believed that additional safety data were needed. It was preferred that these data be collected from a study in several thousand patients to see how ranolazine compares to a beta blocker or calcium channel blocker for serious adverse events. On October 10, 2002, the Agency stated that, in order for the drug to be approved for use in resistant populations it must be shown that

approximately maximal doses of beta blockers and calcium channel blockers have been used. Intolerant subgroups would need to be redefined to include only those patients who are clearly intolerant to conventional therapy; in addition, safety data would be needed for these subgroups to show that ranolazine is not inherently harmful in these populations. Additional controlled safety data will be needed to better quantify the drug's arrhythmogenic potential, although it is possible this information could be obtained post-approval.

D. Other Relevant Information

This is the first application filed for ranolazine.

E. Important Issues with Pharmacologically Related Agents

According to the sponsor, ranolazine is pharmacologically related to trimetazidine. Trimetazidine is marketed in several countries, including France, Hungary, Japan, Spain.[8]

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Chemistry: Ranolazine drug substance is a free base. The drug product is formulated as an extended release tablet formulation in two different strengths 375 mg (Pale blue) and 500 mg (Light orange) film coated tablets. The drug product is manufactured by [redacted] The drug product is found to be stable up to 12 months at 25oC/60%RH and no degradation products were observed. Based on test data, [redacted] of expiry is being considered.

Animal Pharmacology and Toxicology Findings: Pre-clinically, ranolazine has been shown to interact with cardiac ion channels. Approximately 7 of the known major metabolites have also been shown to interact with cardiac ion channels including Ikr. The cardiovascular safety study showed that cumulatively increasing doses of ranolazine caused a deterioration in cardiac function manifested as decreased cardiac output, decreased contractile force and decreased left ventricular systolic pressure. Left ventricular minute work was also decreased while total peripheral resistance was increased. ECG data was not provided.

[8] The reviewer searched Pubmed and google, in addition to a query to the sponsor, but was not able to find much safety information regarding trimetazidine.

Sedation was noted in several of the neurologic safety pharmacology assessments as well as general toxicology studies. Neurologic deficits were noted at doses where sedation was not apparent.

The adrenal gland was identified as a target organ. In general toxicology studies, adrenal weight was increased in both rats and dogs. Where pathology was reported histopathologic findings included diffuse vacuolation and/or cytoplasmic foaminess of the zona fasciculata. Special toxicology studies showed both acute and chronic effects of ranolazine on the hypothalamic-pituitary-adrenal (HPA) axis. Both in vitro and in vivo studies showed that ranolazine treatment caused a decrease in the release of adrenal steroid in the basal state, after ACTH stimulation, after a defined stressor and in the presence of precursors.

Ranolazine and/or one of its metabolites binds to retinal pigmented epithelium with a half life of approximately 8 days, most likely due to melanin binding. Accumulation in the retina and long term effects, if any, upon vision, are unknown.

Biopharmaceutics: The clinical and to be marketed dosage forms for the 500 mg SR tablet were shown to be bioequivalent. Based on the similarity of composition and dissolution performance of the 375 mg and 500 mg SR tablets the lower strength tablet is considered bioequivalent to the higher strength tablet. Food does not impact on either extent or rate of bioavailability of ranolazine released form the SR tablets.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The PK of ranolazine deviate slightly from linearity and dose proportionality in the dose range of between 500 mg and 1500 mg bid. Peak concentrations are reached between 2 and 5 hours following administration. Steady state is reached after 3 days of dosing. The peak to trough ratio ranges between 1.6 and 3.0. The apparent terminal half-life of ranolazine ranges between 6 and 9 hours. The accumulation factor varies between 1.7 and 1.9. The PK of ranolazine are not stereospecific. Ranolazine is mainly nonrenally eliminated. Less than 5 % is excreted in urine as unchanged ranolazine. Eleven metabolites have been identified. The 4 major circulating metabolites display AUC values relative to ranolazine between 5% and 33%. The apparent half-lives of the metabolites range between 7 and 22 hours. Ranolazine is mainly metabolized by CYP 3A4. A small fraction of ranolazine is metabolized by CYP 2D6. The exposure of poor metabolizers of CYP 2D6 to ranolazine is not clinically relevantly increased.

Effects of Size, body weight, gender, race: Body weight is not a clinically significant covariate for either the PK or PK-PD of ranolazine.

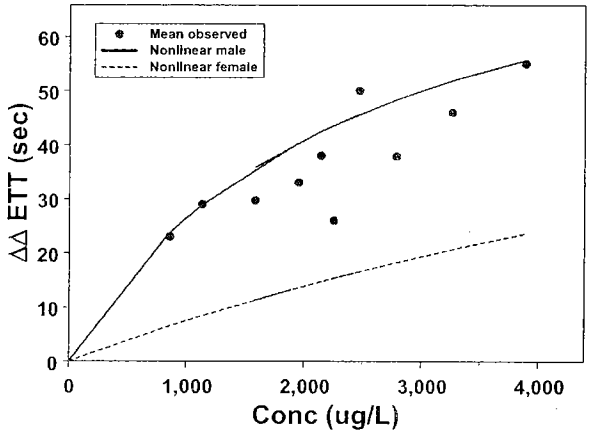
Gender impacts significantly the relationship between ranolazine concentration and effect on ETT. The exercise performance improving effect in females at peak and trough by ranolazine is reduced to 27.5% to 42.2% of that in males within the dose range of 500 mg to 1500 mg bid. However, gender is neither a significant covariate for the ranolazine concentration to QTc relationship nor for the PK of ranolazine.

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

Drug Interactions: In vitro metabolic studies indicate that ranolazine is a substrate of CYP 3A4 and CYP 2D6 and a substrate/inhibitor of P-glycoprotein. Additional in vitro results show that ranolazine can also inhibit the metabolism of statins.
The potent 3A4 inhibitors ketoconazole, diltiazem and verapamil, when co-administered, impact the PK of ranolazine in a clinically significant manner. These in vivo results are in agreement with the in vitro findings indicating that a substantial fraction of ranolazine is metabolized by CYP 3A4.
Co-administered paroxetine, simvastatin, digoxin and cimetidine have no clinically relevant effects on the PK of ranolazine. The small impact on the PK of ranolazine by paroxetine, a potent CYP 2 D6 inhibitor, indicates that a minor fraction of ranolazine is metabolized by this enzyme.
Co-administered ranolazine interacts clinically significantly with simvastatin, digoxin and warfarin. Ranolazine affects the PK of digoxin and simvastatin by increasing the exposure measures of these compounds clinically relevantly. Ranolazine has no impact on the PK of diltiazem.

B. Pharmacodynamics

Concentration – effect relationship: There is a significant nonlinear relationship between ranolazine plasma concentrations and exercise treadmill time. The figure below shows the mean ΔΔETT from the two pivotal clinical trials. The mean data contain ~ 78 % males. The lines depict the model predicted effectiveness in both genders. Since the mean data contain more males, the model predicted line for the males is closer to the mean data than the female predicted line. Females have less proportional (effect relative to placebo) benefit from ranolazine than males; ~ 70 % and 60 % less proportional benefit from ranolazine SR 500 mg q 12 h and 1000 mg q 12 h, respectively.

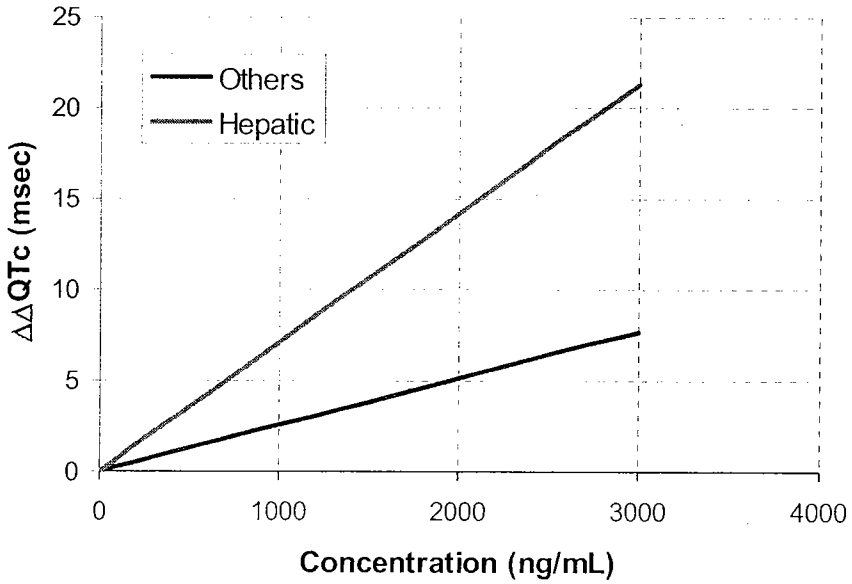


The following table shows the model predicted effectiveness in males and females.

Table 1. Reviewer's model predicted peak and trough mean ΔΔETT (seconds)

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

Concentration – QTc prolongation relationship: The QTc prolonging effect of ranoloazine is linearly related to the plasma concentration of the drug. The estimated mean maximum QTc prolongation at the 500 mg and 750 mg dose levels is < 5msec for patients with risk factors (clinically signicant PK and PK-PD covariates). Mean maximum QTc prolongations at peak in the range of 0-5 msec are not believed to be associated with an increased risk for TdP and sudden death. The 1000 mg dose of ranolazine exerts an estimated mean QTc prolongation at peak of 6.3 msec with 15% of the population displaying an increase exceeding 10 msec.
The only significant covariate found in the ranolazine plasma to QTc relationship is hepatic impairment. Patients with hepatic impairment showed a 2.8 fold increase in the slope of the ranolazine plasma concentration to QTc relationship indicating that at an identical plasma concentration of ranolazine the QTc interval in patients with liver disease is about 3 times longer than in patients without normal hepatic function. The slope of the concentration ΔΔQTc relationship was 2.6 msec per 1000 ng/mL in subjects and patients, while the slope was 7.1 msec per 1000 ng/mL in hepatic impaired patients. (See figure below.)



The ranolazine plasma concentration to QTc effect relationship is similar in males and females.

Interaction studies: In the presence of ranolazine the effect of warfarin on the prothrombin time is increased in a clinically relevant manner (please see the OCPB review for further details).

IV. Description of Clinical Data and Sources

A. Overall Data

The source of the overall data used in the review was the clinical trials program. Electronic data (crt, crf) were used as needed.

B. Tables Listing the Clinical Trials

See the Appendix for a table listing the Clinical Pharmacology Trials. For the efficacy studies, please see the efficacy review.

C. Postmarketing Experience

Ranolazine has never been marketed in any form or complex in any country.

D. Literature Review

In Volume 387 of the NDA submission, the sponsor submitted abstracts of reviews, clinical studies and clinical abstracts presented at scientific meetings. In addition, a Pubmed search of ranolazine by the reviewer failed to disclose any new information that would affect the conclusions in this review.

V. Clinical Review Methods

A. How the Review was Conducted

The efficacy review included analysis of efficacy and pharmacodynamic studies. Emphasis was placed on studies used by the sponsor to demonstrate efficacy, with greater emphasis placed on the two pivotal (Phase III) studies.

B. Overview of Materials Consulted in Review

The primary source of materials for this review involved the paper submission of NDA 21-526. In addition, related IND files (43,735; 30,205) were reviewed as needed.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigations (DSI) audit processes were solicited for selected sites.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials appear to have been conducted in accordance with accepted ethical standards.

E. Evaluation of Financial Disclosure

According to the sponsor, they and the Agency agreed that financial disclosure information would be provided for the following clinical studies: CVT 3031, CVT 3032 (open-label extension to CVT 3031), CVT 3033, CVT 3034 (open-label extension to CVT 3033), CVT 3021, and CVT 3111. The sponsor has certified that it has not entered into any financial arrangement with any of the clinical investigators involved in the conduct of these six studies whereby the value of compensation to the investigator could be affected by the outcome of the studies.

Financial certification/disclosure information was provided for investigators in the above six studies. One clinical investigator, [redacted] received additional payments as a consultant [redacted] The total amount of consulting payments made to Dr. [redacted] A signed Form 3455 was submitted.

Other than the above, no other Form 3455 was submitted.

VI. Integrated Review of Efficacy

Please see the efficacy review for further details.

A. Brief Statement of Conclusions

[9] The role of [redacted] included: research, identification and recommendation of clinical sites, period meeting with the sponsor, contact with study centers to discuss recruitment/issues regarding identification of eligible patients, identification of suitable replacement centers for terminated centers, and coordination with potential new/replacement investigators. The [redacted] did not serve in a supervisory capacity tot he clinical investigators, who were solely responsible for study management at their sites.

1. Results of the two pivotal studies, CVT 3031 and CVT 3033, suggest a significant treatment effect at peak. Because of interpretability issues in the sponsor's crossover analysis of CVT 3031, a statistically significant treatment effect at trough cannot be concluded based on first period data. Therefore, there is insufficient evidence to demonstrate that ranolazine SR, when given bid at the doses studied in the pivotal trials, is effective throughout the inter-dosing interval. Consequently, the dosing schedule and labeling instructions remain uncertain.
2. In addition, the submission contained insufficient data to demonstrate efficacy of the primary endpoint in certain post-hoc subgroups (low BP, reactive airway disease) mentioned in proposed labeling.
3. Symptomatic patients on maximal medical therapy were not studied in the clinical trials supporting efficacy in the Integrated Summary of Efficacy.
4. There are no studies in this submission demonstrating superiority of ranolazine over another anti-anginal medication.

VII. Integrated Review of Safety

Please see the safety review for further details.

A. Brief Statement of Conclusions

QT interval prolongation and T wave morphology changes:
Ranolazine increases the QT/QTc interval on ECG and changes the morphology of the T wave in a dose related manner.

Drug interactions:
CYP3A4 is a major determinant for ranolazine clearance. There was an average increase of plasma concentration of 3- to 4-fold in the presence of the potent CYP3A4 inhibitor ketoconazole (200 mg bid)[10]. QT/QTc was, in turn, prolonged. Use of ranolazine and CYP3A4 would not be recommended.

Concomitant diseases:
Subjects with moderate hepatic impairment had increases in AUC and Cmax as did subjects with creatinine clearance decreasing from 100 mL/min to 30 mL/min. Ranolazine would have to be used cautiously, if at all, in patients with these diseases.

Adverse events and laboratory values:
Commonly reported events in the SR controlled angina studies were dizziness (6.8% placebo subtracted), constipation (6.1%), and nausea (5.0%). Events reported mostly by subjects receiving 1500 mg bid included syncope, sweating, and vomiting. Changes in laboratory values were unremarkable and included small decreases in hematocrit/hemoglobin and small increases BUN and serum creatinine.

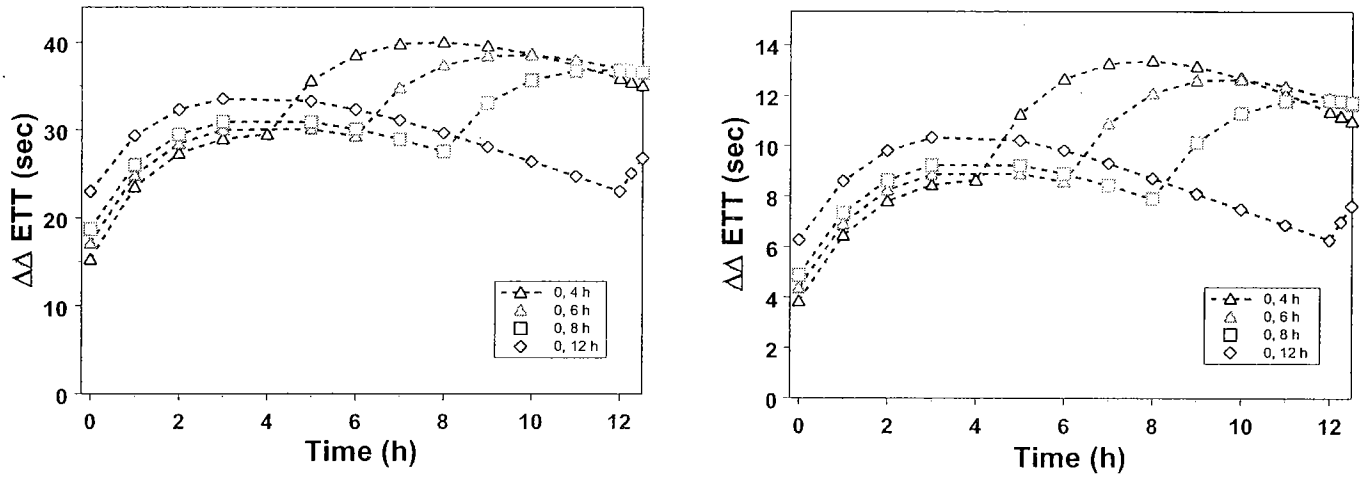
[10] Study CVT 301-10

VIII. Dosing, Regimen, and Administration Issues

1. There is uncertainty about the dose range of ranolazine that provides a consistent statistically significant exercise improving effect during the entire proposed 12 hour dose interval.
2. In one study (CVT 3033), there appeared to be no increase in treatment effect (ITT population) at trough with ranolazine SR 1000 mg bid compared to 750 mg bid. The minimally effective (at trough) dose of SR ranolazine is not clear; the first period analysis of CVT 3031 showed a marginally significant treatment effect at peak (but not trough) for the ranolazine 500 mg bid dose group.

Dosing Interval:
Because of the modest effect at trough in one study, simulations were performed to gain an insight of the effectiveness if ranolazine were dosed differently. One scenario is to aim for effective concentrations while the patient is active. The graphs below show the effectiveness by gender if 500 mg SR were dosed twice daily after 4, 6, 8 and 12 hours. The simulation for the doses given at 9 and 12 hours are similar to actual effectiveness in the clinical trials.

Figure 2. ΔΔETT from 500 mg BID regimens in males (left) and females (right) – Note the different y-axes range



IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The exercise improving effect of ranolazine in females is significantly smaller than in males. At identical ranolazine concentrations women display only 28% to

42 % of the effect in males. The statistical significance of the effect of ranoazine in women has not been demonstrated. However, the relationship between ranolazine concentration and QTc prolongation in females and males is similar.

According to the sponsor (proposed labeling), "population pharmacokinetic evaluation of data from patients and healthy volunteers has revealed no clinically significant age- or gender-related effects on the pharmacokinetics of ranolazine. Dosage requirements...are therefore not required." While the pharmacokinetic results may be true, the observed gender effect bears some further exploration by the sponsor.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

According to the safety reviewer, the effects of gender, race or ethnicity on ranolazine are undeterminable with the current database. However, it is not unreasonable to expect no effect.

With respect to efficacy, the effects of race or ethnicity on ranolazine are undeterminable with the current database. The patient population was mostly Caucasian.

With respect to age, The sponsor did not conduct a study to specifically evaluate the effect of chronological age on the PK or PD of ranolazine. A comparison of the mean concentrations of ranolazine in pivotal Studies CVT 3031 and 3033 showed that patients ≥ 65 years of age display on average 3% and 19%, respectively, greater concentrations than patients < 65 years old. The observed differences are too small to justify a dose adjustment in subjects ≥ 65 years of age. An evaluation of the elderly subgroup population in Study CVT 3033 did not reveal any consistent efficacy differences in effect between elderly and younger subgroup (although the overall effect at trough was marginal).

C. Evaluation of Pediatric Program

In a letter from the Agency dated August 31, 2001, the sponsor was granted a pediatric waiver for ranolazine for all pediatric age groups.

D. Comments on Data Available or Needed in Other Populations

Pharmacokinetic data in patients with hepatic and renal impairment are noted in the Safety and Special Populations sections. There is no information regarding ranolazine use in pregnancy.

X. Conclusions and Recommendations

A. Conclusions

Ranolazine is proposed for the symptomatic treatment of angina. The effect of ranolazine on clinical outcomes (MI, death) are unknown. An anti-anginal effect of ranolazine (including improved exercise tolerance, decrease in angina attacks, decrease in nitroglycerin consumption) is demonstrated mostly clearly in one 823 patient study. The second pivotal trial, a crossover study, presented a dilemma in interpretability, and analysis of the first period marginally supported a treatment effect at peak but not trough. The most serious safety issue for ranolazine is the drug's effect on repolarization. Compounding the safety issue are drug interactions (CYP 3A4) , presence of metabolites that also block Ikr, and increased sensitivity (QT) in patients with hepatic insufficiency. Unresolved issues exist regarding optimal dosing, efficacy in women, and efficacy when added to maximal doses of anginal medication. Consideration of the potential benefit (symptomatic benefit) vs. risk (QT prolongation) leads the reviewer to ask for additional data prior to any approval (see below).

B. Recommendations

In order to obtain approval, the sponsor should attempt to show that the benefit of taking ranolazine outweighs potential risk.

1. The sponsor can perform an appropriately sized outcomes trial showing an improved survival on ranolazine vs. placebo. OR
2. The sponsor should perform an additional study evaluating benefit of ranolazine in a refractory angina population. As an example, the sponsor can show a benefit of ranolazine vs. placebo in a population of symptomatic patients on maximal medical therapy who are not candidates for PCI or surgery (either due to comorbidity or coronary anatomy).
3. The sponsor would also need to clarify appropriate dosing and dosing interval. Since the crossover study design presented interpretability problems for the Agency, the sponsor is encouraged to perform another parallel-group study supporting ranolazine's efficacy at trough.
4. In addition, the sponsor should be asked to evaluate efficacy of ranolazine in women; the sponsor could, potentially, incorporate some type of gender evaluation in a study of refractory patients.

XI. Appendix

Please see the efficacy review for individual study reviews related to efficacy. Please see the safety review for relevant safety issues and discussions.

Table 1. Clinical Pharmacology Studies

Study	Type	Design	Treatment/Dose/Regimen/Route	# on Rx
CVT 3011	Drug Interaction	Double-blind (DB), randomized (rand), placebo-controlled (PBO-contr), parallel, healthy males	Ranolazine (Ran) SR 1000 mg base bid po + dig 0.125 mg po Placebo bid po +dig 0.125 mg po	8 8
CVT 3012	Drug Interaction	DB, rand, PBO-contr, parallel, healthy males	Ran SR 1000 mg po bid + diltiazem (dilt) MR 180, 240, 360 mg or PBO po	34 (tot)
CVT 3013	Bioequivalence	Open, rand, 4 period crossover, healthy males	Ran SR 500 mg po x 2 (reference) Ran SR 500 mg po x 2 (test) Ran SR 750 mg po x 1 (reference) Ran SR 750 mg po x 1 (test)	34 34 34 34
CVT 3014	Food effect	Open, rand, 2 period crossover, healthy volunteers	Ran SR 1000 mg po + fed Ran SR 1000 mg po + fasting	20 20
CVT 3015	PK, dose proportionality, metabolism	Open, multiple dose, rand, 3-way crossover, healthy vol.	Ran SR 500 mg po bid, 1000 mg po bid, 1500 mg po bid	42 (tot)
CVT 3016	Metabolism, Renal impaired	Open, multiple dose, mild/mod/severe renal impairment and healthy volunteers	Ran SR 500 mg po bid (renally impaired) Ran SR 500 mg po bid (healthy volunteers)	21 8
CVT 3017	Drug Interaction	Open, multiple dose, healthy volunteers	Simvastatin 80 mg and ranolazine	16
CVT 3018	Metabolism, hepatic impairment	Open, multiple dose, mild/mod hepatic impairment and healthy volunteers	Ran SR 500 mg po bid Mild hepatic impairment Mod hepatic impairment Healthy volunteers	 8 8 16
CVT 3019	Bioavailability, metabolism	Open, healthy males, radiolabeled RAN	Single pos dose C14-Ran 500 mg	4
CVT 301-10	Metabolism, Drug interaction	DB, ran, multiple dose, parallel	Ran SR 375 mg po bid + keto 200 mg po bid PBO + keto 200 mg po bid Ran SR 1000 mg po bid + keto 200 mg bid PBO + keto 200 mg po bid	15 6 15 6
CVT 301-11	Drug interaction	Open, multiple dose, healthy volunteers	Ran SR 750 mg po bid + verapamil 120 mg po tid	15
CVT 301-13	Metabolism, Drug interaction	Open, multiple dose, healthy volunteers	Ran SR 1000 po bid + paroxetine 20 mg po	15
CVT 301-15	Bioequivalence, PK	Open, repeated single dose	Ran SR 500 mg tablets Lots 1K2754A, 8E2729A, 791771	 107 (tot)
CVT 3021	Drug interaction, CHF	DB, rand, PBO-contr, parallel	Dig 0.125 mg qd with Ran SR 750 mg bid OR PBO dig or PBO Ran SR	85 (tot)
CVT 3111	PK, dose proportionality	DB, rand, PBO-contr, single iv infusion, dose escalation, 4 periods, healthy volunteers	Ran injection, 25 mg/mL Period 1: 2 hr infusion, target peak 2000 ng/mL Period 2: 72 hr infusion, target steady state: 4, 000 or 10, 000 ng/mL Period 3: 72 hr infusion, target steady state: 10,000 or 4, 000 ng/ml Period 4: 72 hr infusion, target steady state: 15,000 ng/ml	 31 30 27 11

RAN 001	PK	DB, ascending dose, rand, crossover, healthy males	Ran injections, 1, 5, 10, 25, 50, 100, 150, 200 mcg/kg or PBO	28 (tot)
RAN 002	PK	DB, ascending dose, rand, crossover, healthy males	Ran solution, 0.7 mg/g in doses of 25 mcg/kg to 500 mcg/kg po or PBO	36 (tot)
RAN 003	PK/PD	Single-dose, single –blind, PBO-contr, asc-dose, CAD patients	Ran injections in doses of 25 -200 mcg/kg	10 (tot)
RAN 004	PD	DB, rand, PBO-contr, parallel, invasive hemodynamics, CAD patients	Ran 200 mcg/kg iv or PBO	9 (tot)
RAN 005	Metabolism	Open-label, single-dose, healthy males	Single PO dose Ran 35 mg, 50 μCi	4
RAN 006A	PD	Open-label, asc-dose, single IV bolus, patients with angina	Ran 50, 100, 150 μg/kg iv	14 (tot)
RAN 008	PK	PBO-contr, ran, 2-phase, crossover, healthy males	Ran IR 10 mg, 20, 30 mg po tid or PBO	35 (tot)
RAN 009	Bioavailability	DB, PBO-contr, rand, 4-phase crossover, healthy males	Ran IR 10, 20 or 30 mg po and Ran injection 9.5 mg iv or placebo iv	16 (tot)
RAN 011	PD	Open-label, males with CAD and normal coronaries	Ran iv 140 mcg/kg bolus + 1.2 mcg/kg/min infusion, Ran iv 200 mcg/kg iv bolus + 20 mcg/kg/min infusion	17 (tot)
RAN 013	PD	Open-label, patients with angina	Ran IR 30-240 mg po tid	60 (tot)
RAN 014	PD	Open-label, patients with angina	Ran iv 50-150 mcg/kg	15 (tot)
RAN 019	Bioavailability, PD	DB, rand, PBO-contr, single-dose, 5-phase, crossover, healthy males	Ran IR 40-120 mg PO + placebo iv, Placebo PO + ran 200 mcg/kg iv	20 (tot)
RAN 021	Food effect	Open-label, rand, crossover, healthy males	Ran IR 120 mg + fed Ran IR 120 mg + fasting	8 8
RAN 023	PK, PD	DB, rand, PBO-contr, crossover, healthy males	Ran IR 120 mg, 180 mg, placebo PO	18 (tot)
RAN 032	Drug Interaction	Open-label, rand, 2-way, crossover, healthy males	Ran IR 200 mg po tid ± cimetidine	24 (tot)
RAN 051	PD	DB, rand, PBO-contr, parallel, healthy males	Ran IR 120, 240 mg, placebo po tid	24 (tot)
RAN 053	PK, PD	DB, rand, PBO-contr, single-dose, 3-phase crossover, healthy males	Ran IR 180, 240 mg, placebo po	19 (tot)
RAN 055	PK, PD	Single-blind, asc-dose, 3-phase, healthy males	Ran iv bolus (7, 21, 42 mcg/kg/min) + infusion ((0.42, 1.25, 2.5 mcg/kg/min)	18 (tot)
RAN 058	PK, PD	DB, PBO-contr, asc-dose, 4-phase, healthy volunteers	Ran iv bolus (21, 42, 70 mcg/kg/min) + infusion (1.25, 2.5, 4.2 mcg/kg/min), placebo infusion	28 (tot)
RAN 059	Bioequivalence PK	Rand, single-dose, 4-phase, crossover, healthy males	Ran IR 60 mg (tablet, capsule), 240 mg (tablet, capsule)	24 (tot)
RAN 061	Bioequivalence PK	DB, rand, PBO-contr, single-dose, 4-phase crossover, healthy males	Ran IR 240 mg or PBO po + PBO or 100, 200 mcg/kg infusion	32 (tot)
RAN 063	PK, Dose proportionality	DB asc single-dose and open multiple dose phases, healthy males	Ran IR 320 to 400 mg po doses	73 (tot)
RAN 066	Bioavailability	Single-dose 4-way crossover, healthy males	Ran SR 205 mg and Ran IR 240 mg capsules	48 (tot)
RAN 067	Bioavailability	Open, single-dose, rand, 4-way crossover, healthy males	Ran SR 341 mg (3 formulations), Ran IR 400 mg capsule	46 (tot)
RAN 068	Drug	DB, rand, PBO-contr, 4-way	Ran IR 240 mg or PBO po tid + dilt 60	48 (tot)

	Interaction	corssover, healthy males	mg or PBO po tid	
RAN 069	PD	DB, PBO-contr, parallel, healthy males	Ran IR 400 mg or PBO po tid	29 (tot)
RAN 070	PD	Single-blind, PBO-contr, single-dose, angina patients	Ran 250 mcg/kg iv + 2 mcg/kg/min iv, Ran 250 mcg/kg iv + placebo iv; 10 μCi C-14 glutamate infusion	20 (tot)
RAN 075	CHF	Open, non-randomized, 1 day dosing, 2 boluses 10 minutes apart	Ran iv boluses 100mcg/kg + 100 mcg/kg, Ran 300 mcg/kg + Ran 200 mcg/kg	30 (tot)
RAN 090	PK	DB, rand, 3-way, crossover, healthy males	Ran IR 400 mg racemate, 200 mg + enantiomer, 200 mg – enantiomer	30 (tot)
RAN 0102	Bioavailability	DB, rand, PBO-contr, 2-way, crossover, healthy males	Ran SR 500 mg or Ran IR 400 mg	12 (tot)
RAN 0103	PK-Gender	DB, rand, PBO-contr, 2-way, crossover, healthy males and females	Ran IR 400 mg or placebo po	27 (tot)
RAN 0110	Drug Interaction	DB, rand, PBO-contr, 2-way, crossover, healthy males	Ran IR 400 mg po tid + warfarin 25 mg or PBO	24 (tot)
RAN 0111	Drug Interaction	DB, rand, PBO-contr, open-label dig, healthy males	Ran IR 400 mg or PBO po tid + dig 0.25 mg qd	16 (tot)
RAN 0112	PK, PD	DB, rand, PBO-contr, asc-dose single-dose crossover, healthy males	Ran SR 500 mg to 2000 mg po x 1, placebo po	79 (tot)
RAN 0113	Food effect	Open, rand, 2-way crossover, healthy males	Ran SR 500 mg po bid ± food	21 (tot)
RAN 0114	PK, PD, Dose proportionality	DB, asc-dose, 4-way crossover, healthy males	Ran SR 500, 750, 1000 mg or placebo po bid	30 (tot)
RAN 0117	PK, PD, Dose proportionality	DB, asc-dose, 4-way crossover, healthy males	Ran SR 500, 750, 1000 mg or placebo po tid	39 (tot)
RAN 0121	Drug Interaction	DB, rand, PBO-contr, 4-way crossover, healthy males	Ran SR 1000 mg po bid or placebo with diltiazem 60 mg or placebo	48 (tot)
RAN 0122	Bioequivalence	Open, rand, 2-way crossover, healthy males	Ran SR 750 mg po bid (as one 750 mg or two 375 mg tablets)	61 (tot)
RAN 0201	PK, PD, Dose proportionality	DB, 3 way crossover, healthy males	Ran SR 1500, 2000 mg, placebo po bid	24 (tot)

Source: Item 3 Volume 1: Table 3.9-2

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/s/

Shari Targum
9/12/03 05:55:56 PM
MEDICAL OFFICER

Date: December 21, 2005
From: Shari Targum, M.D.
To: NDA 21-526
Subject: Correction to Ranolazine addendum

The sponsor called me to clarify that the last patient in Table 2 was listed as taking "placebo" because the onset of the adverse event, back pain, occurred while the patient was in Study 3037 in the placebo group.

This correction and clarification does not alter the safety conclusions in the review of the July 26, 2005 amendment.

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/s/

Shari Targum
12/21/2005 10:35:43 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 21-526: Response to Approvable Letter
Submission Number	N000
Submission Code	BZ
Letter Date	July 26, 2005
Stamp Date	July 27, 2005
PDUFA Goal Date	January 27, 2006
Reviewer Name	Shari L. Targum, M.D.
Review Completion Date	December 5, 2005
Established Name	Ranolazine
(Proposed) Trade Name	Ranexa™
Therapeutic Class	Anti-anginal
Applicant	CV Therapeutics
Priority Designation	S
Formulation	Oral: tablets
Dosing Regimen	500 to 1000 mg BID
Indication	Treatment of chronic angina
Intended Population	Patients who have not achieved an adequate response with other anti-anginal drugs.

CLINICAL REVIEW

Clinical Review Section

Table of Contents

Appears This Way
On Original

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

1. It is recommended that ranolazine be approvable for symptomatic treatment of angina in patients with chronic stable angina and inadequate relief despite maximal treatment with other anti-anginal medications. In order to be approved, the sponsor should address the lingering question of whether ranolazine is a tumor promoter. If ranolazine is approved, with the other safety issue, ranolazine's concentration-related QT prolongation, and the availability of other treatments without effects on repolarization, ranolazine should not be a first-line drug for angina.
2. If ranolazine were to be approved, this reviewer recommends a "black box" warning regarding QT prolongation. This drug should not be directly marketed to consumers.
3. If ranolazine were to be approved, instructions for use will need to take into account ranolazine's interactions with verapamil and diltiazem, as well as the inter-subject variability. In addition, the smaller treatment effect in women and safety profile in the elderly should receive mention in labeling.

Support for efficacy has been based on three double-blind, placebo-controlled studies (CVT 3031, CVT 3033, CVT 3037) which supported a claim of efficacy. Two of these studies (CVT 3031 and CVT 3033) were part of the original submission and review.

In the original submission (2003), CVT 3033 and CVT 3031 supported a treatment effect of increased ETT duration (more convincing at peak). However, given the known ranolazine effect on repolarization, the Agency recommended that the sponsor provide data demonstrating that ranolazine has benefits which offset the concern arising from effects on the QT interval. One possible pathway for the sponsor was to show efficacy in a population not adequately treated with maximally tolerated or labeled doses of an approved anti-anginal. CVT 3037, a study of ranolazine in an angina population with symptoms despite amlodipine 10 mg daily, was reviewed in this submission and supports the reduction in angina attack rate and nitroglycerin consumption seen in CVT 3033.

The medical review concludes, based on the results of CVT 3033, CVT 3031 and CVT 3037, that ranolazine has demonstrated a modest effect on symptoms and exercise duration; thus far there are no data to show effects on cardiovascular outcomes (e.g., MI, death). In this resubmission, the sponsor has demonstrated a treatment effect in a patient population receiving amlodipine and (about half of the study population) nitrates. A safety update from the sponsor, dated November 21, 2005, will be reviewed separately.

Outstanding issues with regard to ranolazine include: 1. resolution of the question of tumor promotion raised in the pharmacology/toxicology review (to be discussed below); 2. ranolazine's effect on cardiac repolarization; 3. exploration of ranolazine effects in females; 4. further exploration of dose-response, including evaluation of doses below 500 mg bid; 5. further understanding of the mechanism of action of ranolazine.

Issues raised by the OCPB reviewer include: 1. marketing ranolazine in one strength only, the non-scored 500 mg tablet, limiting the capability of adjusting the dose; 2. deletion of the 12 hour

value in the dissolution specifications; 3. failure of study 301-16 to definitively delineate the mechanism responsible for serum creatinine elevation in the presence of ranolazine.

The question of tumor promotion, raised by the pharmacology/toxicology reviewer, is based on a publication by Suckow et. al.[1] Standard carcinogenicity testing was negative and there does not appear to be evidence that ranolazine causes tumors.

There is some biological plausibility that ranolazine might facilitate tumor growth. If one expects that ranolazine might lead to more efficient energy production in hypoxic myocardial tissue, there might also be an "unintended consequence" of promoting more efficient energy production in hypoxic tumors. However, there is also some uncertainty here; the Suckow paper involved a model in one mouse and has not been reproduced in other species or other systems. The sponsor has not attempted to replicate the published study (or show that the results are not reproducible). To the best of this reviewer's knowledge, Suckow et. al. did not study a broad range of drugs in this particular model. This reviewer is analyzing the clinical program for incidences of cancer; however, lack of a signal in the clinical program may not be meaningful as the long-term ranolazine exposure may not have included enough cancer patients and did not include a background rate for comparison.

The regulatory options, therefore, include: 1. approval (pending appropriate labeling) with safety information (including drug effects on repolarization and the unresolved question of tumor promotion) communicated to patients and health care providers; 2. "approvable" action, asking the sponsor to convince the Agency that results from the Suckow article are not reproducible or not of conern. This reviewer is choosing the latter option.

The Agency has already stated that further dose exploration is not needed if efficacy were demonstrated in CVT 3037 (e.g., a "resistant population" or population with angina despite treatment).

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There have been no agreed-upon risk management activities between the Agency and the sponsor. However, the sponsor should consider a risk management approach regarding appropriate ECG monitoring for repolarization changes and QT prolongation.

1.2.2 Required Phase 4 Commitments

There are no required phase 4 commitments associated with this review or submission.

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1 Suckow MA, Gutierrez LS et. al. The anit-ischemia agent ranolazine ranolazine promotes the development of intestinal tumors in APC (Min/+) mice. Cancer Lett. 2004 June 25; 209 (2): 165-9.

1.2.3 Other Phase 4 Requests

1. If ranolazine were to be approved, the sponsor should adequately explore and address the question of tumor promotion raised in the Suckow article.
2. The sponsor should explore effectiveness in women in an adequate, well-controlled study in females with coronary artery disease.
3. The sponsor should be encouraged to explore tolerability of ranolazine in the elderly population.
4. The sponsor should explore dose-response, including evaluation of efficacy of lower doses of ranolazine ER.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program:

According to the sponsor, ranolazine is a novel compound proposed for the treatment of angina. Ranolazine is pharmacologically unrelated to the other known calcium channel blockers, beta-blockers and/or nitrates. The mechanism of action of ranolazine is unclear. The sponsor had initially proposed that ranolazine is a partial fatty acid oxidation inhibitor. The current proposed mechanism of action is via late sodium channel inhibition. According to the pharmacology/toxicology review, there may be some evidence of beta blockade with ranolazine; however, there does not appear to be evidence of bradycardia in the safety database.

About 3100 patients/subjects were included in the ISS database and received ranolazine ; 832 patient/subjects were exposed to the drug for at least 1 year. In the ISS database, several formulations have been studied: immediate release (IR) with nearly 1300 patients/subjects, sustained release (SR or ER) with nearly 1760 patients/subjects, and intravenous (IV) with about 100 patients/subjects.

There were 4 placebo controlled ER angina clinical trials (designated as Phase 2/3 ER controlled angina) with a total of 1030 ranolazine and 738 placebo subjects. One of these trials (CVT 3031) was a crossover with doses up to 1500 mg bid. The other trial (CVT 3033) was a parallel group, 12 weeks duration with the highest dose being 1000 mg bid. The third trial (RAN 2240) enrolled only 11 patients. Targeted SR dose range was 500 mg- 1500 mg bid. The fourth study (CVT 3037), the only pivotal study in this resubmission, was a parallel group study of 7 weeks of ranolazine (the first week on 500 mg twice daily, followed by 6 weeks on 1000 mg twice daily) versus placebo added to background therapy of amlodipine 10 mg daily in angina patients with an average of at least 3 attacks per week despite 2 weeks of treatment with amlodipine.

1.3.2 Efficacy

Studies CVT 3033, CVT 3031 and CVT 3037 were used to support ranolazine efficacy. CVT 3033 and CVT 3031 utilized exercise treadmill testing (ETT) duration at trough; weekly angina

attack rates and nitroglycerin consumption (via patient diary) were secondary endpoints in CVT 3033. CVT 3037 utilized weekly angina attack rates (via patient diary) as the primary endpoint and used nitroglycerin consumption as a secondary endpoint. Exercise testing was not an endpoint in CVT 3037.

Table 1. Summary of pivotal studies (CVT 3031, CVT 3033, CVT 3037)

Study number	Design	Treatment groups	Background Rx	Randomized	Primary endpoint
CVT-3031	Multiple dose Crossover	Placebo, Ran SR 500, 1000, 1500 mg bid	Sublingual nitroglycerin (ntg) as needed (prn)	191	ETT duration at trough
CVT-3033	Parallel group	Placebo, Ran SR 750, 1000 mg bid	Amlodipine, diltiazem, or atenolol; sublingual ntg prn.	823	ETT duration at trough
CVT-3037	Parallel group	Placebo, Ran ER 1000 mg bid	All patients were on amlodipine 10 mg qd; long-acting nitrates or prn ntg as needed	565	Average weekly angina attacks

Because of the presence of outliers in study CVT 3037, a non-parametric analysis was used. As seen below, a statistically significant treatment effect was seen.

Table 2. CVT 3037: Primary efficacy variable: Average weekly rate of angina attacks (number/week) (FAS)

	Placebo (N=281)	Ranolazine (N=277)	p-value
Baseline:			
Median	4.50	4.50	NS
25^{th}-75^{th} percentile	3.71-6.00	3.73-6.22	
Min-Max	2.80-206.00	3.00-57.56	
Mean (SEM)	6.89 (0.78)	6.12 (0.31)	
Six-week Treatment Phase:			
Median	2.43	2.18	0.028
25^{th}-75^{th} percentile	1.47-4.17	1.24-3.66	
Min-Max	0.00-160.26	0.00-47.33	
Mean (SEM)	4.30 (0.64)	3.29 (0.26)	

p-value was calculated from Cochran-Mantel-Haenszel test of equality of mean scores based on modified ridit score, stratified by pooled center.

Results of the secondary endpoint, nitroglycerin (ntg) consumption, in CVT 3037 also showed a statistically significant treatment effect and supported results of the primary endpoint. While a baseline imbalance was seen, the sponsor performed an analysis adjusting for the baseline imbalance; the results were consistent with unadjusted results.

Table 3. CVT 3037: Average weekly rate of nitroglycerin consumption (doses/week) (FAS)

	Placebo (N=281)	Ranolazine (N=277)	p-value*
Baseline:			
Median	4.00	3.50	NS
25^{th}-75^{th} percentile	2.33-6.00	2.21-5.50	
Mean (SEM)	5.87 (0.52)	5.35 (0.52)	
Min-Max	0.00-98.00	0.00-98.39	
Six-week treatment phase:			
Median	1.67	1.34	0.014
25^{th}-75^{th} percentile	0.50-4.00	0.47-2.48	
Mean (SEM)	3.57 (0.54)	2.72 (0.38)	
Min-Max	0.00-111.82	0.00-62.21	

*Cochran-Mantel-Haenszel test of equality of mean scores based on modified ridit score, stratified by pooled center.

The results of the CVT 3033 secondary efficacy variables, angina frequency and ntg consumption, also showed a statistically significant treatment effect.

Table 4. CVT 3033: Angina frequency and nitroglycerin consumption (ITT)

Table 13 Study CVT 3033: Angina Frequency and Nitroglycerin Consumption from Patient Diaries (ITT* Population)

Variable	Placebo		Ranolazine ER 750 mg b.i.d.		Ranolazine ER 1000 mg b.i.d.	
	N	Reported Frequency	N	Reported Frequency	N	Reported Frequency
Angina Attacks/Week						
Mean (SE) at Baseline	258	4.63 (0.36)	272	4.37 (0.33)	261	4.44 (0.34)
Mean (SE) during Double-Blind Treatment	258	3.31 (0.30)	272	2.47 (0.23)	261	2.13 (0.24)
p-Value[a]				0.006		< 0.001
Nitroglycerin Consumption/Week						
Mean (SE) at Baseline	247	4.08 (0.43)	258	4.00 (0.49)	244	3.72 (0.45)
Mean (SE) during Double-Blind Treatment	252	3.14 (0.38)	262	2.11 (0.27)	244	1.76 (0.28)
p-Value[a]				0.016		< 0.001

* The ITT population consisted of all patients dosed who had at least one evaluable exercise test on double-blind treatment.

[a] Ranolazine vs. placebo obtained from an ANOVA model using ranked scores data adjusted for treatment, baseline covariate, pooled site, and background therapy.

In CVT 3033, there were statistically significant effects versus placebo in exercise duration, time to angina onset, and time to 1 mm ST depressions (more notable at peak than at trough).

Table 5. CVT 3033: Exercise testing results (ITT)

Table 14 Study CVT 3033: Exercise Treadmill Test Results (ITT* Population)

Parameter	Placebo	Mean Difference from Placebo (SE) Ranolazine ER 750 mg b.i.d.		Ranolazine ER 1000 mg b.i.d.	
	N	N	Result	N	Result
Exercise duration (sec)					
Trough	258	272	23.7 (10.9) p = 0.030	261	24.0 (11.0) p = 0.029
Peak	256	270	34.0 (10.7) p = 0.001	255	26.1 (10.8) p = 0.016
Time to onset of angina (sec)					
Trough	258	272	29.7 (12.1) p = 0.014	261	[illegible] p = 0.033
Peak	256	270	38.0 (12.4) p = 0.002	255	37.9 (12.6) p = 0.003
Time to 1-mm ST-depression (sec)					
Trough	247	260	19.9 (12.2) p = 0.100	244	21.1 (12.4) p = 0.091
Peak	234	248	40.8 (11.8) p < 0.001	236	34.5 (11.9) p = 0.004

* The ITT population consisted of all patients dosed who had at least one evaluable exercise test on double-blind treatment.

Note: p-values from ANCOVA model with effects for baseline covariate, treatment, pooled site and background therapy.

CVT 3031, a crossover study without interim washout periods, presented interpretability issues with the question of period and learning effects. However, an analysis of the first period showed a significant treatment effect at peak for ranolazine 1000 mg and 1500 mg bid groups.

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Table 6. CVT 3031: Exercise testing results (A/NC):

Table 15 Study CVT 3031: Exercise Treadmill Test Results (A/NC Population)

Parameter	Mean Difference from Placebo (SE)						
	Placebo	Ranolazine ER 500 mg b.i.d.		Ranolazine ER 1000 mg b.i.d.		Ranolazine ER 1500 mg b.i.d.	
	N	N	Result	N	Result	N	Result
Exercise duration (sec)							
Trough	178	174	23.8 (7.9) p = 0.003	174	33.7 (8.0) p < 0.001	169	45.9 (8.0) p < 0.001
Peak	176	174	29.3 (7.2) p < 0.001	174	50.1 (7.2) p < 0.001	167	55.5 (7.3) p < 0.001
Time to onset of angina (sec)							
Trough	174	174	27.0 (9.5) p = 0.005	174	45.9 (9.5) p < 0.001	169	59.6 (9.6) p < 0.001
Peak	172	174	35.5 (8.5) p < 0.001	174	56.4 (8.5) p < 0.001	167	68.5 (8.6) p < 0.001
Time to 1-mm ST-depression (sec)							
Trough	164	162	27.6 (8.1) p < 0.001	161	44.5 (8.1) p < 0.001	153	64.6 (8.2) p < 0.001
Peak	163	165	38.8 (8.2) p < 0.001	163	55.6 (8.2) p < 0.001	155	69.0 (8.4) p < 0.001

Note: p-values from ANOVA with effects for pooled site, patient within pooled site, period, and treatment.

Table 7. Study CVT 3031: Comparison of Treatment Differences in ETT duration: First Period Population

	Ran SR 500 mg vs. placebo	Ran SR 1000 mg vs. placebo	Ran SR 1500 mg vs. placebo
ETT duration (**trough**): LS Mean difference (SE)	11.7 (21.5)	12.7 (21)	4.5 (21.5)
95% CI	-30.4, 53.8	-28.4, 53.8	-37.6, 46.7
p-value	NS	NS	NS
ETT duration (**peak**): LS Mean difference (SE)	37.8 (19.5)	56.8 (19)	38.7 (19.7)
95% CI	-0.4, 76.1	19.5, 94	0.1, 77.3
p-value	0.054	0.003	0.051

See original NDA review for further details

A remaining clinical issue is the question of effectiveness in the female subgroup. A smaller effect size was noted in the female subgroup in the exercise studies. In CVT 3037, the effect size appeared to be smaller in the female subgroup.

1.3.3 Safety

1. In the original safety review, the following were noted:
    a. QT interval prolongation and T wave morphology changes (with a greater drug effect at peak and a higher incidence/increased change from baseline at higher doses);
    b. The most commonly reported adverse events in the SR controlled studies were dizziness, constipation, and nausea. Syncope, sweating and vomiting were reported with ranolazine 1500 mg bid; orthostatic hypotension was reported with higher doses.
    c. Laboratory changes included small decreases in hematocrit/hemoglobin and small increases in BUN and creatinine.

2. In this resubmission, the most commonly reported adverse events in the ER controlled studies were: constipation, nausea, dizziness, and asthenia. Increased incidence of asthenia, nausea, vomiting, dizziness, and sweating was noted at higher doses.
3. An increased incidence of adverse events, serious adverse events, and discontinuations due to adverse events were noted in the elderly population. For patients 75 years and older in the phase 2/3 ER controlled studies, the incidence of constipation was 18%; the incidence of dizziness was about 16% and the incidence of any adverse event was 57%. In the ISS database, 61% of patients aged 65 -74 and 70% of patients aged 75 and older reported an adverse event (compared population to 27% of patients aged 65-74 and 36% of patients aged 75 and older on placebo). In the ISS database, there were increased incidences of constipation (19%), nausea (11.7%) and dizziness (19%) in the elderly population ($\geq$ 75 years old) on ranolazine compared to the total ranolazine population (6.4%, 7.8%, and 12.9% for constipation, nausea, and dizziness, respectively). Please see section 7.1.5.6 for further details.
4. An increased incidence of adverse events, serious adverse events, and discontinuations due to adverse events were noted in the diabetic population on ranolazine (vs. nondiabetics on ranolazine or diabetics on placebo). This increased incidence may be due to other factors (i.e., age, comorbidities, sample size differences). However, a drug-disease interaction cannot be excluded. Please see section 7.1.5.6 for further details.
5. Small mean decreases in hemoglobin/hematocrit were seen (as in the original review); small mean increases in BUN/creatinine were seen with shift tables showing an increase from normal to abnormal BUN/creatinine with ranolazine vs. placebo. However, in the Phase 2/3 controlled ER studies there were no imbalances (ranolazine vs. placebo) seen with respect to renal treatment-emergent adverse events, serious adverse events, or discontinuations due to adverse events. An analysis of on-treatment creatinine doubling in the pivotal studies (CVT 3033, CVT 3031, and CVT 3037) showed no evidence of a safety signal with ranolazine.

6. Mean decreases from baseline in systolic and diastolic blood pressure (BP) appear to increase with increasing dose.

1.3.4 Dosing Regimen and Administration

The proposed initial dosing is 500 mg b.i.d. (twice daily) and increased to 1000 mg b.i.d. as needed, based on clinical symptoms. The maximum recommended daily dose is 1000 mg b.i.d. The 500 mg tablet is unscored, limiting flexibility in dosing.

1.3.5 Drug-Drug Interactions

From the original review, in vitro metabolic studies indicate that ranolazine is a substrate of CYP 3A4 and CYP 2D6 and a substrate/inhibitor of P-glycoprotein. Additional in vitro results show that ranolazine can also inhibit the metabolism of statins.
The potent 3A4 inhibitors ketoconazole, diltiazem and verapamil, when co-administered, impact the PK of ranolazine in a clinically significant manner. These in vivo results are in agreement with the in vitro findings indicating that a substantial fraction of ranolazine is metabolized by CYP 3A4.
Co-administered paroxetine, simvastatin, digoxin and cimetidine have no clinically relevant effects on the PK of ranolazine. The small impact on the PK of ranolazine by paroxetine, a potent CYP 2 D6 inhibitor, indicates that a minor fraction of ranolazine is metabolized by this enzyme.
Co-administered ranolazine interacts clinically significantly with simvastatin, digoxin and warfarin. Ranolazine affects the PK of digoxin and simvastatin by increasing the exposure measures of these compounds clinically relevantly. Ranolazine has no impact on the PK of diltiazem.

1.3.6 Special Populations

Gender Differences:
In the original ranolazine review, a population analysis of the relationship between ranolazine plasma concentrations and exercise duration in patients with angina showed that the exercise duration at identical plasma concentrations in women is reduced to between about 28% and 42% of that in men, indicating a significantly smaller extent and time duration of the exercise performance improving effect of ranolazine in women. The reduced exercise improving effects of ranolazine in women have not been shown to be statistically significantly different from placebo.
From the original efficacy review, subgroup analyses by gender focused on one study (CVT 3033); finding showed statistically significant effects in males but not females. This was the only subgroup analysis where results at peak were favorable toward placebo.
In addition, a single dose study in young healthy volunteers with administration of 342 mg ranolazine using an immediate release tablet showed a statistically significantly greater oral clearance and shorter half life in females than in males. However, the mean plasma concentrations in male and female patients with the target disease were comparable.

The efficacy review of CVT 3037 also showed statistically significant effects in males but not females; the effect size appeared to be smaller in females.

Elderly:
No consistent subgroups differences were seen in the elderly subgroup. However, the elderly subgroup on ranolazine appeared to show increased adverse events, serious adverse events, and discontinuations due to adverse events compared to the same population on placebo or younger patients on ranolazine. In the phase 2/3 controlled ER ranolazine studies, the incidence of constipation was 18.4%, dizziness 15.8% and nausea 10.8% in patients $\geq$ 75 years old.

Ethnic/Racial Studies: The study population in studies CVT 3033 and 3031 was over 90% Caucasian. There were insufficient numbers of non-Caucasians studied to provide for a meaningful analysis of racial/ethnic differences.

Hepatic/renal impairment: From the original review, patients with hepatic impairment are more sensitive to the QTc prolonging effects of ranolazine than patients without hepatic impairment and use of ranolazine in this population is not recommended. The slope of the concentration QTc prolongation is steeper in patients with hepatic impairment. Thus, the same concentration produces more QTc prolongation in patients with hepatic impairment compared to patients without hepatic impairment. In the clinical pharmacology section of the resubmission, the sponsor has presented a re-analysis, using different QT criteria, of the QTc data from the hepatic impairment study.

Pediatric studies: A pediatric waiver was granted and no pediatric program is planned for ranolazine.

Use in pregnancy: There are no data concerning use in pregnancy.

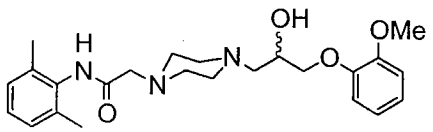
2 INTRODUCTION AND BACKGROUND

Please note: the terms "ranolazine SR" and "ranolazine ER" represent the same formulation and are interchangeable.

2.1 Product Information

2.1.1. Drug Name: Ranolazine (RS 43285)

2.1.2. Chemical Structure: 1-piperazineacetamide, *N*-(2,6-dimethylphenyl)-4-[2-hydroxyl-3-(2-methoxyphenoxy)propyl]-, (±)-.



Molecular Formula: $C_{24}H_{33}N_3O_4$, Molercular Weight: 427.54 g/mole

2.1.3. Proposed Trade Name: Ranexa™

2.1.4. Proposed Indication: According to proposed labeling, ranolazine will be indicated for the treatment of chronic angina in patients who have not achieved an adequate response with other anti-anginal drugs. Ranexa should be used in combination with calcium channel blockers, beta-blockers and/or nitrates.

2.1.5. Drug Class: Ranolazine is pharmacologically unrelated to other calcium channel blockers, beta-blockers and nitrates. The mechanism of action of ranolazine is not clear.

In the original NDA submission, the sponsor's proposed mechanism of action was believed to be partial inhibition of fatty acid oxidation, via inhibition of enoyl-CoA hydratase and carnitine acyl carnitine translocase. The sponsor theorized, at the time, that the shift in fatty acid oxidation and increase in glucose oxidation would lead to more oxygen-efficient production of adenosine triphosphate (ATP), improved cardiac efficiency and reduced ischemia-induced increases in lactic acid and cellular acidosis.

In this resubmission, the sponsor has claimed that ranolazine acts to inhibit the late sodium current (I_{Na}) in myocytes, thereby improving myocardial relaxation and decreasing diastolic contractile tension (diastolic stiffness) of the left ventricle. According to the sponsor, in ischemic conditions this late sodium current is increased, leading to intracellular sodium overload, leading to calcium overload through cell membrane ion transported; calcium overload during ischemia is believed to cause a slowing of left ventricular relaxation and increase in left ventricular stiffness.

Ranolazine also inhibits I_{Kr} with an IC_{50} or 14 μM.

2.1.6. Dose/Regimens: The proposed initial dose of ranolazine is 500 mg b.i.d with titration to 1000 mg b.i.d., as needed, based on clinical symptoms. The maximum recommended daily dose of ranolazine is 1000 mg b.i.d.

2.1.7. Age Groups: Ranolazine has not been studied in the pediatric population. The total number of angina patients in ranolazine ER phase 2/3 studies included 594 (382 ranolazine and 283 placebo) 65-74 years old and 160 (114 ranolazine and 68 placebo) > 75 years old. The Integrated Summary of Safety (ISS) database included 869 patients/subjects (65-74 years) and 205 patients/subjects (> 75 years) on ranolazine (source: ISS, Table 27.5.1).

2.2 Currently Available Treatment for Indications

Currently approved therapeutic options for the treatment of angina include beta-blockers, calcium channel-blockers and nitrates. In addition, non-pharmacologic options, such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) exist for certain patient populations (depending on risk-benefit assessment) with angina pectoris.

2.3 Availability of Proposed Active Ingredient in the United States

Ranolazine is not currently marketed in this country.

2.4 Important Issues With Pharmacologically Related Products

According to the sponsor, ranolazine is pharmacologically related to trimetazidine. Trimetazidine is marketed in several countries, including France, Hungary, Japan, Spain.[2]

2.5 Presubmission Regulatory Activity:

The regulatory history prior to the original NDA can be found in the original review and will be briefly mentioned in this section. For further details, please see the original ranolazine review.

IND # 30,205 for an immediate-release ranolazine was initially filed by Syntex in 1987 and IND # 43,735 for sustained-release ranolazine (SR) was filed in 1993. In 1996, CVT acquired ranolazine from Syntex (a subsidiary of Roche) and began development of ranolazine SR under IND #43,735 for the treatment of angina.

A new drug application (NDA 21-526) was submitted for ranolazine on December 27, 2002 and a 4-month Safety Update was submitted on April 28, 2003. The Agency issued an approvable letter for ranolazine on October 30, 2003 and ranolazine was subsequently the subject of the December 9, 2003 Cardio-Renal Advisory Committee meeting.

2 The reviewer searched Pubmed and google, There is some European literature exploring trimetazidine as an anti-anginal drug. According to a French website, trimetazidine was associated with rare nausea, epigastric pain, headache and giddiness. There has also been a report of drug-induced parkinsonism, gait disorder and tremor with trimetazidine use (see Masso JF et. al. Trimetazidine induces parkinsonism, gait disorders and tremor. Therapie. 2005 Jul-Aug; 60 (4): 419-22).

In the October 30, 2003 approvable letter, the following deficiencies were noted:

1) Potential testicular toxicity, manifest as impaired fertility in rats in study AT-4136116-R-86-43285-PO-RMF. (This issue was later resolved per Agency meeting minutes, April 16, 2004).

2) Delayed cardiac repolarization, manifest clinically as prolongation of the QT interval. An effect on the QT interval was seen in all patient populations studied, particularly at higher blood concentrations of ranolazine, and the sponsor has neither provided sufficient rationale for discounting this as a potential clinical concern nor devised dosing strategies that would avoid significant QT prolongation in some patients. In particular, in certain populations (*e.g.*, patients with hepatic impairment and those taking inhibitors of CYP3A4 or the P glycoprotein transporter), larger effects of ranolazine on the QT interval were seen or can be expected. Given that the sponsor has demonstrated effects on a symptom (*i.e.*, angina), and given the availability of other anti-anginal drugs that do not prolong the QT interval, there needs to be a clear reason to approve a therapy with what appears to be an additional, possibly life-threatening risk.

3) Adequate safety exposure. The database had information on fewer than 1000 patients given relevant doses of ranolazine for at least one month, an exposure well below what is typically expected for a chronic treatment for a symptomatic claim.

It was recommended that the sponsor provide data demonstrating that ranolazine has benefits that offset the concern arising from the effects on the QT interval. In patients with angina, this additional benefit could include showing efficacy in populations not adequately treated with maximally-tolerated or labeled doses of more than one class of approved anti-anginals; demonstration of a benefit on fixed clinical endpoints, such as myocardial infarction or death, also would overcome concerns about effects on the QT interval. It was also recommended that the sponsor explore a broad range of doses of ranolazine. Since the available data suggested a smaller effect of ranolazine in women with angina, it was recommended that future clinical studies further characterize this apparent gender difference.

Since the approvable letter, there have been several meetings and communications between the sponsor and the Agency. Two protocols, CVT 3037 and CVT 3036, were submitted as Special Protocol Assessments.

On March 2, 2004, the sponsor submitted a Special Protocol Assessment (SPA) request for Study CVT 3037 and final SPA agreement was reached on June 1, 2004 (Agency letter).

An April 23, 2004 letter from the Agency contained the following: "As discussed at the meeting with CV Therapeutics on April 16, 2004, the Agency believes that further characterization of the dose-response relationship for Ranexa would not be necessary if CV Therapeutics were to find compelling evidence that Ranexa has beneficial effects on cardiovascular effect in the TIMI trial, or if one dose has demonstrated efficacy in patients with resistant angina (study CVT 3037).

However, if CV Therapeutics is interested in a symptomatic claim for angina, such data are necessary but those data need not be obtained from study CVT 3037."

2.6 Other Relevant Background Information

On March 30, 2004, the sponsor filed an MAA (Marketing Authorization Application) with the EMEA (European Agency for the Evaluation of Medicinal Products. On October 25, 2005, the sponsor disseminated a press release stating that the EMEA had indicated that additional pharmacokinetic information would be needed prior to potential approval. Since the European centralized regulatory procedure did not provide a mechanism for obtaining and adding new information to an MAA, the sponsor withdrew the application with the stated intention of resubmitting the MAA at a later date.[3]

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable):

The CMC review of stability data is currently pending. According to the CMC reviewer, the sponsor has deleted the 12 hour dissolution time point from current acceptance criteria proposed by OCPB. Please see the CMC review for further details.

3.2 Animal Pharmacology/Toxicology

From the pharmacology/toxicology review (Dr. Hausner), two issues have been highlighted:

1. The question of tumor promotion, which is based on the publication by MA Suckow, LS Gutierrez et. al. "The anti-ischemia agent ranolazine promotes the development of intestinal tumors in APC $^{(min/+)}$ mice" (Cancer Letters 209 (2004): 165-169). The Pharmacology/Toxicology Coordinating Committee (PTCC) met on September 15, 2004 to discuss the study and potential concern. According to the review, the PTCC felt that it would be ideal to repeat the study with adequate study conduct and sample sizes. There was no reason to dismiss the findings and the level of concern was determined to be moderate for the general population and higher for cancer patients.
2. The question of mechanism of action of ranolazine, which is currently proposed by the sponsor as an inhibitor of late sodium currents. The pharmacology/toxicology reviewer has questioned the biological significance of this sodium channel-blocking effect; in addition, Dr. Hausner has noted that ranolazine antagonized the positive inotropic effect of isoproterenol, suggesting that ranolazine may exhibit some beta-1 antagonism.

For further details, please see the pharmacology/toxicology review.

[3] The source of this information is a 10/19/2005 communication from the sponsor in addition to a Google search.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The source of the overall data used in the review was the clinical trials program. The primary source of materials for this review involved the paper submission of NDA 21-526. Electronic data (crt, crf) were used as needed. In addition, related IND files (43,735; 30,205) were reviewed as needed. Where applicable, appropriate literature and internet searches were conducted.

4.2 Tables of Clinical Studies

The clinical studies in the original submission have already been reviewed; please see the original review for further details.

Data from five clinical studies (CVT 3037, CVT 3032 (ongoing), CVT 3034 (ongoing), CVT 301-16, and CVT 3112) are provided in this amendment.

Table 8. Clinical studies in the current submission

Study	Status/Location	Study design/duration	Treatment	# Randomized
CVT 3037	Completed (7/30/04-2/16/05)/ Bulgaria, Canada, Georgia, Russia, US	Double-blind, randomized, placebo-controlled, angina patients symptomatic despite amlodipine 10 mg qd/7 weeks treatment	Amlodipine 10 mg po qd + either Ran ER 500 mg →1000 mg po bid OR Placebo po bid	281 284
CVT 3112	Completed (9/10/03-11/21/03)/UK	Open-label, randomized, crossover, healthy subjects/Part 1: 24-hour infusions on Days 1 and 6 Part 2: single dose of moxifloxacin	Part 1: Ran injection, 25 mg/mL at 100 mL/hr x 1 hr, then then 26 mL/hr x 23 hrs (Day 1); 100 mL/hr x 1 hr then 26 mL/hr x 6 hrs, then 16 mL/hr x 17 hrs (Day 6); diltiazem 90 mg po bid on Day 3 and 180 mg po bid on Days 4-6; verapamil 120 mg po bid on Day 3 and 240 mg po bid on Days 4-6; Part 2: moxifloxacin 400 mg po x 1	24 12 12 19
CVT 301-16	Completed (3/14/03-6/10/03)/ UK	Single-blind, randomized, placebo-controlled crossover, multiple dose, healthy male subjects/ dosing bid x 4 days and morning of Day 5 (7 day washout)	Ran ER 500 mg Placebo For each period a single po dose of 1500 mg on the morning of Day 1 followed by 1000 mg po in the evening; 1000 mg po bid Days 2-4; 1000 mg po x 1 in a.m. Day 5.	18 18
CVT 3032	Ongoing (started 1/28/98)/ Canada, Czech Republic, Poland, US	CVT 3031 safety follow-up; long-term, open-label/up to 10 years	Ran SR 375 or 500 mg All patients started on 750 mg po bid with up or down-titration between 750-1000 mg po bid	143
CVT 3034	Ongoing (started 12/16/99)/13 countries US	CVT 3033 and CVT 3037 follow-up: long-term, open label study/up to 8 years	Ran 375 or 500 mg SR tablets. Initial dose Ran 500 mg po bid with up or down-titration between 500, 750 and 1000 mg bid.	603

In addition to the above studies, a QTc reanalysis from study CVT 3018 (hepatic impairment), which was completed in 2001 and part of the original submission, was submitted as part of the clinical pharmacology review.

4.3 Review Strategy

In this review, the pivotal studies (CVT 3037, CVT 3033 and CVT 3031) were primarily used to support efficacy and safety; where applicable, other studies and databases (long-term, open-label, entire ISS database) were used to analyze safety.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) audit processes were solicited for two selected sites (based on the largest enrollment and the smallest p-value) in Study CVT 3037.

4.5 Compliance with Good Clinical Practices

To the best of this reviewer's knowledge, the key ranolazine studies appear to have been conducted in compliance of Good Clinical Practices.

4.6 Financial Disclosures:

For CVT 3037, the sponsor has certified that it has not entered into any financial arrangement with any of the CVT 3037 clinical investigators whereby the value of compensation to the investigator could be affected by the study outcome. Financial disclosure forms were filed by CVT 3037 principal investigators in all 48 sites. From this reviewer's perspective, there do not appear to be any issues of financial conflict with respect to CVT 3037.

5 CLINICAL PHARMACOLOGY

Two *in vivo* clinical pharmacology studies, CVT 3112 and CVT 301-16 and two *in vitro* studies (CVT 303.040-N, CVT 303.045-N) were included in the resubmission and were reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) (Dr. Hinderling). In addition, an assessment of QTc measurements from CVT 3018 was submitted and reviewed (Dr. Bhattaram).
The OCPB review will be summarized in this section. For further detailed information, please see the OCPB review.

5.1 Pharmacokinetics

CVT 3112 was a single-site, open-label partial crossover study of the pharmacokinetics, safety and tolerability of an intravenous (iv) loading dose regimen of ranolazine in the presence and absence of verapamil and diltiazem in healthy male and female volunteers. On Days 1 and 6,

subjects received single 24-hour iv ranolazine infusions. On Days 3-6, subjects received oral doses of either diltiazem or verapamil. Twenty-four subjects enrolled and randomized, 23 completed and one withdrew for personal reasons. The pharmacokinetic results showed an increase in steady state plasma ranolazine concentrations with concomitant diltiazem or verapamil administration. In the presence of verapamil there was a 3-5 msec increase in the PR interval. An increase in QTc F (Fridericia correction method) of generally < 10 msec was seen with ranolazine (alone and in combination); according to the sponsor, within the concentration studies, no clear relationship between ranolazine and the magnitude of QTcF increase was observed. There were no deaths or serious adverse events in this study. Adverse events noted were consistent with adverse events seen in the safety review.
The in vitro binding studies showed that the ranolazine metolites CVT-2514, CVT-4786 and CVT 2537 are 70-75% plasma bound in the presence of each other and additional metabolites.

5.2 Pharmacodynamics

Study 301-16 was a randomized, single-blind, placebo-controlled, two-way crossover study in 18 healthy male subjects. Treatment A consisted of a loading dose of ranolazine SR 1500 mg on the morning of Day 1 followed by an evening dose of 1000 mg and 1000 mg q12 hours on Days 2-4 with the last dose administered on the morning of Day 5. Treatment B consisted of placebo on Days 1-5, with the last dose administed on the morning of Day 5. The study confirmed a rapid, approximately 15% increase in serum creatinine observed in previous studies. Ranolazine did not have a consistent, statistically significant effect on any of the studied volume or renal tubular variables. The serum concentrations of BUN were not increased in the presence of ranolazine. According to the OCPB reviewer, the study was not designed to demonstrate that the creatinine elevation associated with ranolazine is reversible; this short term study did not definitively delineate the mechanism responsible for the observed increase in serum creatinine nor demonstrate reversibility of the phenomenon.

5.3 Exposure-Response Relationships:

There are no new studies regarding exposure-response relationships. CVT 303-010C used prior QT/RR interval results from CVT 3018 (hepatic impairment and healthy volunteer study; ranolazine dosed at 875 mg x 1 (loading dose) and then ranolazine SR 500 mg bid x 4) and recalculated QT intervals. The reanalysis used the median QT out of all available leads and used individual corrections. According to the OCPB review, the reanalysis by the sponsor confirmed that QTc prolongation in patients with moderate hepatic impairment was significantly greater than that seen in patients with mild hepatic impairment and matched healthy volunteers. By contrast, the Agency analysis (original review) determined that patients with both mild and moderate hepatic impairment showed a greater sensitivity toward the QT prolonging activity of ranolazine. The Agency's analysis used the maximum QT interval of all leads and data from 324 healthy volunteers and 16 patients with and 1484 patients without overt hepatic impairment.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Ranolazine's proposed indication is for treatment of chronic angina in patients who have not achieved an adequate response with other anti-anginal drugs.

6.1.1 Methods

The main data source for this review was the ranolazine development program. The primary source of materials for this review involved the paper submission of NDA 21-526. Electronic data (crt, crf) were used as needed. In addition, related IND files (43,735; 30,205) were reviewed as needed. Prior reviews of the original submission were used as references.

For the purposes of this efficacy review, the pivotal studies (CVT 3037, CVT 3033 and CVT 3031) will be emphasized. A more detailed discussion of the other efficacy studies can be found in the original NDA review.

General Discussion of Endpoints

A review of anti-anginal labeling revealed two general kinds of endpoints for symptomatic treatment of exercise-induced angina: an improvement in exercise time (exercise tolerance, symptom limited exercise time, time to ischemia) and a decrease in angina attack rates.

Table 9. Examples of Endpoints in symptomatic treatment of chronic angina

Drug	Indication	Endpoint	Effect
Amlodipine (Norvasc)	Chronic stable angina	1. Symptom-limited exercise time 2. Time to 1 mm ST segment deviation 3. Angina attack rate.	Increase in exercise time of 12.8% (63 sec) for Norvasc 10 mg, 7.9% (38 sec) for Norvasc 5 mg. Norvasc 10 mg qd was noted to increase time to 1 mm ST deviation and decrease angina attack rate.
Diltiazem (Cardizem LA)	Chronic stable angina	Exercise tolerance	For exercise tolerance, there was a placebo-subtracted increase of 20 to 28 seconds for all three doses, and no dose-response was demonstrated
Metoprolol (Metoprolol XL)	Angina pectoris	1. Angina attacks 2. Exercise tolerance 3. Decrease in catecholamine-associated heart rate increase	An immediate release formulation of metoprolol reduced the number of angina attacks and increased exercise tolerance.

Source: respective labeling, PDR and Internet

The sponsor's primary endpoints are consistent with endpoints of previously developed anti-anginal therapies.

6.1.3 Study Design

All three studies (CVT 3033, CVT 3031 and CVT 3037) were randomized, double-blind, placebo-controlled, multicenter studies.

Table 10. Summary of pivotal studies (CVT 3031, CVT 3033, CVT 3037)

Study number	Design	Treatment groups	Background Rx	Randomized	Primary endpoint
CVT-3031	Multiple dose Crossover	Placebo, Ran SR 500, 1000, 1500 mg bid	Sublingual ntg prn	191	ETT duration at trough
CVT-3033	Parallel group	Placebo, Ran SR 750, 1000 mg bid	Amlodipine, diltiazem, or atenolol; sublingual ntg prn.	823	ETT duration at trough
CVT-3037	Parallel group	Placebo, Ran ER 1000 mg bid	All patients were on amlodipine 10 mg qd; long-acting nitrates or prn ntg as needed	565	Average weekly angina attacks

CVT 3033: This was a double-blind, randomized, stratified, placebo-controlled, parallel-group study of ranolazine SR 750 mg bid, 1000 mg bid, or placebo in patients with stable exertional angina who were also taking either amlodipine 5 mg qd, atenolol 50 mg qd or diltiazem 180 mg qd as background therapy. Patients were stratified to background therapy, treated for twelve weeks with a fixed dose of either placebo, ranolazine 750 or 1000 mg PO bid, and then entered a 48 hour rebound assessment phase where they either continued on their dose of ranolazine or received placebo. Exercise testing at peak (4 hours post-dosing) was performed at Weeks 2 and 12 of double-blind treatment. Exercise testing at trough was performed at Weeks 2, 6, and 12 of double-blind treatment, and after the 48 hour rebound assessment period. In addition to the stratified background medication, aspirin, stable doses of ACE inhibitors or diuretics, and sublingual nitroglycerin (for treatment of angina attacks) were allowed in the study. The primary analysis population was the Intent-to treat (ITT) population, all patients who took at least one dose of double-blind drug and had at least one post-randomization trough ETT.
The primary efficacy variable was trough symptom-limited ETT duration at 12 weeks of double-blind treatment.

Secondary efficacy variables included: exercise duration at peak, and time to onset of angina, time to 1 mm ST depression, maximum ST depression, and primary reason for stopping exercise at trough and peak; exercise duration of patients off ranolazine for 48 hours after 12 weeks of treatment vs. those on placebo for 12 weeks; patient-reported frequency, severity and duration of angina and nitroglycerin use (via patient diary) during double-blind treatment.

CVT 3031: This was a double-blind, randomized, placebo-controlled 4-period crossover trial with no interim washout between double-blind treatment periods. Patients were randomized to

either placebo or ranolazine 500 mg bid, 1000 mg bid or 1500 mg bid for one week treatment periods (for a total of 4 weeks on double-blind treatment). At the end of each double-blind treatment period, patients underwent exercise testing at trough and peak (4 hours post-dose). Sublingual nitroglycerin for anginal attacks was allowed. The primary analysis population was the all/near-completers (A/NC) population, including all randomized patients who had evaluable efficacy measurements at baseline and for at least three of the four double-blind periods, was the primary analysis population. The A/NC population included at least 75% of randomized patients.
The primary efficacy variable, as noted in the above table, was trough symptom-limited trough ETT duration after one week of treatment.

Secondary efficacy variables included exercise duration at peak (after each one-week treatment) and time to onset of angina, time to 1 mm ST depression, maximum ST depression and primary reason for stopping exercise at trough and peak.

CVT 3037: This was a double-blind, randomized, placebo-controlled parallel group study in a population with at least 3 average weekly angina attacks despite at least 14 days treatment with amlodipine 10 mg daily. Patients continued on amlodipine and were randomized to add either placebo for 7 weeks or ranolazine 500 mg bid for one week, then up-titrated to 1000 mg bid for 6 weeks. Sublingual nitroglycerin (prn) and long-acting nitrates were allowed. Patients were instructed to keep diaries regarding angina attacks and nitroglycerin consumption. In addition, the Seattle Angina Questionnaire (SAQ) was administered at screening, baseline and study completion. The primary analysis population was the full analysis set (FAS) of all patients who received at least one dose of study medication in the double-blind Treatment Phase and who recorded angina diary data in this phase of the study. The primary efficacy variable was the average weekly angina attacks during the 6-week double-blind treatment period (ranolazine 1000 mg bid vs. placebo). Secondary efficacy variables included the average weekly nitroglycerin consumption during the 6-week double-blind period and dimensions of the SAQ. According to the sponsor, the SAQ has not been validated for use in Eastern European countries, the main source of the study population; hence, the SAQ should be used as an exploratory tool.

Table 11. Statistical Analysis Methods in the Pivotal Studies (CVT 3033, CVT 3031, CVT 3037)

Study	Angina Frequency and Nitroglycerin consumption	Exercise Testing
CVT 3037	CMH test of row mean scores, using rank-based (modified ridit) scores, stratifying by pooled site	Not done
CVT 3033	ANCOVA on rank scores with effects for treatment, pooled site, background therapy, and baseline angina frequency rank	ANCOVA with effects for treatment, pooled site, background therapy, and baseline ETT duration at trough
CVT 3031	Not done	ANOVA with effects for treatment, period, pooled site and patients within pooled site

ANOVA = analysis of variance. ANCOVA = analysis of covariance

Table 12. Comparison of the Number of Randomized vs. Evaluated Patients in CVT 3037, CVT 3033 and CVT 3031

Ranolazine dose	CVT 3037		CVT 3033		CVT 3031**	
	Treated (N)	FAS (N)	Treated (N)	ITT* (N)	Treated (N)	A/NC (N)
500 mg bid	NA	NA	NA	NA	181	174
750 mg bid	NA	NA	279	272	NA	NA
1000 mg bid	281	277	275	261	180	174
1500 mg bid	NA	NA	NA	NA	187	172
Placebo	284	281	269	258	179	174
Total	565	558	823	791	191	175

*All patients dosed with at least one evaluable exercise test on double-blind treatment.
**Note that CVT 3031 was a crossover study; patients received more than one dose of ranolazine.

6.1.4 Efficacy Findings

6.1.4.1. Patient Disposition

CVT 3037: In study CVT 3037, of the 284 and 281 patients randomized to placebo and ranolazine, respectively, > 99% had at least one dose of double-blind study drug and 98% in both groups completed the study. Of the 5 placebo and 7 ranolazine patients who terminated prematurely, adverse events were noted in 3 ranolazine vs. 4 placebo patients, there was one death in each treatment group, and 3 ranolazine patients withdrew consent.

CVT 3033: All 823 randomized patients received at least one dose of double-blind treatment, and 791 patients had at least one evaluable trough ETT and were included in the primary efficacy analysis. Of the randomized patients, 87% of the Ran 1000 mg bid group and 90% of placebo and Ran 750 mg bid completed double-blind and rebound portions of the study. Ten percent of placebo and Ran 750 mg bid and 14% of the Ran 1000 mg bid prematurely discontinued (7-9% of the ranolazine withdrawals were due to unacceptable adverse events.

CVT 3031: A total of 191 patients were randomized to the double-blind treatment phase. The primary analysis population included 175 patients who had evaluable efficacy measurements at baseline and for at least 3 out of 4 double-blind treatment periods. A total of 185 patients (97%) were included in the ITT population, 184 (96%) in the first period population, 135 (71%) in the per-protocol population, and 191 (100%) in the safety population. Fifteen (8%) patients discontinued prematurely due to AE (11 of these were in the highest dose ranolazine group).

6.1.4.2. Baseline Characteristics

CVT 3037: Patients had a mean age of 61.5 ± 8.9 years and were mostly male (72%) and Caucasian (99%). About 45% of patients were taking long-acting nitrates at baseline. All patients in the FAS had a history of CAD and stable angina. About 89% had a history of hypertension, about 80% had a previous MI, about 50% had a history of CHF, 19% had a history of diabetes; few patients had a history of previous beta-blockers (3%) or calcium channel-blockers (<1%).

CVT 3033: Patients had a mean age of 63.9 ± 9.2 years and were mostly male (78%) and Caucasian (98%). In this study patients received concomitant atenolol 50 mg qd (43%), amlodipine 5 mg qd (32%) and diltiazem 180 mg qd (25%). Sublingual nitroglycerin was permitted except within 60 minutes prior to ETT. About 64% had a history of hypertension, about 58% had a prior MI, 30% had a history of CHF, 23% had a history of diabetes, 18% had prior CABG and 19% had prior PTCA.

CVT 3031: Patients had a mean age of 64.3 ± 9.4 years and were also mostly male (73%) and Caucasian (91%). About 64% had a history of hypertension, 52% had a prior MI, 32% had prior PTCA, 28% had prior CABG, 24% had a history of diabetes, and 17% had a history of CHF. Prior anti-anginal treatment with beta-blockers (57%), calcium channel blocerks (38%) and long-acting nitrates (58%) were discontinued before qualifying baseline ETT.

6.1.4.3. Weekly angina attacks/Nitroglycerin consumption

CVT 3037: During the qualifying phase, patients received amlodipine 10 mg qd and placebo for 2 weeks. Baseline rates of angina attacks and nitroglycerin consumption were assessed during this phase; the primary endpoint was based on average weekly angina attacks during the 6-week treatment phase (where ranolazine patients were dosed with 1000 mg bid). Due to the presence of outliers, a non-parametric analysis was used.

Table 13. CVT 3037: Primary efficacy variable: Average weekly rate of angina attacks (number/week) (FAS)

	Placebo (N=281)	Ranolazine (N=277)	p-value
Baseline:			
Median	4.50	4.50	NS
25^{th}-75^{th} percentile	3.71-6.00	3.73-6.22	
Min-Max	2.80-206.00	3.00-57.56	
Mean (SEM)	6.89 (0.78)	6.12 (0.31)	
Initial Treatment Phase:			
Median	4.00	4.00	NS

25th-75th percentile	3.00-6.00	3.00-6.00	
Min-Max	0.00-183.00	0.00-47.00	
Mean (SEM)	6.16 (0.70)	5.29 (0.31)	
Six-week Treatment Phase:			
Median	2.43	2.18	0.028
25th-75th percentile	1.47-4.17	1.24-3.66	
Min-Max	0.00-160.26	0.00-47.33	
Mean (SEM)	4.30 (0.64)	3.29 (0.26)	

p-value was calculated from Cochran-Mantel-Haenszel test of equality of mean scores based on modified ridit score, stratified by pooled center.

In study CVT 3037, nitroglycerin consumption was a secondary endpoint.

Table 14. CVT 3037: Average weekly rate of nitroglycerin consumption (doses/week) (FAS)

	Placebo (N=281)	Ranolazine (N=277)	p-value*
Baseline:			
Median	4.00	3.50	NS
25th-75th percentile	2.33-6.00	2.21-5.50	
Mean (SEM)	5.87 (0.52)	5.35 (0.52)	
Min-Max	0.00-98.00	0.00-98.39	
Initial Treatment Phase:			
Median	3.00	2.80	NS
25th-75th percentile	1.00-5.60	1.00-5.00	
Mean (SEM)	4.88 (0.50)	4.24 (0.40)	
Min-Max	0.00-97.00	0.00-60.00	
Six-week treatment phase:			
Median	1.67	1.34	0.014
25th-75th percentile	0.50-4.00	0.47-2.48	
Mean (SEM)	3.57 (0.54)	2.72 (0.38)	
Min-Max	0.00-111.82	0.00-62.21	

*Cochran-Mantel-Haenszel test of equality of mean scores based on modified ridit score, stratified by pooled center.

For the analysis of nitroglycerin consumption, the sponsor also performed an analysis adjusting for baseline imbalances in nitroglycerin consumption; these results were consistent with the unadjusted analysis.

Angina frequency and nitroglycerin consumption, measured by patient diary, were secondary endpoints in CVT 3033. The results in CVT 3033 were consistent with results seen in CVT 3037.

Table 15. CVT 3033: Angina frequency and nitroglycerin consumption (ITT)

Table 13 Study CVT 3033: Angina Frequency and Nitroglycerin Consumption from Patient Diaries (ITT* Population)

Variable	Placebo		Ranolazine ER 750 mg b.i.d.		Ranolazine ER 1000 mg b.i.d.	
	N	Reported Frequency	N	Reported Frequency	N	Reported Frequency
Angina Attacks/Week						
Mean (SE) at Baseline	258	4.63 (0.36)	272	4.37 (0.33)	261	4.44 (0.34)
Mean (SE) during Double-Blind Treatment	258	3.31 (0.30)	272	2.47 (0.23)	261	2.13 (0.24)
p-Value[a]				0.006		< 0.001
Nitroglycerin Consumption/Week						
Mean (SE) at Baseline	247	4.08 (0.43)	258	4.00 (0.49)	244	3.72 (0.45)
Mean (SE) during Double-Blind Treatment	252	3.14 (0.38)	262	2.11 (0.27)	244	1.76 (0.28)
p-Value[a]				0.016		< 0.001

* The ITT population consisted of all patients dosed who had at least one evaluable exercise test on double-blind treatment.

[a] Ranolazine vs. placebo obtained from an ANOVA model using ranked scores data adjusted for treatment, baseline covariate, pooled site, and background therapy.

It should be noted that, in study CVT 3033, no statistically significant difference from placebo was seen with regard to maximum and average duration of angina, and maximum and median severity of angina.

6.4.1.4. Exercise testing:

In the pivotal studies, CVT 3033 and CVT 3031 employed exercise testing as part of their primary efficacy analyses. Studies CVT 3033 and CVT 3031 were reviewed in the original NDA submission; however, the exercise testing results are summarized in the next tables:

Table 16. CVT 3033: Exercise testing results (ITT)

Table 14 Study CVT 3033: Exercise Treadmill Test Results (ITT* Population)

Parameter	Mean Difference from Placebo (SE)				
	Placebo	Ranolazine ER 750 mg b.i.d.		Ranolazine ER 1000 mg b.i.d.	
	N	N	Result	N	Result
Exercise duration (sec)					
Trough	258	272	23.7 (10.9) p = 0.030	261	24.0 (11.0) p = 0.029
Peak	256	270	34.0 (10.7) p = 0.001	255	26.1 (10.8) p = 0.016
Time to onset of angina (sec)					
Trough	258	272	29.7 (12.1) p = 0.014	261	26.0 (12.2) p = 0.033
Peak	256	270	38.0 (12.4) p = 0.002	255	37.9 (12.6) p = 0.003
Time to 1-mm ST-depression (sec)					
Trough	247	260	19.9 (12.2) p = 0.100	244	21.1 (12.4) p = 0.091
Peak	234	248	40.8 (11.8) p < 0.001	236	34.5 (11.9) p = 0.004

* The ITT population consisted of all patients dosed who had at least one evaluable exercise test on double-blind treatment.

Note: p-values from ANCOVA model with effects for baseline covariate, treatment, pooled site and background therapy.

A statistically significant (although not compelling) effect vs. placebo is seen with respect to exercise duration and time to onset of angina; for time to 1-mm ST-depression, a statistically significant effect is seen at peak although not at trough. Of note, results for the primary efficacy endpoint (trough exercise duration) were indistinguishable between ranolazine 750 mg and 1000 mg bid.

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Table 17. CVT 3031: Exercise testing results (A/NC):

Table 15 Study CVT 3031: Exercise Treadmill Test Results (A/NC Population)

Parameter	Mean Difference from Placebo (SE)						
	Placebo	Ranolazine ER 500 mg b.i.d.		Ranolazine ER 1000 mg b.i.d.		Ranolazine ER 1500 mg b.i.d.	
	N	N	Result	N	Result	N	Result
Exercise duration (sec)							
Trough	178	174	23.8 (7.9) p = 0.003	174	33.7 (8.0) p < 0.001	169	45.9 (8.0) p < 0.001
Peak	176	174	29.3 (7.2) p < 0.001	174	50.1 (7.2) p < 0.001	167	55.5 (7.3) p < 0.001
Time to onset of angina (sec)							
Trough	174	174	27.0 (9.5) p = 0.005	174	45.9 (9.5) p < 0.001	169	59.6 (9.6) p < 0.001
Peak	172	174	35.5 (8.5) p < 0.001	174	56.4 (8.5) p < 0.001	167	68.5 (8.6) p < 0.001
Time to 1-mm ST-depression (sec)							
Trough	164	162	27.6 (8.1) p < 0.001	161	44.5 (8.1) p < 0.001	153	64.6 (8.2) p < 0.001
Peak	163	165	38.8 (8.2) p < 0.001	163	55.6 (8.2) p < 0.001	155	69.0 (8.4) p < 0.001

Note: p-values from ANOVA with effects for pooled site, patient within pooled site, period, and treatment.

Table 18. Exercise duration at Trough by Period (study 3031).

Period	Statistic	Ran 500 mg vs. placebo (A vs. D)	Ran 1000 mg vs. placebo (B vs. D)	Ran 1500 mg vs. placebo (C vs. D)
1	Mean difference	*11.7*	*12.7*	*4.5*
	p-value	0.59	0.55	0.83
2	Mean difference	*7*	*42*	*41*
	p-value	0.77	0.071	0.084
3	Mean difference	*34*	*57*	*68*
	p-value	0.17	0.026	0.008
4	Mean difference	*37*	*34*	*67*
	p-value	0.16	0.20	0.013

Source: Sponsor's Table 2.10.0, Vol. 146: original NDA submission

Table 19. Differential Period (Learning) Effects in Study CVT 3031					
Comparison	**Statistics**	**Treatment**			
		Placebo	**Ran SR 500 mg**	**Ran SR 1000 mg**	**Ran SR 1500 mg**
Exercise Duration at Trough (sec.),	**Mean Difference**	36	70	54	97
Period 4 minus Period 1	**P-value**	0.15	0.005	0.024	<0.001
Exercise Duration at Trough (sec.),	**Mean Difference**	25	42	64	82
Period 3 minus Period 1	**P-value**	0.32	0.046	0.004	<0.001
Exercise Duration at Trough (sec.),	**Mean Difference**	12	4	29	45
Period 2 minus Period 1	**P-value**	0.62	0.84	0.16	0.044
Test for Period Effect Over All Four Periods	**P-value**	0.50	0.018	0.027	<0.001

Source: Sponsor's Table ET 13A, 17 June 2003 Submission.

Table 20. Study CVT 3031: Placebo-Subtracted Exercise Duration by Preceding Treatment

Ranolazine treatment (Period)	Treatment effect in the First period	Preceding Treatment			
		Placebo	Ran SR 500 mg	Ran SR 1000 mg	Ran SR 1500 mg
Ran SR 500 mg	11.7 (1)	34 (3)	--	37 (4)	7 (2)
Ran SR 1000 mg	12.7 (1)	34 (4)	42 (2)	--	57 (3)
Ran SR 1500 mg	4.5 (1)	41 (2)	67 (4)	68 (3)	--

See original NDA review for further details

In the original NDA review, study CVT 3031 presented interpretability issues because of the possibility of period and carryover effects. However, an analysis of the first period population did show a marginally statistically significant treatment effect at peak.

Table 21. Study CVT 3031: Comparison of Treatment Differences in ETT duration: First Period Population

	Ran SR 500 mg vs. placebo	Ran SR 1000 mg vs. placebo	Ran SR 1500 mg vs. placebo
ETT duration (**trough**): LS Mean difference (SE)	11.7 (21.5)	12.7 (21)	4.5 (21.5)
95% CI	-30.4, 53.8	-28.4, 53.8	-37.6, 46.7
p-value	NS	NS	NS
ETT duration (**peak**): LS Mean difference (SE)	37.8 (19.5)	56.8 (19)	38.7 (19.7)
95% CI	-0.4, 76.1	19.5, 94	0.1, 77.3
p-value	0.054	0.003	0.051

See original NDA review for further details

6.4.1.5 Seattle Angina Questionnaire (SAQ):

The Seattle Anginal Questionnaire (SAQ) was originally a pre-specified secondary endpoint in study CVT 3037. However, in the study report, it was noted that this instrument has not been validated in the Eastern European countries which comprised a majority of the study population.[4] Therefore, this endpoint should be exploratory and not a part of decision-making or labeling.[5] Results of the SAQ analysis showed a statistically significant treatment effect *only* in the dimension of angina frequency, supporting the primary endpoint in study CVT 3037 (decrease in average weekly angina attacks).

6.4.1.6. Subgroup analyses:

6.4.1.6.1. Concomitant anti-anginal drugs:

Concomitant calcium channel blockers: In study 3037, all patients were on amlodipine 10 mg qd and continued on the same dose of amlodipine while randomized to either ranolazine or placebo as add-on therapy.

[4] This point was confirmed by the Study Endpoint and Label Development Team (SEALD Team, OND, CDER).
[5] The Study Endpoint and Label Development (SEALD) Team had other issues regarding the Seattle Angina Questionnaire including but not limited to: lack of demonstrated internal reliability or unidimensionality based on the documentation available; and lack of evidence that the items included in each scale adequately measure the concept.

In study 3033, patients received one of three background anti-anginal drugs (amlodipine 5 mg qd, diltiazem 180 mg qd, or atenolol 50 mg qd).

As seen below, there was a statistically significant difference between ranolazine vs. placebo in ETT duration in patients receiving background diltiazem therapy. The LS mean difference is higher in the group receiving background diltiazem therapy; this difference is consistent with known pharmacokinetic interactions with diltiazem (see original review). However, the diltiazem-ranolazine interaction is not as clear when viewing results of angina attacks/nitroglycerin consumption.

Table 22. CVT 3033: Change from baseline to Week 12 in ETT duration at *Peak* (sec) by Treatment and Background Therapy (ITT LOCF)

	Ran 750 vs. placebo			Ran 1000 vs. placebo		
	Diltiazem	Atenolol	Amlodipine	Diltiazem	Atenolol	Amlodipine
LS mean difference (SE)	56.4 (21.1)	24.4 (16.1)	29.7 (19.2)	66.6 (21.8)	4.4 (16.4)	24.5 (19.3)
95% CI	14.9, 97.9	-7.2, 56	-8, 67.5	23.8, 109.4	-27.7, 36.5	-13.4, 62.5

Source: Table 2.1.2. LS= least squared. SE = standard error. LS mean differences, SE, and p-values calculated from ANCOVA Model 2, including effects for treatment, baseline covariate, pooled site, background therapy and treatment by background therapy interaction using type III sum of squares. (This table also appeared in the original NDA review)

Table 23. CVT 3033: Angina Attack Frequency and Nitroglycerin Use During 12 Weeks by Use of Diltiazem, Amlodipine or Atenolol (ITT*)

Variable by Background Therapy	Placebo		Ranolazine ER 750 mg b.i.d.		Ranolazine ER 1000 mg b.i.d.	
	N	Reported Frequency	N	Reported Frequency	N	Reported Frequency
Angina Attacks/Week						
Diltiazem (180 mg q.d.)	66	4.36 (0.63)	70	2.97 (0.59)	63	2.74 (0.58)
Amlodipine (5 mg q.d.)	77	2.77 (0.51)	86	2.67 (0.38)	86	1.61 (0.24)
Atenolol (50 mg q.d.)	115	3.06 (0.45)	116	2.01 (0.29)	112	2.18 (0.43)
Nitroglycerin Consumption/Week						
Diltiazem (180 mg q.d.)	64	4.58 (0.96)	67	2.26 (0.52)	58	1.82 (0.48)
Amlodipine (5 mg q.d.)	76	2.84 (0.70)	85	2.13 (0.42)	80	1.29 (0.30)
Atenolol (50 mg q.d.)	112	2.52 (0.46)	110	2.01 (0.45)	106	2.09 (0.54)

* The ITT population consisted of all patients dosed who had at least one evaluable exercise test on double-blind treatment.

Long-Acting Nitrate Use: In study CVT 3037, long-acting nitrates were allowed.

Table 24. CVT 3037: Average weekly rate of angina attacks during 6-week double-blind treatment by concomitant use of LAN

	Placebo (N=281)	Ranolazine (N=277)	p-value
LAN-user (n)	122	129	
Median	2.65	2.13	.15 (CMH)
25th-75th percentile	1.52-4.43	1.33-3.96	
Mean (SEM)	5.67 (1.44)	3.80 (0.49)	
Non-LAN-user (n)	159	148	
Median	2.29	2.20	.16 (CMH)
25th-75th percentile	1.34-3.76	1.15-3.35	
Mean (SEM)	3.26 (0.26)	2.84 (0.23)	

CMH = Cochran-Mantel-Haenszel test of equality of mean scores based on modified ridit score, stratified by pooled center.

6.4.1.6.2. Gender:

Efficacy by gender subgroups is presented from studies CVT 3037 and CVT 3033 (because of interpretability issues, subgroup analyses in CVT 3031 are not presented). While the female subgroup may be underpowered, a statistically significant treatment effect has not been demonstrated in women in either study and the effect size has been consistently smaller compared to results in the male subgroup.

In CVT 3037, the 25th-75th percentiles for weekly angina attacks, as well as the results for nitroglycerin consumption, do trend in a direction favorable toward ranolazine.

The sponsor has claimed that females showed less improvement than men in ETT variables because of differences in maximal aerobic capacity and propensity for peripheral fatigue. According to the sponsor, the smaller subgroup (females) had reduced power to show differences.

Table 25. CVT 3037: Efficacy variables by gender

	Placebo (N=281)	Ranolazine (N=277)	p-value
Average weekly angina attacks (no./week)			
Female (n)	76	79	
Median	2.38	2.43	NS*
25th-75th percentile	1.23-4.44	1.17-3.50	
Min-Max	0.00-21.00	0.00-47.33	
Mean (SEM)	3.84 (0.47)	3.57 (0.67)	
95% CI (Mean)	(2.92, 4.76)	(2.26, 4.89)	
Effect Size (Mean)†		0.045	
Male (n)	205	198	
Median	2.43	2.09	0.026*
25th-75th percentile	1.50-4.00	1.30-3.71	

Min-Max	0.00-160.26	0.00-21.62	
Mean (SEM)	4.47 (0.87)	3.18 (0.25)	
95% CI (Mean)	(2.73, 6.21)	(2.69, 3.67)	
Effect Size (Mean)†		0.37	
Average weekly rate of nitroglycerin consumption			
Female (n)	76	79	
Median	1.54	1.33	NS*
25^{th}-75^{th} percentile	0.44-4.27	0.50-2.83	
Min-Max	0.00-19.83	0.00-60.00	
Mean (SEM)	2.98 (0.44)	3.00 (0.82)	
Male (n)	205	198	
Median	1.75	1.35	0.008*
25^{th}-75^{th} percentile	0.57-3.66	0.33-2.33	
Min-Max	0.00-111.82	0.00-62.21	
Mean (SEM)	3.79 (0.73)	2.62 (0.42)	

*CMH= Cochran-Mantel-Haenszel test of equality of mean scores based on modified ridit score, stratified by pooled center.
. †Effect size = (mean ranolazine-mean placebo)/standard deviation of ranolazine (source: statistical reviewer)

Table 26. CVT 3033. Change from baseline ETT duration (sec) *peak* and *trough* by Gender (ITT LOCF)

	Ran SR 750 (N=272)		Ran SR 1000 (N=261)	
peak	*Female (N=59)*	*Male (N=211)*	*Female (N=47)*	*Male (N=208)*
LS Mean Difference (SE) vs. placebo	-1.9 (22)	44.3 (12.2)	-12.7 (23.5)	35.3 (12.2)
95% CI	-45.1, 41.3	20.4, 68.2	-58.7, 33.4	11.3, 59.3
p-value	NS	<0.001	NS	0.004
trough				
	Female (N=59)	*Male (N=213)*	*Female (N=51)*	*Male (N=210)*
LS Mean Difference (SE) vs. placebo	1.3 (22.5)	28.9 (12.4)	8.6 (23.4)	26.1 (12.5)
95% CI	(-42.9, 45.5)	(4.5, 53.2)	(-37.4, 54.6)	(1.6, 50.6)
p-value	NS	0.02	NS	0.037

6.4.1.6.3. Age:

Results from studies CVT 3037 and CVT 3033 by age are presented below. Results are inconsistent, although the majority of variables trend in a direction that is favorable for

ranolazine. For ETT duration (CVT 3033), the trend is in the same direction and favorable for ranolazine. With respect to average weekly angina attacks (CVT 3037), the median angina attack rate is lower in the placebo group although the means trend toward ranolazine.

Table 27. CVT 3037. Primary Efficacy Variable by Age

	Placebo (N=281)	Ranolazine (N=277)	p-value*
Average weekly rate of angina attacks (no./week)			
Under 65 years (n)	166	162	
Median	2.46	2.09	0.074
25^{th}- 75^{th} percentile	1.47-4.32	1.24-3.26	
Mean (SEM)	4.41 (0.98)	3.13 (0.27)	
65 years and over (n)	115	115	
Median	2.33	2.43	0.15
25^{th} – 75^{th} percentile	1.46-4.00	1.24-3.71	
Mean (SEM)	4.14 (0.70)	3.52 (0.50)	

* p-value calculated from Cochran-Mantel-Haenszel test of equality of mean scores based on modified ridit score, stratified by pooled center.

Table 28. CVT 3033: Change from baseline ETT duration (sec) at *trough* and *peak* by Age (ITT LOCF)

	Ran SR 750 (N=272)		Ran SR 1000 (N=261)	
trough				
Age (years)	*< 65 (N=140)*	*≥ 65 (N=132)*	*< 65 (N=134)*	*≥ 65 (N=127)*
LS Mean Difference (SE) vs. placebo	27.9 (15.5)	16.9 (15.3)	25.8 (15.6)	19.2 (15.4)
95% CI	(-2.5, 58.3)	(-13.1, 46.9)	(-4.9, 56.5)	(-11, 49.4)
p-value	0.07	NS	NS	NS
peak				
Age (years)	*< 65 (N=139)*	*≥ 65 (N=131)*	*< 65 (N=133)*	*≥ 65 (N=122)*
LS Mean Difference (SE) vs. placebo	39.7 (15.2)	26.2 (15)	27.8 (15.3)	21.9 (15.2)
95% CI	10, 69.5	-3.3, 55.6	-2.3, 57.9	-8, 51.8
p-value	0.009	0.08	0.07	NS

Source: Tables 2.1.7, 2.1.7.1, 2.1.8, 2.1.8.1, 2.1.9, 2.1.9.1, 2.1.10, 2.1.10.1. LSM, SE and p-values from ANCOVA Model 6 with effects for treatment, baseline covariate, pooled site, background therapy, subgroup and treatment by subgroup interaction. Baseline covariate is the visit 2 data.

According to the sponsor, treatment by subgroup interaction terms (above) were non-significant.

6.4.1.6.4. Race:

Because the study population was mostly Caucasian in all pivotal studies (99% in CVT 3037, 98% in CVT 3033, and 91% in CVT 3031), no meaningful analysis of subgroups by race was possible.

6.1.5 Clinical Microbiology

Since ranolazine has not been reviewed as an antimicrobial, this section is not applicable.

6.1.6 Efficacy Conclusions

1. Efficacy by ETT duration has been demonstrated in CVT 3033 as well as peak effects in CVT 3031 (first period population), where modest and marginally significant treatment effects were shown.
2. CVT 3037 met its primary endpoint, decrease in weekly angina attack rates in the ranolazine group vs. placebo.
3. Results of the CVT 3037 secondary endpoint, decrease in nitroglycerin consumption, were consistent with the primary endpoint.
4. Results of CVT 3037, decrease in weekly angina attack rates and nitroglycerin consumption, were consistent with the results of CVT 3033.
5. Because the Seattle Angina Questionnaire (SAQ) has not been validated in the study population (and the Agency has raised questions about validation in the U.S. population), the SAQ will not be used in the regulatory decision-making.
6. However, the results of CVT 3033, CVT 3031, and CVT 3037 support a conclusion of a treatment effect (how clinically meaningful is not clear).
7. While effectiveness cannot be excluded, the effect size of the primary endpoint appears to be smaller in the female subgroup in CVT 3037. Results of the CVT 3033 primary endpoint have also shown a smaller effect in the female subgroup; in the original submission, the sponsor has claimed that this result reflects differences in exercise capacity in the female subgroup.
8. The above efficacy conclusions have been made with the assumption that auditing and inspections have revealed no substantive deficiencies or issues with data integrity.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Methods:
The safety analyses included all subjects/patients who received at least one dose of ranolazine or placebo subsequent to any run-in period. Baseline was generally defined as the last non-missing measurement before the first dose of study drug; for long-term open-label studies, a patient's baseline value from the preceding controlled study was used for evaluations requiring a baseline value.

According to the sponsor, an adverse event (AE) was defined as any unfavorable or unintended sign (including laboratory values), symptom or disease that appeared or worsened during the clinical trial, whether or not deemed causally associated with the study drug. AEs occurring prior to the first dose of study drug were not included in the ISS database. Events attributed

exclusively to other comparators, such as atenolol in study RAN 080, were not included in the ISS database.

For crossover studies, if an AE occurred in one treatment period and recurred in a subsequent period, it was counted as treatment-emergent in the subsequent period only if the event increased in severity or was serious.

All concomitant medication trade names were standardized where possible based on the WHO Drug Reference List using generic term, therapeutic class and anatomic system.

In studies were ECGs were obtained, PR, QRS, QT and QTc intervals were analyzed. The QTc analysis utilized the longest QT/QTc from any lead of 12-lead ECG. The QTc was calculated using both the Fridericia (QTcF)[6] and Bazett (QTcB)[7] correction formulae.

Findings:

1. In the original safety review, the following were noted:
    a. QT interval prolongation and T wave morphology changes (with a greater drug effect at peak and a higher incidence/increased change from baseline at higher doses);
    b. The most commonly reported adverse events in the SR controlled studies were dizziness, constipation, and nausea. Syncope, sweating and vomiting were reported with ranolazine 1500 mg bid; orthostatic hypotension was reported with higher doses.
    c. Laboratory changes included small decreases in hematocrit/hemoglobin and small increases in BUN and creatinine.

2. In this resubmission, the most commonly reported adverse events in the ER controlled studies were: constipation, nausea, dizziness, and asthenia. Increased incidence of asthenia, nausea, vomiting, dizziness, and sweating was noted at higher doses.
3. An increased incidence of adverse events, serious adverse events, and discontinuations due to adverse events were noted in the elderly population. For patients 75 years and older in the phase 2/3 ER controlled studies, the incidence of constipation was 18%; the incidence of dizziness was about 16% and the incidence of any adverse event was 57%. In the ISS database, 61% of patients aged 65 -74 and 70% of patients aged 75 and older reported an adverse event (compared population to 27% of patients aged 65-74 and 36% of patients aged 75 and older on placebo). In the ISS database, there were increased incidences of constipation (19%), nausea (11.7%) and dizziness (19%) in the elderly population ($\geq$ 75 years old) on ranolazine compared to the total ranolazine population (6.4%, 7.8%, and 12.9% for constipation, nausea, and dizziness, respectively). Please see section 7.1.5.6 for further details.
4. An increased incidence of adverse events, serious adverse events, and discontinuations due to adverse events were noted in the diabetic population on ranolazine (vs. nondiabetics on ranolazine or diabetics on placebo). This increased incidence may be due to other factors (i.e., age, comorbidities, sample size differences). However, a drug-disease interaction cannot be excluded. Please see section 7.1.5.6 for further details.

6 QTcF = QT/ (RR interval) $^{1/3}$ where RR = 60/ventricular heart rate.
7 QTcB = QT/ (RR interval) $^{1/2}$ where RR = 60/ventricular heart rate.

5. Small mean decreases in hemoglobin/hematocrit were seen (as in the original review); small mean increases in BUN/creatinine were seen with shift tables showing an increase from normal to abnormal BUN/creatinine with ranolazine vs. placebo. However, in the Phase 2/3 controlled ER studies there were no imbalances (ranolazine vs. placebo) seen with respect to renal treatment-emergent adverse events, serious adverse events, or discontinuations due to adverse events. An analysis of on-treatment creatinine doubling in the pivotal studies (CVT 3033, CVT 3031, and CVT 3037) showed no evidence of a safety signal with ranolazine.
6. Mean decreases from baseline in systolic and diastolic blood pressure (BP) appear to increase with increasing dose.

7.1.1 Deaths

In the original safety review (Dr. Gordon, 7/30/2003), there were 37 reported deaths (33 ranolazine and 4 placebo) in all 81 studies. For the total ranolazine group (IR, SR and IV), the mortality rate was 1.2% (33/2682). The controlled studies randomized 749 subjects to ranolazine with a mortality rate of 0.7% (5/749) and 455 subjects to placebo with a mortality rate of 0.7% (3/455).[8] An additional 20 deaths were reported in the 4-month safety update.

Since the 4-month Safety Update cut-off on October 31, 2002, an additional 26 patients died, including two patients (one ranolazine and one placebo) in Study CVT 30379 and 24 patients in the long-term open-label studies (CVT 3032 and CVT 3034).

As of October 1, 2004, a total of 83 (2.1%, 83/3,930) deaths were identified in all 84 ranolazine clinical studies. The Phase 2/3 ER controlled studies randomized 1,030 subjects to ranolazine with a mortality rate of 0.5% (5/1,030) and 738 subjects to placebo with a mortality rate of 0.5% (4/738). A total of 12 deaths (8 ranolazine and 4 placebo) occurred during the controlled observation period from the Phase 2/3 controlled studies (both IR and ER). It is noted that 70 deaths occurred during the long-term, open-label follow-up studies. One additional death (a patient who received placebo in an early study, RAN 1789) is not included in the ISS database.

Table 29. Summary of Demographics and Cause of Death—Phase 2/3 IR and ER controlled studies and long-term, open-label follow-up studies

	Frequency Count of Patients Who Died			
	Phase 2/3 IR and ER controlled studies		Open-label IR and ER studies	
	Ranolazine	Placebo[a]	Ranolazine[c]	Off-treatment
Mean age (yrs)	62.8	61.2	64.5	64.5
Male	7	5	48	16
Female	1	0	4	2

8 According to the sponsor (verbal communication, November 23, 2005) there were 4 ranolazine deaths in the original controlled studies.
[9] A review of the two deaths from study CVT 3037 can be found in the Individual Study Review.

Cause of Death:				
Sudden	3	1	12[d]	2
VT/VFR/CA	1	1	4[e]	1
MI	2	1	17	7[f]
Other CV	2	2[b]	9	2
Other	0	0	7[g]	6
Unknown	0	0	3	0

[a] Includes 1 non-ISS patient, a 70 year old male (RAN 1789_2302) with multiple organ failure after treatment with placebo.
[b] Includes patient (RAN 1513-4609) who died 45 days after discontinuation of ranolazine.
[c] Includes patients who died 1 day after taking last dose of ranolazine.
[d] Includes patients (CVT 3034-706-7575) and (CVT 3034-714-9627) who died from heart failure and MI, respectively.
[e] Includes patient (RAN 2074-39711 5008): According to the sponsor, this patient was part of an open-label long-term extension study (on ranolazine)—however, the timing of the last ranolazine dose and the patient's death are unknown.
[f] Includes patient (CVT 3034-188-7009) whose cause of death was post-surgical hemorrhage.
[g] Does not include patient (CVT 3034-493-9680) who died from lung cancer and the death was not captured in the ISS database.

A majority of the deaths in the database are cardiovascular in nature. Cases of cardiac arrest and sudden death (see below) are noted; in this population, with a high likelihood of underlying coronary disease, it might be expected that these deaths represent myocardial infarction or ischemic arrhythmias; however, without further documentation this reviewer cannot distinguish these potential causes from a possible drug effect.

Number	Subject/patient ID	Dose/duration	Cause of death
1	3037/5705-7003	Ran 1000 mg bid/10 days	Pneumonia, acute cardiopulmonary failure (possible MI)
2	3037/6103-7012	Placebo/ 27 days	MI
3	3032/133-1021	Ran 1000 mg bid/2075 days	Cardiac arrest*
4	3032/517-1333	Ran 1000 mg bid/1852 days	Renal failure, myeloma, tachy-brady syndrome, cardiac arrest.
5	3034/181-9357	Ran 750 mg bid//1072 days	Small bowel obstruction, pneumonia
6	3034/182-9080	Ran 1000 mg bid/950 days (CABG). Exp. Day 954.	Post-CABG pulmonary emboli, RV failure
7	3034/182-9435	Ran 500 mg bid/last dose Day 951, exp. Day 976	MI, CABG, GI bleed, CVA, respiratory failure
8	3034/188-7009	Ran 1000 mg bid/1223 days	Post-surgical (left kidney cancer) hemorrhage
9	3034/188-7011	Ran 1000 mg bid/1208 days	MI, cardiogenic shock
10	3034/493-9680	Ran 1000 mg bid/235 days	Lung cancer
11	3034/502-8118	Ran 1000 mg bid/1006 days	Pneumonia

12	3034/508-8100	Ran 750 mg bid/1054 days	MI/CHF per autopsy
13	3034/519-9243	Ran 1000 mg bid/619 days	MI, shock, cardiac arrest
14	3034/530-8248	Ran 1000 mg bid/1242 days	Traumatic subarachnoid hemorrhage
15	3034/706-7575	Ran 1000 mg bid/839 days	Sudden death**
16	3034/707-9585	Ran 1000 mg bid/760 days	MI
17	3034/710-7626	Ran 1000 mg bid/575 days	Acute Coronary Syndrome (per autopsy)
18	3034/710-8727	Ran 1000 mg bid/250 days	Pneumonia, MI
19	3034/710-9584	Ran 1000 mg bid/751 days	Chest pain, cardiac arrest≠
20	3034/710-9620	Ran 1000 mg bid/7 months	Unknown-found in bed
21	3034/711-7597	Ran 1000 mg bid/823 days	Found on the road***
22	304/711-7598	Ran 1000 mg bid/258 days	Sudden death†
23	304/711-8652	Ran 1000 mg bid/349 days	MI (autopsy)
24	3034/713-7603	Ran 1000 mg bid/850 days	CVA
25	3034/714-9627	Ran 1000 mg bid/704 days	MI (autopsy)
26	3034/753-9390	Ran 500 mg bid/876 days	MI

* Coded as "acute myocardial infarction" by investigator. Patient had history of coronary disease and angina. On the day he died, the patient awoke from a nap with shortness of breath followed by collapse and then cardiac arrest. No ECG or autopsy was documented.
** Coded as "angina, heart failure," this patient with a history of increasing angina died while removing snow. The autopsy showed coronary atherosclerosis, myocardial hypertrophy, pulmonary edema and cerebral edema, among other finding.
*** Coded as "Heart Failure." According to the narrative, the autopsy report revealed the cause of death "was due to acute coronary insufficiency and atherosclerosis of the aorta (2^{nd}-3^{rd} degree)."
† The patient expired while watching television; the death was witnessed and no resuscitation was apparently performed. The last ECG on Day 239 showed a QTc of 460 msec.
≠ Coded as "myocardial infarction," the patient developed chest pain and was taken to the emergency room where he went into cardiac arrest; no cardiac enzymes, ECG or autopsy was done.

The sponsor provided a Kaplan-Meier estimated survival (on treatment analysis) for angina patients receiving ranolazine (any dose) in CVT 3031, CVT 3033 and their open-label follow-up studies, CVT 3032 and CVT 3034. Survival during the first year of ranolazine ER treatment was 97.8% (95% CI: 96.8%, 98.9%) with a corresponding mortality value of 2.2% (95% CI: 3.2%, 1.1%). The 4-year mortality estimate remained below 10%; the sponsor has compared mortality estimates for similar high-risk CAD (coronary artery disease) populations based on Duke score (5-10%). However, it should be noted that there were no long-term exposures to a blinded concurrent placebo,

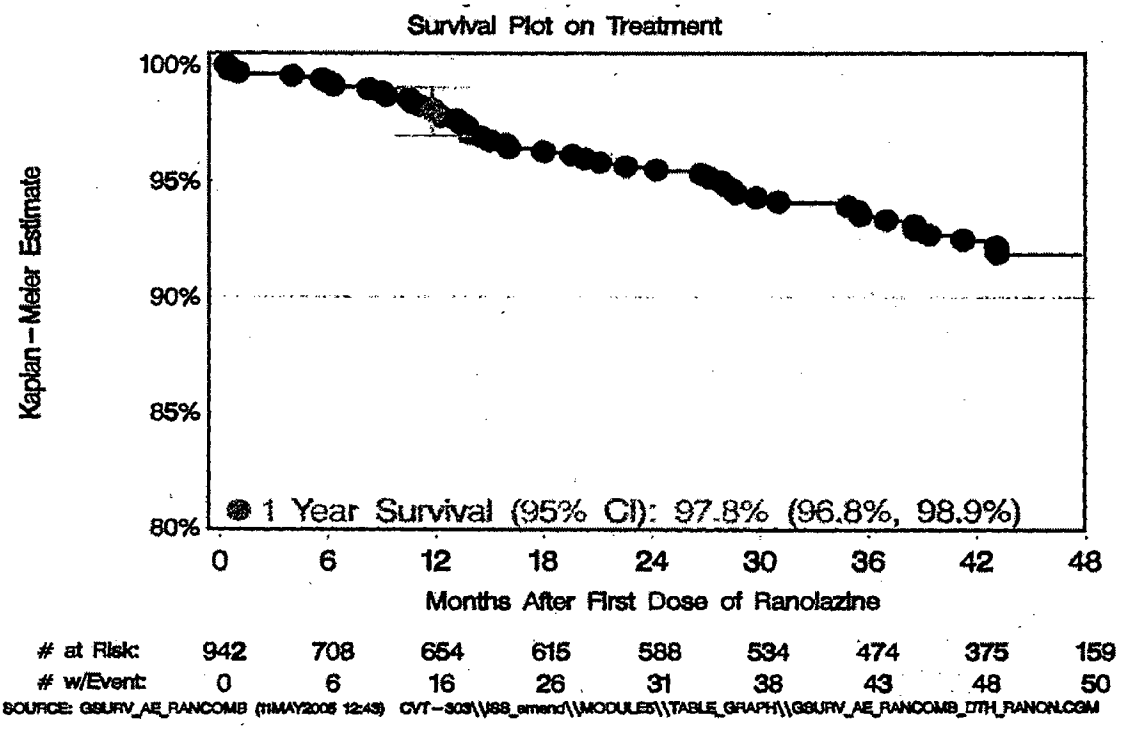

Figure 1. Kaplan-Meier Plot of Survival of Chronic Angina Patients on Ranolazine ER (CVT 3031-3034, on treatment)

7.1.2 Other Serious Adverse Events

In the phase 2/3 ER controlled studies, SAE occurred in 5.4% (56/1,030) ranolazine patients compared to 3% (22/738) placebo patients.

Table 30. Serious Adverse Events reported > 0.1% in the Phase 2/3 ER Controlled Studies and greater incidence in the ranolazine group compared to placebo

Preferred Term	Ranolazine (N=1030)	Placebo (N=738)
Mean Duration of Exposure (days)	61	52
Total Patients with any SAE	56 (5.4)	22 (3.0)
Accidental injury	1 (0.1)	0
Allergic Reaction	1 (0.1)	0
Asthenia	1 (0.1)	0
Carcinoma	1 (0.1)	0
Headache	3 (0.3)	0
Sudden Death	2 (0.2)	1(0.1)
Arteriosclerosis	1 (0.1)	0
Bradycardia	1 (0.1)	0

Cerebral Ischemia	1 (0.1)	0
Cerebrovascular Accident	1 (0.1)	0
Coronary Artery Disorder	4 (0.4)	2 (0.3)
Heart Arrest	2 (0.2)	0
Hypotension	1 (0.1)	0
Myocardial infarction	7 (0.7)	2 (0.3)
Myocardial ischemia	2 (0.2)	0
Postural hypotension	1 (0.1)	0
Shock	1 (0.1)	0
Sinus bradycardia	1 (0.1)	0
Syncope	4 (0.4)	0
Ventricular fibrillation	1(0.1)	0
Cholecystitis	1 (0.1)	1 (0.1)
Colitis	1 (0.1)	0
Nausea	1 (0.1)	0
Dehydration	1 (0.1)	0
Bone Disorder	1 (0.1)	0
Dizziness	4 (0.4)	0
Meningitis	1 (0.1)	0
Vertigo	2 (0.2)	0
Apnea	1 (0.1)	0
Pneumonia	3 (0.3)	1 (0.1)
Sweating	1(0.1)	0
Tinnitus	1 (0.1)	0

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Table 31. Subject/Patient Disposition and Reasons for Discontinuation Phase 2/3 ER Controlled Angina Studies and ISS Database

	Number of Subjects/Patients			
	Phase 2/3 ER Controlled Angina Studies		ISS Database	
	Ranolazine (N=1030)	Placebo (N=738)	Ranolazine (N=3106)	Placebo (N=1829)
Mean duration of exposure (days)	61	52	319	28
Discontinuation N (%)	98 (9.5)	40 (5.4)	682 (22.0)	68 (3.7)
Reason for discontinuation				
Adverse Event	62 (6.0)	19 (2.6)	252 (8.1)	32 (1.7)

Inappropriate enrollment	1 (0.1)	0	7 (0.2)	0
Noncompliance	2 (0.2)	2 (0.3)	33 (1.0)	5 (0.3)
Need for prohibited medication	0	0	2 (0.1)	5(0.3)
Lost to follow-up	1 (0.1)	0	12 (0.4)	0
Elective withdrawal	10 (1.0)	4 (0.5)	112 (3.6)	5 (0.3)
Death*	5 (0.5)	3 (0.4)	68 (2.2)	3 (0.3)
Study termination by sponsor	0	1 (0.1)	75 (2.4)	3 (0.3)
Other	17 (1.7)	11 (1.5)	121 (3.9)	20 (1.1)

* Three additional deaths occurred which were not included in the ISS database and discovered through the sponsor's pharmacovigilance efforts. On additional death, a patient who received placebo in RAN 1789 is also not included in the ISS database. (Source: Table 4, ISS)

7.1.3.2 Adverse events associated with dropouts

From the Phase 2/3 ER controlled angina studies, the most common treatment-emergent AE leading to study discontinuation were the following:

Table 32. Incidence of Most Common Treatment-Emergent Adverse Events Reported for ≥ 0.5% of Patients resulting in Discontinuation in the Phase 2/3 ER Controlled Angina Studies

Preferred Term	Ranolazine (N=1030)	Placebo (N=738)
Asthenia	5 (0.5)	0
Headache	6 (0.6)	0
Angina pectoris	10 (1.0)	6 (0.8)
Myocardial Infarct	5 (0.5)	1 (0.1)
Nausea	10 (1.0)	0
Constipation	6 (0.6)	0
Dizziness	13 (1.3)	1 (0.1)

Source: sponsor, ISS, Table 15

The most common adverse events leading to discontinuation were dizziness and angina.

7.1.3.3 Other significant adverse events

Please see section 7.1.7.3.1 and 7.1.7.3.2 for data concerning small mean increases in BUN and creatinine. Also noted was an increase in the shift table for BUN/creatinine (7.1.7.3.2) from normal to high in the ranolazine group (vs. placebo).

7.1.4 Other Search Strategies

With regard to the pharmacology/toxicology review and the question of tumor promotion, this reviewer searched the summary tables and is currently reviewing the database for cancer incidence; thus far, no signal has been seen. It is possible that cancer patients may have been

excluded from the clinical program; in addition, the largest placebo-controlled study (CVT 3033) included ranolazine exposures up to 12 weeks. Long-term studies were open-label and without a concurrent placebo group.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All AEs, either observed by the investigator or professional collaborators, or reported spontaneously by the patient or in response to a question, were evaluated by the investigator and noted as verbatim terms in the case report form. Verbatim terms were subsequently mapped, using a COSTART thesaurus, to a preferred term and body system.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

This reviewer disagreed with the coding of three deaths (see section 7.1.1.). Otherwise, this reviewer felt that, in general, the coding appeared to be appropriate.

7.1.5.3 Incidence of common adverse events

The Phase 2/3 ER placebo-controlled studies were highlighted in this review for evaluation of common adverse events (AEs). In the Phase 2/3 ER controlled angina studies (RAN 2240, CVT 3031, CVT 3033, CVT 3037), adverse events occurred in 38% (394/1,030) of ranolazine-treated patients and 28% (204/738) of placebo-treated patients.

Common adverse event tables

Table 33. Treatment-Emergent Adverse events in Phase 2/3 controlled studies (ER formulation) occurring > 1% in the total ranolazine group and more frequently in ranolazine than placebo.

	Placebo (N=738) n (%)	Ranolazine (R=1030) n (%)
Asthenia	13 (1.8)	38 (3.7)
Headache	16 (2.2)	31 (3.0)
Pain	6 (0.8)	12 (1.2)
Angina Pectoris	23 (3.1)	34 (3.3)
Peripheral Edema	11 (1.5)	21 (2.0)
Constipation	9 (1.2)	75 (7.3)
Dyspepsia	5 (0.7)	20 (1.9)
Nausea	6 (0.8)	51 (5.0)
Dyspnea	8 (1.1)	17 (1.7)

Sweating	3 (0.4)	13 (1.3)
Dizziness	13 (1.8)	73 (7.1)

Source: ISS, Appendix 5, Table G-2.3

Given the difference in exposure between ranolazine (mean duration 319 days) and placebo (mean duration 28 days), it is not clear how to interpret comparisons to placebo in the ISS database. Consistent findings in the ISS database included a higher incidence of dizziness (12.9% ranolazine vs. 2.9% placebo), constipation (6.4% ranolazine 0.5% placebo), peripheral edema (4.0% ranolazine, 0.9% placebo), asthenia (9.8% ranolazine, 3% placebo), headache (12.8% ranolazine, 5.9% placebo). Also noted were the ISS incidences of hypertension (3% ranolazine, 0.5% placebo), angina (8.4% ranolazine, 1.9% placebo), syncope (2% ranolazine, 0.2% placebo), and dyspnea (3.3% ranolazine, 1.2% placebo).

Identifying common and drug-related adverse events

An exploration of dose-related AEs was also presented in the original review. The following table presents an updated version:

Table 34. Treatment-Emergent Adverse Events ≥ 2% by Dose in Phase 2/3 ER studies

Preferred term	Number (%) of Angina Patients					
	Ranolazine ER					Placebo (N=738)
	500 mg (N=181)	750 mg (n=279)	1000 mg (n=740)	1500 mg (N=187)	Total (N=1030)	
Mean duration of exposure (days)	8	82	51	8	61	52
Any AE	28 (15.5)	87 (31.2)	253 (34.2)	63 (33.7)	394 (38.3)	204 (27.6)
Abdominal Pain	1 (0.6)	2 (0.7)	16 (2.2)	1 (0.5)	20 (1.9)	4 (0.5)
Asthenia	**0**	**5 (1.8)**	**23 (3.1)**	**11 (5.9)**	**38 (3.7)**	**13 (1.8)**
Headache	1 (0.6)	7 (2.5)	18 (2.4)	5 (2.7)	13 (3.0)	15 (2.2)
Infection	1 (0.6)	2 (0.7)	11 (1.5)	3 (1.6)	17 (1.7)	22 (3.0)
Peripheral Edema	0	3 (1.1)	18 (2.4)	0	21 (2.0)	11 (1.5)
Angina pectoris	7 (3.9)	11 (3.9)	11 (1.5)	6 (3.2)	34 (3.3)	23 (3.1)
Palpitation	0	2 (0.7)	5 (0.7)	4 (2.1)	10 (1.0)	8 (1.1)
Constipation	**0**	**18 (6.5)**	**50 (6.8)**	**8 (4.3)**	**75 (7.3)**	**9 (1.2)**
Dyspepsia	1 (0.6)	7 (2.5)	10 (1.4)	2 (1.1)	20 (1.9)	5 (0.7)
Nausea	**1 (0.6)**	**9 (3.2)**	**25 (3.4)**	**16 (8.6)**	**51 (5.0)**	**6 (0.8)**
Vomiting	**0**	**2 (0.7)**	**5 (0.7)**	**4 (2.1)**	**11 (1.1)**	**1 (0.1)**

Dizziness	**1 (1.1)**	**10 (3.6)**	**41 (5.5)**	**22 (11.8)**	**73 (7.1)**	**13 (1.8)**
Sweating	**0**	**3 (1.1)**	**5 (0.7)**	**5 (2.7)**	**13 (1.3)**	**3 (0.4)**
Urine Abnormality	0	0	4 (0.5)	4 (2.1)	8 (0.8)	0

Bolded AEs appear to show a relationship with increasing dose. The incidence of constipation may also increase with duration of treatment (since the incidence w/1000 mg treatment is higher after 12 weeks (CVT 3033: (20/275, 7.3%) vs. 1 week (CVT 3031: 3/180, 1.7%) of treatment).

7.1.6 Additional analyses and explorations

Subgroup analysis by underlying disease: The sponsor presented a subgroup analysis of common adverse events (≥ 2%, ranolazine vs. placebo) in the Phase 2/3 controlled ranolazine ER studies by presence of diabetes, CHF, or reactive airway disease. At least 100 patients were in each subgroup (e.g., diabetics on ranolazine = 231 patients; diabetics on placebo = 156 patients; nondiabetics on ranolazine = 799 patients; nondiabetics on placebo = 582 patients). No unusual trends were seen.

With respect to the ISS database, diabetics on ranolazine (N=444) appeared to show the highest incidence of AE (64%) and SAE (24%) compared to nondiabetics on ranolazine (N=2659; 59% any AE, 12.4% any SAE) and compared to diabetics on placebo (N = 271; any AE 26.6%, any SAE 2.6%). It is difficult to know how to interpret these differences. These differences in AE incidence may be related to other differences, such as differences in age, underlying disease (s), or sample size. No study was specifically designed to show whether or how ranolazine interacts with diabetes.

In the diabetic-ranolazine subgroup, there was a higher incidence of angina pectoris (13.3% compared to 7.6% of nondiabetics on ranolazine; diabetics on ranolazine also had a higher incidence of peripheral edema (7.7%) compared to nondiabetics on ranolazine (3.4%) or diabetics on placebo (1.5%). Diabetics on ranolazine had a higher incidence of constipation (8.1% vs. nondiabetics on ranolazine 6.1%), diarrhea (4.1% vs. nondiabetics on ranolazine 2.2%)), anemia (4.1% vs. 1.1% nondiabetics on ranolazine), diabetes (2.5% vs. 1.3% nondiabetics on ranolazine), hyperglycemia (3.4% vs. 0.6% nondiabetics on ranolazine) and hypoglycemia (2.0% vs. < 0.1% nondiabetics on ranolazine) compared to diabetics on placebo and nondiabetics on ranolazine.

Subgroup analysis by demographic characteristics:

With increased age (65-74 and 75 years and over) there appears an increased incidence of adverse events, serious adverse events, and adverse events leading to discontinuation (next table). This is seen both in the Phase 2/3 ER controlled studies and in the entire ISS database. The reviewer acknowledges the differences in sample sizes (elderly vs. younger population, ranolazine vs. placebo). The numbers of non-Caucasians are too small, and the numerical differences between Caucasians are too large, for this reviewer to analyze.

Table 35. Incidence of Treatment-Emergent Adverse Events, Serious Adverse Events and Adverse Events leading to discontinuation by Treatment, Age, Gender, Race: Phase 2/3 ER controlled studies and ISS database

and ISS Database

Subgroup	Number (%) of Patients[a]							
	Ranolazine				Placebo			
	N	Total AEs	Total SAEs	Total DC	N	Total AEs	Total SAEs	Total DC
Phase 2/3 ER Controlled Angina Studies								
Age [Years]								
< 65	534	176 (33.0)	24 (4.5)	20 (3.7)	387	99 (25.6)	11 (2.8)	10 (2.6)
65–74	382	153 (40.1)	22 (5.8)	28 (7.3)	283	82 (29.0)	9 (3.2)	9 (3.2)
≥ 75	114	65 (57.0)	10 (8.8)	17 (14.9)	68	23 (33.8)	2 (2.9)	3 (4.4)
Gender								
Female	249	107 (43.0)	10 (4.0)	19 (7.6)	191	63 (33.0)	4 (2.1)	6 (3.1)
Male	781	287 (36.7)	46 (5.9)	46 (5.9)	547	141 (25.8)	18 (3.3)	16 (2.9)
Race								
Caucasian	991	371 (37.4)	52 (5.2)	60 (6.1)	715	48 (6.7)	22 (3.1)	22 (3.1)
Non-Caucasian	39	23 (59)	4 (10.3)	5 (12.8)	23	2 (8.7)	0	0

[a] Number of patients reflects the number of patients who received at least one dose of study drug.

Abstracted from **Appendix III D Table G-8.1, Appendix III D Table G-9.1, Appendix III D Table G-10.1, Appendix III F Table I-4.1, Appendix III F Table I-5.1, Appendix III F Table I-6.1, Appendix III G Table J-5.1, Appendix III G Table J-6.1, Appendix III G Table J-Appendix V D Table G-8.3, Appendix V D Table G-9.3, Appendix V D Table G-10.3, Appendix V F Table I-4.3, Appendix V F Table I Appendix V F Table I-6.3, Appendix V G Table J-5.3, Appendix V G Table J-6.3, Appendix V G Table J-7.3.**

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Subgroup	Number (%) of Patients[a]							
	Ranolazine				Placebo			
	N	Total AEs	Total SAEs	Total DC	N	Total AEs	Total SAEs	Total DC
	ISS Database							
Age [Years]								
< 65	2032	1183 (58.2)	207 (10.2)	129 (6.3)	1149	343 (29.9)	20 (1.7)	17 (1.5)
65–74	869	527 (60.6)	181 (20.8)	113 (13.0)	559	148 (26.5)	14 (2.5)	15 (2.7)
≥ 75	205	144 (70.2)	54 (26.3)	48 (23.4)	121	43 (35.5)	2 (1.7)	3 (2.5)
Gender								
Female	618	401 (64.9)	92 (14.9)	80 (12.9)	399	126 (31.6)	5 (1.3)	7 (1.8)
Male	2488	1453 (58.4)	350 (14.1)	210 (8.4)	1430	408 (28.5)	31 (2.2)	28 (2.0)
Race								
Caucasian	2710	1631 (60.2)	421 (15.5)	263 (9.7)	1642	466 (28.4)	34 (2.1)	35 (2.1)
Non-Caucasian	218	142 (65.1)	20 (9.2)	26 (11.9)	116	40 (34.5)	2 (1.7)	0

[a] Number of patients reflects the number of patients who received at least one dose of study drug.

Abstracted from **Appendix III D Table G-8.1, Appendix III D Table G-9.1, Appendix III D Table G-10.1, Appendix III F Table I-4.1, Appendix III F Table I-5.1, Appendix III F Table I-6.1, Appendix III G Table J-5.1, Appendix III G Table J-6.1, Appendix III G Table J-7.1 Appendix V D Table G-8.3, Appendix V D Table G-9.3, Appendix V D Table G-10.3, Appendix V F Table I-4.3, Appendix V F Table I-5. Appendix V F Table I-6.3, Appendix V G Table J-5.3, Appendix V G Table J-6.3, Appendix V G Table J-7.3.**

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Table 36. Most common treatment-emergent adverse events (≥ 5% in ≥ 75 years on ranolazine in phase 2/3 ER controlled studies) in subjects/patients ≥ 75 years in phase 2/3 ER controlled studies and ISS database.

Preferred Term	Phase 2/3 ER controlled studies				ISS Database			
	Ranolazine ≥ 75 years (N=114)	Placebo ≥ 75 years (N=68)	Total Ranolazine (N=1030)	Total Placebo (N=738)	Ranolazine ≥ 75 years (N=205)	Placebo ≥ 75 years (N=121)	Total Ranolazine (N=3106)	Total Placebo (N=1829)
Asthenia	10 (8.8)	2 (2.9)	38 (3.7)	13 (1.8)	23 (11.2)	9 (7.4)	305 (9.8)	54 (3.0)
Headache	7 (6.1)	0	31 (3.0)	16 (2.2)	17 (8.3)	3 (2.5)	398 (12.8)	107 (5.9)
Angina pectoris	6 (5.3)	1 (1.5)	34 (3.3)	23 (3.1)	33 (16.1)	2 (1.7)	262 (8.4)	34 (1.9)
Constipation	21 (18.4)	1 (1.5)	75 (7.3)	9 (1.2)	39 (19.0)	0	31 (1.0)	2 (0.1)
Nausea	12 (10.5)	1 (1.5)	51 (5.0)	6 (0.8)	24 (11.7)	2 (1.7)	242 (7.8)	20 (1.1)
Dizziness	18 (15.8)	2 (2.9)	73 (7.1)	13 (1.8)	39 (19.0)	3 (2.5)	401 (12.9)	53 (2.9)

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

This resubmission included updated laboratory test results, incorporating CVT 3037 and the open-label follow-up studies.
With the exception of CVT 3037, a central laboratory was used for the Phase 2/3 ER controlled studies as well as the long-term follow-up studies CVT 3032 and 3034.
CVT 3033, CVT 3037, and CVT 3031 did not include routine laboratory testing after study completion.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This review highlighted the Phase 2/3 ER controlled angina studies (placebo-controlled ranolazine studies) for an evaluation of laboratory changes; however, data from the open-label studies will be presented when appropriate.

7.1.7.3 Standard analyses and explorations of laboratory data

Hematology results are consistent with results from the original safety review, where small mean decreases from baseline in hemoglobin and hematocrit were seen. With respect to glucose, glycosylated hemoglobin (HbA1c) levels were not measured in CVT 3037; the sponsor claims that glycosylated hemoglobin levels were decreased in ranolazine-treated diabetics in CVT 3033 but states that the "clinical significance of ranolazine's effect on HbA1c has not been established." Plasma lipids were not evaluated in CVT 3037; only the long-term exposure data has been updated.

7.1.7.3.1. Analyses focused on measures of central tendency

Small mean increases from baseline in BUN and creatinine are noted.

Table 37. Mean Changes from Baseline in Renal function: Phase 2/3 Controlled Angina Studies and Long-Term, Open-Label Studies

Laboratory Parameter	Phase 2/3 ER Controlled Angina Studies		Open-Label Studies				
			Ranolazine ER				
	Ranolazine ER	Placebo	> 6–12 Wks	> 12 Wks – 6 Months	> 6–12 Months	> 12–24 Months	> 24 Months
Mean Duration of Exposure (days)	61	52	1080				
BUN (mg/dL)							
N[a]	974	598	384	714	680	630	573
Mean Value[b]	16.5	14.9	18.0	17.9	18.2	18.3	18.8
Mean Difference from Baseline	0.9	0.0	0.7	0.6	0.9	1.1	1.7
Creatinine (mg/dL)							
N[a]	976	599	384	714	680	630	573
Mean Value[b]	1.1	1.0	1.0	1.0	1.0	1.1	1.1
Mean Difference from Baseline	0.1	0.0	0.1	0.1	0.1	0.1	0.1

[a] Number of patients at baseline for Phase 2/3 ER controlled angina studies and the number of patients at each time point for open-label studies.

[b] Mean post-baseline value for Phase 2/3 ER controlled angina studies and the mean value at each time point for open-label studies.

Abstracted from Appendix V B Table E-1.3, Appendix VI B Table E-1.4, Appendix V H Table L-1.3, and Appendix VI H Table L-7.

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Table 38. Mean Changes from Baseline in Hematology Parameters in Phase 2/3 ER Controlled Angina Studies and Long-Term, Open-Label Studies

Laboratory Parameter	Phase 2/3 ER Controlled Angina Studies		Open-Label Studies				
			Ranolazine ER				
	Ranolazine ER	Placebo	> 6–12 Weeks	> 12 Weeks-6 Months	> 6–12 Months	> 12–24 Months	> 24 Months
Mean Duration of Exposure (Days)	61	52	1080				
Hemoglobin (g/dL)							
N[a]	928	580	377	691	674	626	567
Mean Value[b]	14.0	14.2	14.2	14.2	14.2	14.3	14.2
Mean Difference from Baseline	-0.5	-0.1	-0.5	-0.5	-0.5	-0.4	-0.5
Red Blood Cells ($10^6/\mu L$)							
N[a]	928	580	377	690	674	626	567
Mean Value[b]	4.5	4.6	4.6	4.6	4.6	4.6	4.6
Mean Difference from Baseline	-0.2	-0.0	-0.2	-0.2	-0.2	-0.2	-0.2
Hematocrit (%)							
N[a]	920	579	373	688	674	626	567
Mean Value[b]	41.5	42.0	42.0	42.1	41.8	42.2	42.4
Mean Difference from Baseline	-1.2	-0.0	-1.0	-0.7	-1.1	-0.8	-0.6
Eosinophils (%)							
N[a]	922	577	377	690	674	626	567
Mean Value[b]	2.8	2.6	2.5	2.3	2.5	2.4	2.4
Mean Difference from Baseline	0.2	0.1	-0.3	-0.3	-0.2	-0.2	-0.3
Lymphocytes (%)							
N[a]	926	580	377	690	673	626	567
Mean Value[b]	28.3	29.7	28.6	28.9	28.8	29.0	29.6
Mean Difference from Baseline	-1.5	-0.4	-0.7	-1.0	-1.0	-0.9	-0.5

[a] Number of patients at baseline for Phase 2/3 ER controlled angina studies and the number of patients at each time point for open-label studies.

[b] Mean post-baseline value for Phase 2/3 ER controlled angina studies and the mean value at each time point for open-label studies.

Abstracted from **Appendix V B Table E-1.3, Appendix VI B Table E-1.4, Appendix V H Table L-1.3,** and **Appendix VI H Table L-7.**

Table 39. Mean Changes from Baseline in Glucose and Lipid Metabolism Parameters: Phase 2/3 ER Controlled Angina Studies and Long-Term, Open-Label Studies

Laboratory Parameter	Phase 2/3 ER Controlled Angina		Open-Label Studies Ranolazine ER				
	Ranolazine ER	Placebo	> 6–12 Wks	> 12 Wks–6 Mos	> 6–12 Mos	> 12-24 Mos	> 24 Mos
Mean Duration of Exposure (days)	61	52	1080				
Serum Glucose (mg/dL)							
N[a]	961	590	379	707	679	630	568
Mean Value[b]	115.8	111.2	120.6	121.3	119.7	119.1	117.3
Mean Difference from Baseline	2.0	1.4	-2.4	-0.6	-1.6	-2.2	-3.6
HbA1c (%)							
N[a]	122	48	60	136	133	144	145
Mean Value[b]	6.9	7.2	6.9	7.0	7.0	6.8	6.7
Mean Difference from Baseline	-0.7	0.0	-0.5	-0.6	-0.6	-0.7	-0.8
Triglycerides (mg/dL)							
N[a]	698	320	384	447	656	625	561
Mean Value[b]	186.8	179.2	185.1	186.8	183.5	182.0	169.5
Mean Difference from Baseline	9.0	-1.8	5.4	12.8	2.2	0.8	-12.1
Total Cholesterol (mg/dL)							
N[a]	698	320	384	447	656	625	561
Mean Value[b]	217.4	209.0	221.6	215.8	217.8	214.8	210.1
Mean Difference from Baseline	10.1	-3.4	11.8	8.9	9.6	7.5	1.9

[a] Number of patients at baseline for Phase 2/3 ER controlled angina studies and the number of patients at each time point for open-label studies.

[b] Mean post-baseline value for Phase 2/3 ER controlled angina studies and mean value at each time point for open-label studies.

Abstracted from **Appendix V B Table E-1.3, Appendix VI B Table E-1.4, Appendix V H Table L-1.3,** and **Appendix VI H Table L-7.**

In the Phase 2/3 ER controlled angina studies, there were small mean increases from baseline (< 5 mg/dL) in HDL, LDL, and VLDL measurements in the ranolazine ER group (table not shown).

7.1.7.3.2. Analyses focused on outliers or shifts from normal to abnormal

Shift tables for BUN and creatinine are presented below. For both BUN and creatinine, an increase in the shift from baseline "normal" to endpoint "high" can be seen in ranolazine vs. placebo; the incidence appears to be particularly increased in doses of 1000 mg bid or greater.

Table 40. Shift Tables of BUN and Creatinine Values (at Baseline and Endpoint) by Dose: Phase 2/3 Controlled Ranolazine ER Studies

		Placebo	Ranolazine ER (mg)				Total Ranolazine
			500 BID	750 BID	1000 BID	1500 BID	
BUN (Urea Nitrogen) (mg/dL)							
Total N		578	41	262	576	55	933
Baseline	Endpoint						
Normal	Normal	477 (82.5)	37 (90.2)	228 (87.0)	469 (81.4)	45 (81.8)	778 (83.4)
	Low	0	0	0	0	0	0
	High	**28 (4.8)**	2 (4.9)	14 (5.3)	48 (8.3)	4 (7.3)	**68 (7.3)**
	Total	505 (87.4)	39 (95.1)	242 (92.4)	517 (89.8)	49 (89.1)	846 (90.7)
	Total	3 (0.5)	0	0	5 (0.9)	0	5 (0.5)
High	Normal	35 (6.1)	2 (4.9)	10 (3.8)	28 (4.9)	3 (5.5)	43 (4.6)
	Low	0	0	0	0	0	0
	High	35 (6.1)	0	10 (3.8)	26 (4.5)	3 (5.5)	39 (4.2)
	Total	70 (12.1)	2 (4.9)	20 (7.6)	54 (9.4)	6 (10.9)	82 (8.8)
Creatinine (mg/dL)							
Total N		579	41	263	578	55	936
Baseline	Endpoint						
Normal	Normal	465 (80.3)	38 (92.7)	219 (83.3)	431 (74.6)	44 (80.0)	732 (78.2)
	Low	5 (0.9)	0	0	2 (0.3)	0	2 (0.2)
	High	**30 (5.2)**	2 (4.9)	19 (7.2)	52 (9.0)	6 (10.9)	**78 (8.3)**
	Total	500 (86.4)	40 (97.6)	238 (90.5)	485 (83.9)	50 (90.9)	812 (86.8)
High	Normal	30 (5.2)	1 (2.4)	3 (1.1)	25 (4.3)	0	39 (3.1)
	Low	1 (0.2)	0	0	0	0	0
	High	38 (6.6)	0	22 (8.4)	53 (9.2)	5 (9.1)	80 (8.5)
	Total	69 (11.9)	1 (2.4)	25 (9.5)	78 (13.5)	5 (9.1)	109 (11.6)

Source: ISS, Appendix 5, Table L-8.3. Missing category was not presented because the results were uniformly "0"; there were few numbers in the "Low Baseline" category (not presented).

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

In the Phase 2/3 controlled ranolazine ER studies, there were two cases of discontinuation of study medication due to increased BUN (none in the placebo group). Both cases occurred with

higher doses of ranolazine: one case occurred in the ranolazine 1000 mg bid group and the other occurred in the 1500 mg bid group. Of the other laboratory-related discontinuations on ranolazine, 3 patients discontinued due to leukopenia, 3 patients had abnormal liver tests, and 2 patients discontinued ranolazine treatment due to anemia.
Laboratory-related serious adverse events in patients treated with ranolazine included: anemia (4 patients), hypoglycemia (2 patients), and single patients with leukopenia, hyperkalemia, hyponatremia, and increased BUN/creatinine.

In response to a request from the medical review, the sponsor provided the following data:

Table 41. Number and Proportion of Patients with On-Treatment Doubling of Creatinine compared to baseline (CVT 3031, CVT 3033, CVT 3037).

Number and Proportion of Patients with On-Treatment Serum Creatinine ≥ Twice Baseline
CVT 3031, CVT 3033 and CVT 3037
(Patients with Both Baseline and On-Treatment Serum Creatinine Values)

	Ranolazine ER				
Placebo (n=572)	500 mg BID (n=41)	750 mg BID (n=263)	1000 mg BID (n=575)	1500 mg BID (n=55)	All Ranolazine (n=933)
7 (1.2%)	0	0	2 (0.3%)	1 (1.8%)	3 (0.3%)

Source: S:\CVT-303\NDA_requests\ISSAmend_M1S\Table_Graph\TCRE2xBASE.rtf (29nov2005 15:05)

It should be noted that the sample size for 1500 mg bid is relatively small compared to placebo and 1000 mg bid. However, it is reassuring that the incidence of creatinine doubling for "all ranolazine" and "ranolazine 1000 mg bid" were less than the incidence on placebo.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital sign data were presented in the original safety review. In this updated safety review, vital sign data were added from CVT 3037 as well as the long-term open-label studies.

Please note that syncope and orthostatic hypotension were noted, particularly with doses of 1500 mg and 2000 mg, in the original safety review (see pages 25-26 of Dr. Gordon's safety review).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Overall drug-control comparisons can be best found in the Phase 2/3 controlled ranolazine ER studies. These studies will be presented in the next sections.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Table 42. Mean Change from Baseline to Endpoint in Pre-Exercise Standing Vital Sign Parameters at Peak by Dose (Phase 2/3 Controlled Angina Studies: CVT 3033 and CVT 3031)

Parameter	Placebo	Ranolazine ER (mg)				Total Ranolazine
		500 b.i.d.	750 b.i.d.	1000 b.i.d.	1500 b.i.d.	
Peak						
Systolic BP (mm Hg)						
N[a]	432	177	270	432	169	707
Mean Change from Baseline (SD)	-4.1 (15.9)	-5.3 (15.1)	-4.3 (14.8)	-6.2 (16.8)	-7.2 (15.3)	-6.1 (16.1)
Percent Change from Baseline	-2.3	-3.1	-2.6	-3.7	-4.5	-3.8
Diastolic BP (mm Hg)						
N[a]	432	177	270	432	169	707
Mean Change from Baseline (SD)	-0.8 (8.5)	-2.2 (8.6)	-3.4 (9.4)	-2.7 (9.1)	-2.7 (8.5)	-3.2 (9.3)
Percent Change from Baseline	-0.4	-2.1	-3.8	-2.7	-2.9	-3.5
Heart Rate (bpm)						
N[a]	432	177	270	434	169	707
Mean Change from Baseline (SD)	1.1 (11.9)	2.0 (11.4)	-0.8 (12.0)	-0.6 (11.0)	-0.7 (10.3)	-0.6 (11.6)
Percent Change from Baseline	2.9	3.8	0.4	0.5	0.4	0.6

[a] This refers to the number of patients with vital sign measurements at baseline. The number of patients with measurements at endpoint may have been slightly less.

Table 43. Mean Change from Baseline to Endpoint in Pre-Exercise Standing Vital Sign Parameters at Trough by Dose (Phase 2/3 Controlled Angina Studies: CVT 3033 and CVT 3031)

Parameter		Ranolazine ER (mg)				Tot Ranol
	Placebo	500 b.i.d.	750 b.i.d.	1000 b.i.d.	1500 b.i.d.	
			Trough			
Systolic BP (mm Hg)						
N[a]	724	177	272	721	171	99
Mean Change from Baseline (SD)	-0.5 (13.7)	-3.1 (14.8)	1.7 (15.7)	-1.7 (14.8)	-2.9 (17.3)	-0.9 (1
Percent Change from Baseline	0.1	-1.7	(2.1)	-0.5	-1.4	0.
Diastolic BP (mm Hg)						
N[a]	724	177	272	721	171	99
Mean Change Baseline (SD)	0.2 (8.6)	-0.4 (8.7)	0.5 (8.0)	-0.2 (8.7)	-0.2 (8.2)	-0.1 (
Percent Change from Baseline	0.9	0.3	1.2	0.3	0.2	0.
Heart Rate (bpm)						
N[a]	726	177	272	723	171	99
Mean Change from Baseline (SD)	-0.7 (11.4)	-0.8 (11.1)	-1.5 (11.9)	-1.5 (11.0)	-3.6 (11.4)	-1.6 (1
Percent Change from Baseline	0.4	0.1	-0.3	-0.8	-3.1	-0.

[a] This refers to the number of patients with vital sign measurements at baseline. The number of patients with measurements at endpoi have been slightly less.

Abstracted from **Appendix V I Table M-1.3.1.**

Table 44. Mean Change in Vital Sign Parameters from Baseline to Last Measurement in the Double-Blind Treatment Phase of CVT 3037

Parameter	Mean Change from Baseline (± SD) at the End of the 6-Week Double-Blind Treatment Phase	
	Placebo (N = 281)	Ranolazine (N = 278)
Supine Measurements[a]		
Systolic BP (mm Hg)	-1.7 (± 10.7)	-2.0 (± 10.0)
Diastolic BP (mm Hg)	-0.6 (± 7.6)	-1.0 (± 7.0)
Heart rate (bpm)	-1.6 (± 9.0)	-2.0 (± 9.2)
Standing Measurements[b]		
Systolic BP (mm Hg)	-1.8 (± 11.6)	-2.9 (± 10.9)
Diastolic BP (mm Hg)	-0.6 (± 7.9)	-0.6 (± 7.2)
Heart rate (bpm)	-1.1 (± 8.7)	-1.8 (± 9.7)
Postural Changes[c]		
Systolic BP (mm Hg)	-0.1 (± 7.2)	-0.9 (± 7.7)
Diastolic BP (mm Hg)	0.0 (± 6.2)	0.4 (± 5.9)
Heart rate (bpm)	0.6 (± 4.4)	0.2 (± 4.0)

[a] Abstracted from Section 14.8.2, CSR CVT 3037 Item 8 Section 8.16.1.

[b] Abstracted from Section 14.8.3, CSR CVT 3037 Item 8 Section 8.16.1.

[c] Abstracted from Section 14.8.4, CSR CVT 3037 Item 8 Section 8.16.1.

7.1.8.4 Additional analyses and explorations

As seen in the next table, the small mean decreases from baseline in systolic and diastolic blood pressure and heart rate appear to be maintained in the long-term open-label studies. The mean decrease in heart rate appears to be slightly increased over the long-term studies.

Table 45. Mean Changes from Baseline to Last Standing Vital Sign Measurement on Treatment in the Phase 2/3 ER Controlled and Long-Term, open-Label Studies

Parameter	Phase 2/3 ER Controlled Studies		Open-Label Studies Ranolazine	
	Ranolazine	Placebo	> 12–24 Months	> 24 Mont
	Trough			
Systolic BP (mm Hg)				
N	997	724	628	562
Mean Change from Baseline (SD)	-0.9 (15.5)	-0.5 (13.7)	-0.3 (15.9)	-0.7 (16.8
Percent Change from Baseline	0.1	0.1	0.9	0.7
Diastolic BP (mm Hg)				
N	997	724	628	562
Mean Change from Baseline (SD)	-0.1 (8.6)	0.2 (8.6)	-0.3 (8.9)	-0.7 (9.3
Percent Change from Baseline	0.5	0.9	0.6	0.1
Heart Rate (bpm)				
N	998	726	628	562
Mean Change from Baseline (SD)	-1.6 (11.3)	-0.7 (11.4)	-3.8 (13.1)	-4.0 (13.6
Percent Change from Baseline	-0.7	0.4	-2.6	-2.7

[a] Data provided in original ISS.
Abstracted from **Appendix V I Table M-1.3.1** and **Appendix VI I Table M-7.1.**

7.1.9 Electrocardiograms (ECGs)

ECG data were not routinely collected in CVT 3037 (one ranolazine patient was reported to have "mild QT prolongation" as an adverse event but completed the study); therefore, data from the Phase 2/3 ER controlled angina studies reported in the original submission/ISS are unchanged.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

As this is a resubmission, please see the original safety review for further details.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The only new ECG data are derived from long-term open-label studies (see next table). The analysis of QTc from these studies utilized the longest QT/QTc lead from any lead of a 12-lead ECG. The mean changes from baseline were only performed with Bazett's formula, and were not correlated with peak/trough measurements, compliance with medication or concomitant therapies.

7.1.9.3 Standard analyses and explorations of ECG data

Please see the original safety review for standard analyses of ECG data.

7.1.9.4 Additional analyses and explorations

As seen below, there appears to be an increased incidence of outliers (patients with ≥ 60 msec increase from baseline in QTc or patients with QTc > 500 msec) in patients treated with higher doses of ranolazine (≥ 1000 mg bid). This finding is consistent with previous findings of a concentration-related increase in QT.

Table 46. Summary of Bazett QTc Outliers by Treatment in CVT 3031, CVT 3032, CVT3033, and CVT 3034.

Treatment	Number of Patients Treated	Number (%) of Patients with a QTc Increase ≥ 60 msec from Baseline	Number (%) of Patients with a QTc > 500 msec	Number (%) of Patients with Either[a]	Number (%) of Patients with Both[b]
Placebo	436	7 (1.6)	7 (1.6)	11 (2.5)	3 (0.7)
Placebo (Rebound Phase)	245	0	1 (0.4)	1 (0.4)	0
Ranolazine 500 mg b.i.d.	698	15 (2.1)	13 (1.9)	21 (3.0)	7 (1.0)
Ranolazine 750 mg b.i.d.	727	18 (2.5)	8 (1.1)	21 (2.9)	5 (0.7)
Ranolazine 1000 mg b.i.d.	654	29 (4.4)	25 (3.8)	44 (6.7)	10 (1.5)
Ranolazine 1500 mg b.i.d.	173	12 (6.9)	13 (7.5)	21 (12.1)	4 (2.3)
Off-Treatment	119	0	0	0	0

Abstracted from **Appendix VII F Table N-35.1**.

7.1.10 Immunogenicity

No new studies of immunogenicity were submitted.

7.1.11 Human Carcinogenicity

The conventional studies submitted with the IND for ranolazine did not show evidence of carcinogenic potential.

7.1.12 Special Safety Studies

As ranolazine has already demonstrated a linear relationship between plasma levels and QTc, no thorough QT study was requested.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Study CVT 3033 included, as part of the study design, a 48 hour rebound assessment period. During this period, patients on ranolazine at the end of the 12 week treatment period were randomized, in a double-blind procedure, to either continue their blinded ranolazine treatment or receive matching placebo for a 48 hour period. At the end of 48 hours, these patients underwent an ETT at trough.
As noted in the original CVT 3033 individual study review, differences in the change from baselinein ETT duration at trough were seen between Ran 1000/placebo vs. Ran 1000/Ran 1000 group (ITT and evaluable populations). However, no significant differences were seen between either Ran/placebo group vs. placebo/placebo. In addition, there were no reports of worsening angina. No patients terminated the study during this period.
These results appear consistent with a marginally significant treatment effect in the Ran 1000/placebo vs. Ran 1000/Ran 1000 group and support the sponsor's claim of maintenance of efficacy after 12 weeks of treatment, lack of tolerance and lack of demonstrated rebound effects.

7.1.14 Human Reproduction and Pregnancy Data:

There is no information concerning ranolazine use in preganacy.

7.1.15 Assessment of Effect on Growth:

This section is not applicable since ranolazine has not been studied in children.

7.1.16 Overdose Experience

There has been no reported overdose experience with ranolazine.

7.1.17 Postmarketing Experience

This section is not applicable since ranolazine is not marketed in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

In the resubmission, more patients have been exposed to ranolazine (both in terms of placebo-controlled short-term studies as well as long-term, open-label exposure).
According to the ICH (E1), the recommended exposure for a chronic-use drug includes 1500 total subjects exposed, including 300-600 subjects for 6 months and a minimum of 100 subjects for one year. In this submission, a total of 3106 subjects/patients were exposed to ranolazine in

the ISS database; 925 subjects/patients were exposed to ranolazine for > 6 months, 832 subjects/patients were exposed to ranolazine for > 12 months, and 391 subjects/patients were exposed to ranolazine for > 36 months. The Phase 2/3 controlled ranolazine ER exposed 1,030 subjects/patients to short-term ranolazine treatment.
Therefore, the ranolazine exposure in the resubmission appears to have been adequate. Please see section 7.2.1.3. for additional details.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The main data source for this review was the ranolazine development program. This review has referred to the original ranolazine safety review (Dr. Maryann Gordon; 7/30/03). According to the original safety review, the sponsor performed 81 studies (including older studies by Syntex) to support efficacy and safety of ranolazine. Sixty-four of those studies were included in the original ISS database; seventeen studies (16 early, low-dose studies and one bioequivalence study, CVT 301-15) were not integrated into the database. In the resubmission, the sponsor has updated the ISS database to include 3,626 patients/subjects in 68 studies (adding CVT 301-15, CVT 301-16, CVT 3037 and CVT 3112). In this update, the overall clinical development program for ranolazine has consisted of 3,930 subjects/patients in 84 studies. The overall program included studies of extended release (ER), immediate release (IR) and intravenous (IV) formulations.

Table 47. Number of Subjects/Patients in the Ranolazine Development Program

Category	Number of Subjects/Patients*					
	Ranolazine Formulation			Total number exposed		
	IR	ER	IV	Ranolazine	Placebo	Total
ISS database (68 studies)**	1299	1759	101	3106	1829	3626
16 early studies¶	86	0	151	237	159	304
Total of all ranolazine-treated patients/subjects	1385	1759	252	3343	1988	3930

*Number who received at least one dose of study drug. For studies with a crossover design, subjects/patients were only counted once in the overall total number of subject/patient column.
**Four additional studies (CVT 3037, CVT 301-15, CVT 301-16 and CVT 3112) were integrated into the updated ISS database.
¶Per the original NDA submission, these studies were not integrated into the original or updated ISS database.

7.2.1.1 Study type and design/patient enumeration

Table 48. Studies Completed and Ongoing since the Original ISS

Study/Phase	Number of patients enrolled/treated	Study Title
Completed studies		
CVT 3037/Phase 3	565/564	A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group study of Ranolazine SR at a Dose of 1000 mg Twice a Day in patients with Chronic Angina Who Remain Symptomatic Despite Treatment with Amloidipine 10 mg Once a Day
CVT 301-16/Phase 1	18/17	A Study to Investigate the Renal Effects of Ranolazine in Healthy Male Subjects
Ongoing studies		
CVT 3032/Phase 3	143/143	A Phase 3, Open-Label, Long-Term, Safety study of Ranolazine ER for Chronic Stable Angina Pectoris at Doses of 750 mg and 1000 mg bid
CVT 3034/Phase 3	603/603	A Phase 3, Open-Label, Long-term, Safety Study of Ranolazine ER for Chronic Stable Angina Pectoris at Doses of 500 mg, 750 mg, and 1000 mg Twice a Day Administered in Combination With Background Anti-Anginal Therapy

In addition, the clinical pharmacology study CVT 301-15 was separately reported in the original ISS and is now integrated into the ISS database.

The 68 studies in the ISS database included:

- Twelve randomized, placebo-controlled studies in patients with chronic angina:
  - RAN 015, RAN 020, RAN 054, RAN 072, RAN 080, RAN 1490, RAN 1513, RAN 1514, RAN 2240, CVT 3031, CVT 3033 and CVT 3037;
- Five uncontrolled, long-term follow-up studies in patients with chronic angina;
  - RAN 081, RAN 1515, RAN 2074, RAN 3032, CVT 3032, CVT 3034 (extension studies for RAN 080, RAN 1513, RAN 1514, CVT 3031 and CVT 3033, respectively);
- Two studies (1 controlled and 1 uncontrolled) in patients with CHF:
  - CVT 3021 and RAN 075;
- Two controlled studies in patients with intermittent claudication:
  - RAN 2302 and RAN 2320;
- Forty-seven clinical pharmacology studies:
  - One controlled pharmacokinetic (PK) study in patients with renal impairment and matched healthy subjects (CVT 3016); one controlled PK study in patients with hepatic impairment and healthy subjects (CVT 3018);
  - RAN 009, RAN 013, RAN 017, RAN 019, RAN 021, RAN 023, RAN 032, RAN 051, RAN 053, RAN 058, RAN 059, RAN 061, RAN 063, RAN 064,

RAN 066, RAN 067, RAN 068, RAN 069, RAN 090, RAN 0102, RAN 0103, RAN 0110, RAN 0111, RAN 0112, RAN 0113, RAN 0114, RAN 0117, RAN 0121, RAN 0122, RAN 0201, CVT 301-10, CVT 301-11, CVT 301-13, CVT 301-14, CVT 301-15, CVT 301-16, CVT 3011, CVT 3012, CVT 3013, CVT 3014, CVT 3015, CVT 3017, CVT 3019, CVT 3111, and CVT 3112.

For further details concerning individual studies, please see the current and original reviews.

In this resubmission, the following populations were analyzed:

Controlled studies:

1. Phase 2/3 IR and ER controlled angina studies (12 randomized placebo-controlled studies: RAN 015, RAN 020, RAN 054, RAN 072, RAN 080, RAN 1490, RAN 1513, RAN 1514, RAN 2240, CVT 3031, CVT 3033, CVT 3037) (Total number of patients: 2,667).

2. Phase 2/3 ER controlled angina studies: (CVT 3031, CVT 3033, CVT 3037 and RAN 2240). RAN 2240, which was discontinued due to low enrollment, randomized a total 11 patients (4 on ranolazine and 7 on placebo); thus, the majority of patients in this database were derived from CVT 3031, CVT 3033, and CVT 3037 (Total number of patients: 1,589).

Long-term Open-Label studies: In these analysis sets, patients had to have been treated in both the controlled and long-term open-label studies:

1. Phase 2/3 IR and ER controlled angina studies and long-term open-label follow-up: (RAN 080, RAN 1513, RAN 1514, CVT 3031 and CVT 3033, RAN 081, RAN 1515, RAN 2074, CVT 3032 and CVT 3034) (Total number of patients: 1,008).
2. Phase 2/3 ER controlled angina studies and long-term open-label follow-up: CVT 3031 and CVT 3032, CVT 3033 and CVT 3034 (Total number of patients: 746).

7.2.1.2 Demographics:

In the Phase 2/3 ranolazine ER program, as well as the ISS database, there were no gross imbalances between ranolazine and placebo-treated patients. In the Phase 2/3 ranolazine ER program, the study population was about 75-76% male and 96-97% Caucasian; the mean age was about 63-64 years and about 48% were at least 65 years old.

One hundred percent of patients had coronary disease. About 63-65% had a history of previous MI, about 75% had a history of unstable angina, about 21-22% were diabetic, about 33% had a CHF history, 5-6% had a history of valvular heart disease, 12% had ventricular arrhythmias, 70-74% had hypertension, 4-5% had a prior stroke, and 19% had prior angioplasty.

In the ISS database (which included healthy subjects), the population was younger (mean age 56-57 years, and about 35% 65 and older) with less CHF (16%), diabetes (14-15%), and previous

MI (40-47%). The ISS population was also primarily a male (78-80%) and Caucasian (87-89%) population.

7.2.1.3 Extent of exposure (dose/duration)

A summary of exposure is listed in the two following tables. During the development program, individual patient exposure to ranolazine ranged from a single dose to dosing for at least 3 years. Doses ranged from 10-2000 mg bid; according to the sponsor, total exposure to ranolazine in the ISS database population represents 2,710 subject/patient years of exposure.

Table 49. Extent of Exposure for Patients in Phase 2/3 ER controlled Angina Studies by Dose

Category	Number (%) of Subjects/Patients*					
	Ranolazine ER (bid)					Placebo (N=738)
	500 mg (N=181)	750 mg (N=279	1000 mg (N=740)	1500 mg (N=187)	Total ER (N=1030)	
< 7 days	8 (4.4)	4 (1.4)	15 (2.0)	19 (10.2)	13 (1.3)	19 (2.6)
7-13 days	170 (93.9)	1 (0.4)	188 (25.4)	165 (88.2)	28 (2.7)	169 (22.9)
14-27 days	3 (1.7)	8 (2.9)	13. (1.8)	3 (1.6)	188 (18.3)	18 (2.4)
28-41 days	0	4 (1.4)	3 (0.4)	0	18 (1.7)	1 (0.1)
42-55 days	0	3 (1.1)	229 (30.9)	0	232 (22.5)	229 (31.0)
56-83 days	0	45 (16.1)	99 (13.4)	0	144 (14.0)	79 (10.7)
> 84 days**	0	214 (76.7)	193 (26.1)	0	407 (39.5)	223 (30.2)
Average duration (days)	8	82	51	8	61	52

*This is not a cumulative count. A patient was only counted in the cell corresponding to the longest period of exposure and not counted in other cells.
** Maximum period of exposure for any patient in CVT 3033 and RAN 2240 was 103 days.

The average duration of exposure for ranolazine ER and placebo was 61 and 52 day, respectively.

Table 50. Exposure for all treated Subjects/patients—ISS database

	Number (%) of Subjects/Patients *	
Exposure	Total Ranolazine (N=3106)	Total Placebo (N=1829)
0-1 week	679 (21.9)	469 (25.6)
>1-2 weeks	270 (8.7)	504 (27.6)
>2-3 weeks	76 (2.4)	78 (4.3)
> 3-4 weeks	172 (5.5)	60 (3.3)
> 4-6 weeks	416 (13.4)	179 (9.8)

>6-12 weeks	458 (14.7)	332 (18.2)
> 12 weeks-6 months	110 (3.5)	207 (11.3)
> 6-12 months	93 (3.0)	0
>12-24 months	220 (7.1)	0
>24-36 months	221 (7.1)	0
>36 months	391 (12.6)	0
Average duration (days)	319	28

*This is not a cumulative count. A patient was only counted in the cell corresponding to the longest period of exposure and was not counted in any other cells.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There are few secondary sources of information, since ranolazine is not currently marketed. Other than the article cited by the pharmacology/toxicology review, a literature search did not find other safety issues.

7.2.2.1 Other studies

CVT 3036 (TIMI 36 or MERLIN) is an ongoing ranolazine study; safety data will be submitted as part of a safety review.

7.2.2.2 Postmarketing experience

This section is not applicable since ranolazine is not marketed anywhere in the world.

7.2.2.3 Literature

A Pubmed search of ranolazine did not reveal new safety concerns that have not been already referenced.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience is limited by inadequate numbers of non-Caucasian patient/subject exposure to ranolazine, and by inadequate exploration of the drug's effects in women. In addition, the sponsor has not conducted further explorations of dose-response.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The sponsor's attempts to discern mechanism of action appear to have been limited; please see Dr. Hausner's review for further details. In addition, the sponsor's response to the Suckow article (please see the pharmacology/toxicology review) appears to have been inadequate.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing appears to have been adequate in the development program.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The metabolic, clearance and interaction workup appear to be adequate. Please see the original reviews for further details.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Since this drug appears to be in a new class, it is difficult to complete this section.

7.2.8 Assessment of Quality and Completeness of Data

The data appear to be adequate.

7.2.9 Additional Submissions, Including Safety Update

According to the sponsor, they will be submitting a second safety update; however, this update is not available in a timely manner at the time of this review. A review of the safety update will be submitted separately.
A review of IND #43,735 reviews (Division File System) reveals three cases of renal failure from ongoing studies; these patients had multiple medical conditions and were taking concomitant medications (reviewed by Dr. Marciniak).

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

For a summary and conclusions, please see section 7.1.

7.4 General Methodology

For safety assessment, this review concentrated on the combined placebo-controlled studies; however, where applicable, the review also considered long-term open-label studies as well as the entire ISS database.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

For the safety assessment and comparisons with background rates, this review concentrated on the combined placebo-controlled studies; however, where applicable, the review also considered

long-term open-label studies as well as the entire ISS database. Since this NDA was a resubmission, this review also considered the prior safety review.

7.4.2 Explorations for Predictive Factors

Please see sections 7.1.5.5., 7.1.7.3.1., 7.1.7.3.2., 7.1.8.3. for explorations of dose dependency and time dependency. Section 7.1.5.6 contains subgroup analyses that explore potential drug-disease and drug-demographic interactions.

7.4.3 Causality Determination

Causality determination was made by evaluating incidence on drug compared to placebo, as well as analyzing relationship to dose/concentration.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Additional exploration of dose-response, recommended at the time of the approvable action, has not been submitted at this time and remains an outstanding issue.

8.2 Drug-Drug Interactions

No additional formal drug interaction studies have been conducted.

8.3 Special Populations

As this is a resubmission, no new studies have been conducted in patients with renal or hepatic disease.
There have been inadequate numbers of non-Caucasians to allow for exploration of efficacy or safety. In addition, statistically significant treatment effects have not been demonstrated in the female population.
Please see the original and current review (efficacy and safety reviews) for further information.

8.4 Pediatrics

In a letter from the Agency dated August 31, 2001, the sponsor was granted a pediatric waiver for ranolazine for all pediatric age groups.

8.5 Advisory Committee Meeting

No additional advisory committee meeting is planned at the present time.

8.6 Literature Review

A Pubmed search of ranolazine has revealed no new issues that have not been referenced elsewhere.

8.7 Postmarketing Risk Management Plan

No postmarketing risk management plan has been submitted.

8.8 Other Relevant Materials

A consultation by the Study Endpoints And Label Development Team evaluated the Seattle Angina Questionnaire (CVT 3037) and felt that this questionnaire was not adequate to support labeling claims.

9 OVERALL ASSESSMENT

9.1 Conclusions

The medical review concludes, based on the results of CVT 3033, CVT 3031 and CVT 3037, that ranolazine has demonstrated a modest effect on symptoms and exercise duration; thus far there are no data to show effects on cardiovascular outcomes (e.g., MI, death). In this resubmission, the sponsor has demonstrated a treatment effect in a patient population receiving amlodipine and (about half of the study population) nitrates. A safety update from the sponsor, dated November 21, 2005, will be reviewed separately.

Outstanding issues with regard to ranolazine include: 1. resolution of the question of tumor promotion raised in the pharmacology/toxicology review (to be discussed below); 2. ranolazine's effect on cardiac repolarization; 3. exploration of ranolazine effects in females; 4. further exploration of dose-response, including evaluation of doses below 500 mg bid; 5. further understanding of the mechanism of action of ranolazine.

Issues raised by the OCPB reviewer include: 1. marketing ranolazine in one strength only, the non-scored 500 mg tablet, limiting the capability of adjusting the dose; 2. deletion of the 12 hour value in the dissolution specifications; 3. failure of study 301-16 to definitively delineate the mechanism responsible for serum creatinine elevation in the presence of ranolazine.

The question of tumor promotion, raised by the pharmacology/toxicology reviewer, is based on a publication by Suckow et. al. Standard carcinogenicity testing was negative and there does not appear to be evidence that ranolazine causes tumors.

There is some biological plausibility that ranolazine might facilitate tumor growth. If one expects that ranolazine might lead to more efficient energy production in hypoxic myocardial tissue, there might also be an "unintended consequence" of promoting more efficient energy production in hypoxic tumors. However, there is also some uncertainty here; the Suckow

method involved one animal species and has not been reproduced in other species or other systems. The sponsor has not attempted to replicate the published study (or show that the results are not reproducible). This reviewer is analyzing the clinical program for incidences of cancer; however, lack of a signal in the clinical program may not be meaningful as the long-term ranolazine exposure may not have included enough cancer patients and did not include a background rate for comparison.

As already noted, the Agency has already stated that further dose exploration is not needed if efficacy were demonstrated in CVT 3037 (e.g., a "resistant population" or population with angina despite treatment).

With respect to two other known issues, the drug's effect on repolarization and pharmacokinetic/drug interactions, the situation remains the same as in the previous review.

From this reviewer's perspective, the regulatory options are, therefore, the following: 1. approval with information on repolarization and the question of tumor promotion clearly communicated to patients and health care providers; 2. "approvable" action, asking the sponsor to show that results from the Suckow article are not reproducible.

The reviewer recognizes that there may be a population with severe coronary disease and symptoms despite maximal or maximum tolerated medical therapy; for various reasons (coronary artery anatomy, comorbidities, poor medical condition), these patients may not be candidates for coronary bypass or percutaneous coronary intervention. For these patients, there is a possibility that ranolazine might provide some symptomatic relief.

9.2 Recommendation on Regulatory Action

1. It is recommended that ranolazine be approvable for symptomatic treatment of angina in patients with chronic stable angina and inadequate relief despite maximal treatment with other anti-anginal medications. In order to be approved, the sponsor should address the lingering question of whether ranolazine is a tumor promoter. If ranolazine is approved, with the other safety issue, ranolazine's concentration-related QT prolongation, and the availability of other treatments without effects on repolarization, ranolazine should not be a first-line drug for angina.
2. If ranolazine were to be approved, this reviewer recommends a "black box" warning regarding QT prolongation. This drug should not be directly marketed to consumers.
3. If ranolazine were to be approved, instructions for use will need to take into account ranolazine's interactions with verapamil and diltiazem, as well as the inter-subject variability. In addition, the smaller treatment effect in women and safety profile in the elderly should receive mention in labeling.
4. Ttreatment effect in women and safety profile in the elderly should receive mention in labeling.

9.3 Recommendation on Postmarketing Actions

Until the sponsor convinces the Agency otherwise, the sponsor should adequately explore the question of tumor promotion raised in the Suckow article.
The sponsor should explore efficacy in women in an adequate, well-controlled study in females with coronary artery disease. In addition, the sponsor should be encouraged to explore tolerability of ranolazine in the elderly population.

9.3.1 Risk Management Activity

No risk management plan has been submitted. The sponsor should consider a risk management plan for ECG monitoring for QT changes.

9.3.2 Required Phase 4 Commitments

There are currently no required Phase 4 commitments.

9.4 Labeling Review

Please see the line-by-line labeling review for specific recommendations.
This reviewer has recommended:

1. Adding a "black box" warning concerning QT prolongation.
2. Adding specific events and incidences of commonly reported adverse events to the Geriatric section.
3. Deleting any reference to ranolazine lowering hemoglobin A1c. In the absence of an evaluation of the drug's effect on glucose metabolism and diabetes, the notion that ranolazine might improve hemoglobin A1c has not been proven.
4. Changed the analysis of CVT 3037 to show medians (rather than "trimmed means").

9.5 Comments to Applicant

The recommendations in section 9.3 should be conveyed to the applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

Medical-Statistical Review of Study CVT 3037:
Medical reviewer: Shari L. Targum, M.D.
Statistical reviewer: Valeria Freidlin, Ph.D.

Title: A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of Ranolazine SR at a Dose of 1000 mg Twice a Day in Patients with Chronic Angina Who Remain Symptomatic Despite Treatment with Amlodipine 10 mg Once a Day (protocol date: February 27, 2004; study initiated July 30, 2005 and completed February 16, 2005)

Primary Objective: Determine the effect of ranolazine SR 1000 mg twice daily compared to placebo on angina frequency during 6 weeks of double-blind dosing in patients with chronic angina who remain symptomatic despite treatment with amlodipine 10 mg daily.

The primary efficacy variable was the average weekly frequency of patient-reported angina episodes during the 6 week double-blind treatment phase dosing with ranolazine or placebo.

Secondary objectives:

1. Determine effect of ranolazine, compared to placebo, on nitroglycerin consumption.
2. Determine effect of ranolazine, compared to placebo, via the Seattle Angina Questionnaire (SAQ).
3. Assess safety and tolerability of ranolazine.

Study Design: This was a double-blind, randomized, placebo-controlled, parallel group study of ranolazine SR 1000 mg bid vs. placebo in patients with angina who remained symptomatic despite treatment with amlodipine 10 mg daily. Prior to study entry, patients were required to have been treated with amlodipine 10 mg daily for at least 14 days, with the discontinuation of other anti-anginal therapy (except for long-acting nitrates and sublingual nitroglycerin as needed for angina attacks) at least 5 days prior to the screening visit (visit 1). In the first phase of the study, patients were given treatment consisting of amlodipine 10 mg daily and single-blind placebo twice daily. Patients reporting an average weekly rate of ≥ 3 angina attacks (total number of angina attacks/number of weeks) during this period qualified for randomization (visit 2).

In the second phase of the study, eligible patients continued to receive amlodipine 10 mg daily, and were randomized to receive either ranolazine 500 mg or placebo twice daily for one week (double-blind initial phase). Patients completing this one week initial phase of double-blind treatment (visit 3) then entered the third phase (visits 4, 5), a 6 week treatment phase where, in addition to the amlodipine, the patients on ranolazine were up-titrated to receive ranolazine 1000 mg bid (in a blinded manner).
(Reviewer: this study did not include stress testing).

Relevant Inclusion criteria: Patients were at least 18 years old, with at least 3 months documented history of effort-induced angina relieved by rest and/or sublingual nitroglycerin, and a with a diagnosis of coronary artery disease documented by $\geq$ 60% stenosis (by angiogram) in at least one major coronary artery, or history of documented MI, or cardiac imaging study diagnostic of coronary artery disease.

Relevant Exclusion criteria: NYHA Class IV CHF; MI or unstable angina within the past 2 months; 2nd or 3rd degree AV block in the absence of a functioning ventricular pacemaker or uncontrolled clinically significant arrhythmias; acute myocarditis/pericarditis; hypertrophic cardiomyopathy; uncontrolled hypertension; history of torsades de pointes (TdP); QTc > 500 msec at the screening visit; need for prohibited concomitant medication; significant hepatic disease or creatinine clearance < 30 mL/min.

Prohibited Concomitant Medications/Food:

1. Anti-anginal medications other than amlodipine 10 mg daily and sublingual nitroglycerin as needed to relief acute angina; long-acting nitrates were not allowed in the original protocol, but this was changed in the first protocol amendment; beta-blockers and calcium channel blockers (other than amlodipine) were not allowed;
2. Medications known to prolong the QTc interval;
3. Medications affecting cytochrome P450 3A4;
4. Digoxin;
5. Consumption of > 1 L/daily of grapefruit/grapefruit juice;
6. Agents known to inhibit fatty acid oxidation (e.g., perhexiline and trimetazidine).

Allowed concomitant Medications:

1. Sublingual nitroglycerin for the treatment of acute angina (prophylactic use of sublingual nitroglycerin was not allowed); **long-acting nitrates were allowed in a protocol amendment.**
2. Stable doses of anti-hypertensive medication, including diuretics and ACE inhibitors;
3. Aspirin;
4. Statins;

Assessments:

1. 12-lead ECGs (visits 1, 2, 3, 4, and 5). If the patient's QTc interval widened to $\geq$ 130% of baseline (visit 2) duration and was longer than 500 msec, that patient was withdrawn from the study and monitored until the QTc returned to baseline.
2. At Visits 1, 2, 3, 4, and 5 supine and standing BP and pulse rates were measured.
3. Angina frequency and nitroglycerin use were recorded by the patient throughout the study.
4. Laboratory testing, including CBC and chemistry panel, was done at Screening (visit 1) and study completion (visit 5)
5. The Seattle Angina Questionnaire (SAQ) quantifies five clinically relevant dimensions of coronary artery disease: physical limitation, anginal stability, angina frequency, treatment satisfaction, and disease perception. Scale scores are transformed to a range of 0-100,

where higher scores indicate better function, less angina, and higher quality of life. The SAQ was administered at Visits 0 or 1, Visit 2 and Visit 5.

6. Adverse events were recorded throughout the study.

Criteria for Withdrawal:

Serious adverse event; Gross non-compliance; Patient's health being jeopardized by continued participation; QTc widening to $\geq$ 130% of baseline duration and longer than 500 msec; Unsatisfactory therapeutic response; Patient electing to withdraw; Sponsor electing to end the study.

Statistical Analysis Plan:

The primary efficacy variable was each patient's average weekly rate of angina attacks during the 6-week double-blind treatment phase during which the treatments were ranolazine 1000 mg bid and placebo. Secondary efficacy variables were: 1. each patient's average weekly rate of nitroglycerin consumption during the 6-week double-blind Treatment Phase, and 2. the patient's score for each of the five dimensions of the SAQ score at the end of the 6-week double-blind Treatment Phase10.

In the protocol, the planned primary efficacy analysis was to compare the primary efficacy variable between ranolazine and placebo groups using the Cochran-Mantel-Haenszel (CMH) test of mean scores, using the actual angina attack rates as the scores, and stratifying by pooled center. The centers were to be pooled by geographic region using an algorithm determined before database lock and unblinding.

The primary analysis used the full analysis set (FAS) of all patients who received at least one dose of study medication in the double-blind Treatment Phase and who recorded angina diary data in this phase of the study. The average weekly rate of angina attacks for patients who did not complete the 6-week Treatment Phase was calculated based on the available weeks and partial weeks of diary data. Nitroglycerin consumption was analyzed using the same statistical methods as the primary endpoint. For the SAQ, each of the five dimensions was scored on a scale from 0 to 100. For each dimension, the change in score from baseline to the end of the 6-week Treatment Phase was compared between treatment groups using an analysis of covariance model with effects for treatment, pooled center, and baseline score. The visit 2 score (assessment before randomization) was used as the baseline.

All hypothesis testing was done using a two-sided test at the 5% level of significance. The null hypothesis was that there is no difference between treatment groups. A sample size of at least 450 patients in the full analysis set (225 per group) gave 95% power to detect a reduction of 1.0 in the average weekly angina attack rate relative to placebo in the primary efficacy analysis, assuming an exponential distribution and placebo attack rate of 3.3 attacks/week.

(Reviewer: This study was reviewed as a Special Protocol Assessment by Drs. Marciniak (medical officer) and Freidlin (statistical reviewer).

Protocol Amendments:

1. (May 13, 1994):

10 In the study report, the SAQ was mentioned as an exploratory analysis since it was not validated in Eastern Europe, the source for the majority of the study population.

a. Allowed the use of long-acting nitrates (LAN) in the form of a patch or isosorbide mononitrate;
b. Extended the duration of the study from about 13 to up to 18 weeks, including the addition of a repeat Visit 1 for patients using a LAN;
c. Modified exclusion criteria for end stage renal disease to specify "requiring dialysis;"
d. Specified that patients should take amlodipine at the same time of day throughout the study;
e. Added collection of the time of day of angina episodes;
f. Specified additional analyses of angina frequency, nitroglycerin use and SAQ scores by geographic region;
g. Specified that two original 12-lead ECGs should be printed out for every ECG performed;
h. Included the requirement of ECG submission to the sponsor for any ECGs collected as part of the cardiovascular adverse events
i. Added serum pregnancy tests to Visits 2-5;
j. Changed the dispensing for amlodipine;

2. Amendment 2 (October 26, 2004):
   a. Updated the Seattle Angina Questionnaire with a version available from the developer (JA Spertus).

Changes to the Planned Analyses:
The original statistical analysis plan was completed on November 3, 2004. On February 9, 2005 the analysis plan was amended to add specific criteria to determine when the SAQ dimensions would be analyzed by non-parametric methods instead of the planned ANCOVA. Also added was a sensitivity assessment of the primary efficacy analysis with regard to missing angina diary data due to early terminations. The method of pooling study centers was also modified for low-enrolling regions.

According to the sponsor, in March, 2005, during a blinded review of accumulating data, a few isolated outlying data points were noted in the angina diary data, representing average weekly angina rates that were substantially higher than in other patients. In order to reduce the influence of these outlying data points, the statistical analysis plan was amended on March 18, 2005, changing the scoring method in the CMH row mean scores test to use rank-based (modified ridit) scores **(These changes were reviewed by the Agency)**. In addition, the sponsor added a "trimmed mean statistic" and its standard error to the suite of summary statistics in the plan (median, 25th percentile, 75th percentile, mean and standard error, minimum and maximum). The trimmed mean was to be calculated as the average of the observations up to the 98th percentile within each treatment group (trimming the top 2% of the observations). **(The Agency did not use trimmed means.)** The study database was locked on April 13, 2005 and the study unblinded on April 14, 2005.

Results:
A total of 627 patients entered the qualifying phase; of these, 565 patients satisfied entry criteria and were randomized into the double-blind phase of the study. Forty-two patients were

ineligible because they no longer met inclusion/exclusion criteria and 20 patients had < 3 average weekly angina attacks.

Of the 565 randomized patients from 48 sites, only 3% (17 patients) were from sites in the USA (2 sites) or Canada (one site); the rest were recruited from sites in Eastern Europe. A majority (64%, or 362 patients) were recruited from Russia. The rest of the study population was recruited from sites in Bulgaria, Romania, and the country of Georgia. As seen below (Table 1), the study population was mostly male and almost exclusively Caucasian.

Almost all (98%) randomized patients completed treatment and completed the study. Three ranolazine and five placebo patients withdrew from the study because of adverse events; in addition, there was one death in each treatment group. Three ranolazine patients withdrew consent (accounting for seven premature terminations in the ranolazine group and six in the placebo group).

Four percent (10 patients) of placebo and two percent (6 patients) of ranolazine patients were noted to have some protocol deviation; no imbalances were seen across treatment groups and there were no withdrawals due to protocol violations. In addition, the numbers of patients excluded from the full analysis set or safety analysis were small (< 5 patients per group) and balanced across groups.

The primary analysis used the full analysis set (FAS), all patients who received at least one dose of study drug in double-blind treatment and had any recorded angina diary data in that phase of the study.

Table 51. Baseline characteristics (all randomized patients)

	Placebo (N=284)	Ranolazine (N=281)
Mean (SD) age	61.3 (9.0)	62 (8.7)
< 65 years (%)	167 (59 %)	164 (58 %)
> 65 years (%)	117 (41 %)	117 (42 %)
Gender:		
Female (%)	78 (27 %)	80 (28%)
Male (%)	206 (73%)	201 (72%)
Race		
Caucasian (%)	282 (99%)	276 (98%)
Black (%)	2 (1%)	4 (1%)
Asian (%)	0	1 (<1%)
Geographic Region		
Eastern Europe	276 (97%)	272 (97%)
North America	8 (3%)	9 (3%)
Long-acting nitrate(LAN) user	124 (44%)	130 (46%)
Non-LAN user	160 (56%)	151 (54%)
Current tobacco user	73 (26%)	59 (21%)
Former tobacco user	86 (30%)	84 (30%)
Never used tobacco	125 (44%)	138 (49%)

Source: Table 14.3.1, Volume 19.

The above table displays baseline characteristics of the study population. The two treatment groups were balanced with respect to the demographic characteristics listed in the above table. Mean baseline weight was about 81 kg; mean height was 170 cm.
In terms of cardiovascular history, 19% of the safety analysis set (n=564) were diabetics (15-18% of the total had NIDDM); about 63% had previous MI; about 35-36% had unstable angina; about 51% had a history of CHF; and 10-12% of patients were post-CABG. In both the full analysis and safety populations, there was a small imbalance in patients with a single-vessel CABG (9% of ranolazine vs. 12% of placebo (10-12%) patients, CMH p-value =0.054) but the total percentage of patients with a CABG history was balanced across groups. In the full analysis set, about 21-25% of patients had a COPD history. About half (47-51%) of patients had a history of nitrate use. Few patients (< 4%) had a history of beta-blocker or calcium channel-blocker use; there was a baseline imbalance with respect to previous calcium channel-blocker use (4 patients on placebo; none in the ranolazine group; CMH p-value of 0.027, FAS11). **(Reviewer: It is unlikely that the 4 patient imbalance with respect to prior calcium channel blocker treatment will have affected the results. However, it is worth noting that this study population was <u>not</u> on maximal medical therapy for angina).**

<u>Concomitant Medications</u>: About 88-90% of patients received concomitant antiplatelet agents; about 51-54% received an ACE inhibitor; and about 10-12% were on an oral antidiabetic agent. Less than 2% were taking a concomitant angiotensin II antagonist. A higher percentage (39%) of ranolazine patients (compared to 33% placebo patients) received a concomitant statin; it is not clear whether this difference points to any baseline imbalance in the patient population (vs. differences in care). Otherwise, no imbalance in concomitant medication was noted.

Table 52. Baseline Average Weekly Rate of angina attacks, nitroglycerin consumption and Seattle Angina Questionnaire (SAQ) scores—Full analysis set (FAS)

	Placebo (N=281)	Ranolazine (N=277)
Average weekly rate of angina attacks (no/week)		
Median	4.50	4.50
25^{th}-75^{th} percentile	3.71-6.00	3.73-6.22
Min-Max	2.80-206.00	3.00-57.56
Mean (SEM)	6.89 (0.78)	6.12 (0.31)
*Average weekly rate of nitroglycerin consumption (doses/week)**		
Median	4.00	3.50
25^{th}-75^{th} percentile	2.33-6.00	2.21-5.50
Min-Max	0.00-98.00	0.00-98.39
Mean (SEM)	5.87 (0.52)	5.35 (0.52)
Baseline scores of SAQ		
Angina frequency Mean (SD)	40.0 (14.92)	40.6 (13.19)
Physical limitation Mean (SD)	48.9 (17.26)	49.2 (17.43)
Anginal stability Mean (SD)	57.2 (17.66)	54.7 (17.95)
Disease perception Mean (SD)	41.5 (17.78)	41.6 (17.18)
Treatment satisfaction Mean (SD)	75.4 (14.04)	74.6 (14.34)

11 Source: Table 14.3.9, CVT 3037 study report.

* p=0.18 from CMH test of equality of mean scores based on modified ridit score, stratified by pooled center.

Baseline average weekly anginal attacks, nitroglycerin consumption and SAQ functional dimension scores are shown above.
Of note, baseline mean and median nitroglycerin consumptions are lower in ranolazine patients compared to those on placebo—although the differences are not statistically significant.

The reviewers noted the upper limit of average weekly baseline angina attacks in the placebo group (206 episodes per week). Given the presence of such outliers, this review will concentrate on the non-parametric analyses, medians and percentiles.

Table 53. Primary and secondary efficacy measurements: Frequency of angina attacks and nitroglycerin consumption (FAS)

	Placebo (N=281)	Ranolazine (N=277)	p-value*
Initial Treatment Phase			
Average weekly rate of angina attacks (no./week)			
Median	4.00	4.00	NS
25^{th}-75^{th} percentile	3.00-6.00	3.00-6.00	
Mean (SEM)	6.16 (0.70)	5.29 (0.31)	
Min-Max	0.00-183.00	0.00-47.00	
Average weekly rate of nitroglycerin consumption (doses/week)			
Median	3.00	2.80	NS
25^{th}-75^{th} percentile	1.00-5.60	1.00-5.00	
Mean (SEM)	4.88 (0.50)	4.24 (0.40)	
Min-Max	0.00-97.00	0.00-60.00	
Six-week double-blind treatment phase			
Average weekly rate of angina attacks (no./week)			
Median	2.43	2.18	0.028
25^{th}-75^{th} percentile	1.47-4.17	1.24-3.66	
Mean (SEM)	4.30 (0.64)	3.29 (0.26)	
Min-Max	0.00-160.26	0.00-47.33	
Average weekly rate of nitroglycerin consumption (doses/week)			
Median	1.67	1.34	0.014
25^{th}-75^{th} percentile	0.50-4.00	0.47-2.48	
Mean (SEM)	3.57 (0.54)	2.72 (0.38)	
Min-Max	0.00-111.82	0.00-62.21	

Results confirmed by statistical reviewer.
*Cochran-Mantel-Haenszel test of equality of mean scores based on modified ridit score, stratified by pooled center.

The primary efficacy variable, average weekly rate of angina attacks, is presented above. A statistically significant treatment effect is demonstrated. As a sensitivity analysis, the sponsor adjusted for baseline rate of angina attacks, using a non-parametric analysis. The results yielded a p-value of 0.005 for treatment effect which supported the primary analysis results.

The results for the secondary variable of nitroglycerin consumption are also shown above and support the results of the primary efficacy variable. Since a baseline imbalance was seen

with respect to nitroglycerin consumption (see Table 2), the sponsor performed a sensitivity analysis adjusting for baseline differences; the results were consistent with the unadjusted analysis.

Table 54. Change in SAQ Scores from Baseline to the End of the 6-week Double-Blind Treatment Phase

SAQ score dimension	Placebo (N=281)	Ranolazine (N=277)	p-value
Angina frequency			
N	279	277	
LSM (SEM)	18.6 (1.27)	22.7 (1.25)	
LSM Difference (SEM)		4.1 (1.55)	0.008 (ANCOVA)
Physical Limitation			
N	270	269	
LSM (SEM)	6.6 (0.94)	6.9 (0.93)	
LSM Difference (SEM)		0.3 (1.15)	NS
Anginal Stability			
N	279	277	
LSM (SEM)	18.2 (1.57)	19.7 (1.57)	
LSM Difference (SEM)		1.5 (1.94)	NS
Disease Perception			
N	279	277	
LSM (SEM)	10.9 (1.14)	12.4 (1.13)	
LSM Difference (SEM)		1.5 (1.39)	NS
Treatment Satisfaction			
N	279	277	
LSM(SEM)	8.2 (0.81)	7.9 (0.80)	
LSM Difference (SEM)		-0.2 (0.99)	NS

Results confirmed by the statistical reviewer.
LSM (SEM) and LSM Difference are Least Square mean estimates from ANCOVA model. The p-values were calculated from ANCOVA testing the difference of change in SAQ scores between ranolazine and placebo treatment groups, using the baseline score and pooled center as covariates.

While SAQ is listed in the original protocol as a secondary efficacy variable, the sponsor notes (study report) that the SAQ is an exploratory tool that has not been validated for use in Eastern Europe.

Analyses by Subgroup:

Concomitant use of long-acting nitrates (LAN):

Table 55. Average weekly rate of angina attacks during 6-week double-blind treatment by concomitant use of LAN

	Placebo (N=281)	Ranolazine (N=277)	p-value
LAN-user (n)	122	129	
Median	2.65	2.13	.15 (CMH)
25^{th}-75^{th} percentile	1.52-4.43	1.33-3.96	

Mean (SEM)	5.67 (1.44)	3.80 (0.49)	
Non-LAN-user (n)	159	148	
Median	2.29	2.20	.16 (CMH)
25^{th}-75^{th} percentile	1.34-3.76	1.15-3.35	
Mean (SEM)	3.26 (0.26)	2.84 (0.23)	

CMH = Cochran-Mantel-Haenszel test of equality of mean scores based on modified ridit score, stratified by pooled center.

While no statistical significance is seen, the results by nitrate use trend in the same direction (favorable for ranolazine).

Gender:

A subgroup analysis by gender is presented below. Significant differences are seen for males but not for females. For the primary endpoint, the median rate of angina attacks in females is higher in the ranolazine group (favorable toward placebo). The sponsor claims that the reduced sample size reduces the power to detect a treatment effect in all of the subgroups; in addition, the sponsor claims that women and men treated with ranolazine appeared to have similar reductions in angina attack rates and nitroglycerin consumption rates; for the primary efficacy variable, the 25^{th} and 75^{th} percentiles were lower in females treated with ranolazine.

Table 56. Efficacy variables by gender

	Placebo (N=281)	Ranolazine (N=277)	p-value
Average weekly angina attacks (no./week)			
Female (n)	76	79	
Median	2.38	2.43	NS*
25^{th}-75^{th} percentile	1.23-4.44	1.17-3.50	
Min-Max	0.00-21.00	0.00-47.33	
Mean (SEM)	3.84 (0.47)	3.57 (0.67)	
95% CI (Mean)	(2.92, 4.76)	(2.26, 4.89)	
Effect Size (Mean)†		0.045	
Male (n)	205	198	
Median	2.43	2.09	0.026*
25^{th}-75^{th} percentile	1.50-4.00	1.30-3.71	
Min-Max	0.00-160.26	0.00-21.62	
Mean (SEM)	4.47 (0.87)	3.18 (0.25)	
95% CI (Mean)	(2.73, 6.21)	(2.69, 3.67)	
Effect Size (Mean)†		0.37	

Average weekly rate of nitroglycerin consumption			
	Placebo (N=281)	Ranolazine (N=277)	p-value
Female (n)	76	79	
Median	1.54	1.33	NS*
25^{th}-75^{th} percentile	0.44-4.27	0.50-2.83	
Min-Max	0.00-19.83	0.00-60.00	
Mean (SEM)	2.98 (0.44)	3.00 (0.82)	
Male (n)	205	198	
Median	1.75	1.35	0.008*
25^{th}-75^{th} percentile	0.57-3.66	0.33-2.33	
Min-Max	0.00-111.82	0.00-62.21	
Mean (SEM)	3.79 (0.73)	2.62 (0.42)	

Results confirmed by statistical reviewer. *CMH= Cochran-Mantel-Haenszel test of equality of mean scores based on modified ridit score, stratified by pooled center.
†Effect size = (mean ranolazine-mean placebo)/standard deviation of ranolazine (source: statistical reviewer).

Age:

Table 57. Primary Efficacy Variable by Age

	Placebo (N=281)	Ranolazine (N=277)	p-value*
Average weekly rate of angina attacks (no./week)			
Under 65 years (n)	166	162	
Median	2.46	2.09	0.074
25^{th}- 75^{th} percentile	1.47-4.32	1.24-3.26	
Mean (SEM)	4.41 (0.98)	3.13 (0.27)	
65 years and over (n)	115	115	
Median	2.33	2.43	0.15
25^{th} – 75^{th} percentile	1.46-4.00	1.24-3.71	
Mean (SEM)	4.14 (0.70)	3.52 (0.50)	

* P-value calculated from Cochran-Mantel-Haenszel test of equality of mean scores based on modified ridit score, stratified by pooled center.

The primary efficacy variable by age is shown above; no statistically significant effect is seen. For both young and elderly the mean angina attack rate is lower in the ranolazine group compared to placebo (although the median angina attack rate in the elderly is slightly higher in the ranolazine group). With respect to nitroglycerin consumption, there were median decreases in nitroglycerin consumption in both younger (under 65) and older (65 and over) groups without statistical significance via CMH.

Race: There were too few non-Caucasians in this trial to allow for an adequate subgroup analysis.

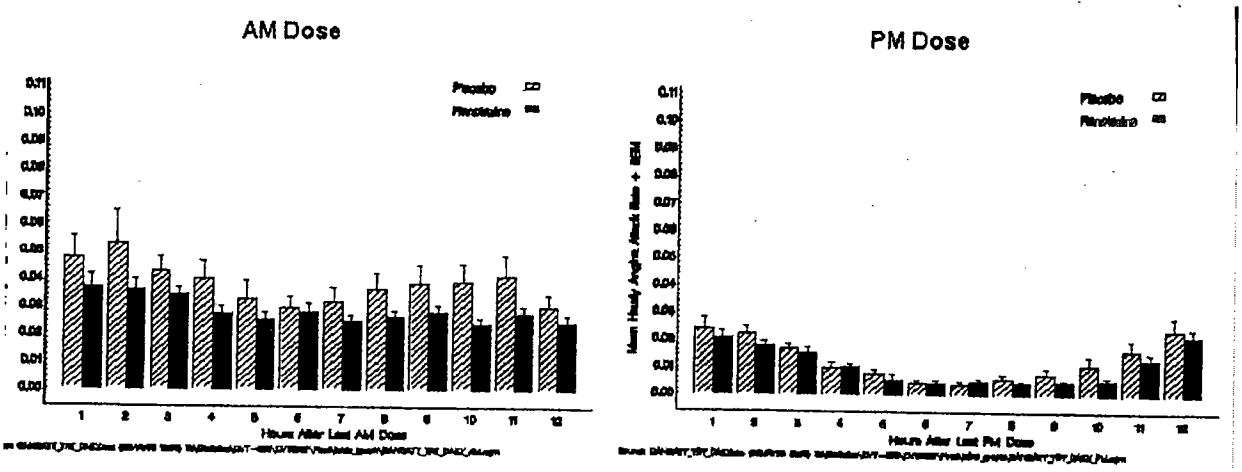
Geographic Region: There were too few patients outside Eastern Europe to allow for an adequate subgroup analysis. However, the median results of the primary efficacy endpoint were

consistent across the six pooled centers (North America [n=17], Bulgaria/Romania [n=80], Georgia [n=103], Russia 1 [n=143], Russia 2 [n=120], Russia 3 [n=96])

Other Analyses:

Temporal Pattern of Angina Attacks:

Correspondence from the Agency (signed 4/23/04) indicated that the Agency desired information regarding timing of angina relative to the last dose of study drug. In response, the sponsor provided the following data:



eproduced from Section 14.4.3.4

Reproduced from Section 14.4.3.5

Figure 2. Mean Hourly Angina Attack Rate as a Function of Time since Last AM or PM Dose of Study Drug in the 6-week Treatment Phase.

Most of the angina attacks appear to have occurred during daytime, prior to the PM dose.

Handling of Missing Data:

As a sensitivity analysis, the primary efficacy analysis was repeated for all patients randomized with intent-to-treat using an imputation analysis for premature withdrawals (regardless of whether the patients received treatment); in this analysis, the number of angina attacks for a patient who prematurely withdrew was imputed by multiplying the highest observed angina attack rate over the 6-week double-blind treatment phase (FAS) by the number of weeks from early withdrawal to the planned end of treatment. The total number of attacks for that patient was then equal to the sum of the number of reported attacks through the time of early termination and the imputed number of attacks thereafter. The highest observed angina rate in the double-blind period, 160 attacks/week, was imputed for the remaining study time for every patient (7 ranolazine, 6 placebo) who terminated early. The resulting ITT analysis with this imputed value for premature discontinuations yielded a p-value (CMH of row means scores) of 0.057.

Another sensitivity analysis imputed each patient's baseline attack rate to the time between early termination and planned end of study participation. The p-value for the treatment comparison in this sensitivity analysis was 0.030.

Safety:
The safety population included 283 patients on placebo and 281 on ranolazine. One randomized patient (# 8603-7013) excluded from this analysis population withdrew from study drug (due to atrial fibrillation) before receiving double-blind study drug.

Exposure: The mean days of exposure were comparable between ranolazine and placebo. The mean duration of the initial treatment phase was 7.3 days; the mean duration of double-blind treatment for efficacy (calculated as the difference in days between the start and end dates of the 6-week double-blind treatment phase) was 43.8-43.9 days and the mean duration of the double-blind phase for safety was about 51 days. There were no observed imbalances between treatment groups.

Deaths: Two deaths (one ranolazine, one placebo) were reported during the study. Patient # 5705-7003 (ranolazine) died about 10 days after starting double-blind study drug (death attributed to pneumonia); patient # 6103-7012 (placebo) died after a myocardial infarction 27 days after starting double-blind study drug.

- #6103-7012: This was a 67 year old White male former tobacco user with a history of hypertension, prior MI x 2, COPD, and unstable angina 3 months prior to screening; according to the CRF there was no history of prior angiography. About one month after starting study drug (placebo), the patient apparently developed pain, was treated with morphine, furosemide, intravenous nitroglycerin and dopamine, and died; the death was attributed to a myocardial infarction.
- #5705-7003: This was a 67 year old White male nonsmoker with a history of angina, class II heart failure, first degree AV block, hyperlipidemia, and chronic renal failure. Screening BP was 150-160/80 and HR was 56-62; a baseline GGT was 115 IU/L and hematocrit was 36%. Concomitant medications included amlodipine, enalapril, lovastatin, furosemide, and acenocoumarol. Ten days after starting ranolazine, the patient developed chest pain and dyspnea; the patient was subsequently hospitalized with fever, bloody sputum, and hypotension; ECG showed atrial fibrillation with lateral ST depressions, labs showed leukocytosis, elevated INR/PTT and CPK-MB 7.0 U/L. A CXR showed a massive right-sided pneumonia (per narrative). The patient was diagnosed with pneumonia and acute cardiopulmonary failure, treated with antibiotics and a pressor, and subsequently went into cardiac arrest and died. The death was attributed to pneumonia (**Medical Reviewer: there was likely some cardiac component given the ST depressions and elevated CPK-MB**).

Serious Adverse Events (SAEs): From randomization through the 14-day follow-up contact, a total of 11 patients (6 placebo, 5 ranolazine) experienced one or more SAEs; for one ranolazine and one placebo patient, these SAEs were fatal (described above).

The four non-fatal SAEs for ranolazine-treated patients are listed below:

- #8609-7011: This 60 year old female with a history of CAD and osteochondrosis was randomized to ranolazine and, on Day 16, developed pain unrelieved by sublingual nitroglycerin. She was hospitalized with a diagnosis of unstable angina and treated with intravenous nitroglycerin; cardiac enzymes were reportedly normal and ECG showed no changes from baseline (**the medical reviewer did not see the ECGs or enzymes**). The patient was diagnosed with osteochondrosis of the neck and she was discharged 9 days after symptom onset in an improved condition. She continued in the study without change/interruption of regimen.
- #8614-7009: This 67 year old male with CAD, hypertension, hyperlipidemia, COPD, was hospitalized for cerebral atherosclerosis. Twenty days after starting ranolazine, he developed dizziness and weakness associated with BP 170/100 mm Hg. He was hospitalized with an initial diagnosis of ischemic stroke; magnetic resonance imaging (MRI) showed multifocal changes of a vascular nature and a single lacunar cyst in the subcortical brain. His BP decreased to 140/80 mm Hg and ECG/labs were normal (per narrative). He was discharged and prematurely terminated from the study.
- #8624-7008: This 68 year old male with a history of CAD, MI, COPD and hemangioma/cysts of the live, was hospitalized for an MI. Forty-five days after starting ranolazine, he developed sudden chest pain, weakness, diaphoresis and mild dyspnea. His BP was 120/80 mm Hg and HR was 99 bpm; ECG revealed ST elevation in the inferior leads with reciprocal ST depression in the anterolateral leads. He was given intravenous streptokinase and nitroglycerin, was discharged 16 days later, and prematurely terminated from the study.
- #1301-7001 (after study termination): This 76 year old male with CAD, pulmonary fibrosis, mediastinal adenopathy and pulmonary nodule (unclear if worked up) developed shortness of breath 57 days after starting ranolazine. Two days later, he was hospitalized with a fever and leukocytosis; the patient was treated with oxygen, bronchodilator, acetaminophen and antibiotic with improvement. The patient recovered and was discharged.

Adverse Events (AE) leading to withdrawal: Seven patients (4 placebo, 3 ranolazine) discontinued due to an adverse event. For the three ranolazine patients, the adverse events included: mild face and peripheral edema (patient # 5710-7003); severe cerebral arteriosclerosis (patient #8614-7009, classified as an SAE, see SAE section); and myocardial infarction (patient #8624-7008, classified as an SAE, see SAE section). Adverse events in the placebo group that led to discontinuation of study drug included: accidental injury (broken leg, patient # 5709-7008); ventricular extrasystoles (patient #8604-7010); myocardial infarction (#8608-7009, classified as an SAE); and urolithiasis (patient #8609-7017, classified as an SAE).

Treatment-emergent adverse events:

Table 58. Treatment-emergent adverse events with an incidence of at least 1% and ≥ 1% higher incidence in the ranolazine group vs. placebo (from randomization to study termination: safety analysis set)

Preferred term	Placebo (N=283) n (%)	Ranolazine (N=281) n (%)
Constipation	5 (1.8)	25 (8.9)
Nausea	2 (0.7)	8 (2.8)
Peripheral Edema	8 (2.8)	16 (5.7)
Dizziness	7 (2.5)	11 (3.9)
Dry mouth	1 (0.4)	4 (1.4)
Dyspepsia	1 (0.4)	4 (1.4)
Asthenia	3 (1.1)	6 (2.1)
Abdominal Pain	1 (0.4)	5 (1.8)

Source: Table 14.7.1.3, Table 21

Adverse Events by Subgroup:

LAN use:

The question is whether concomitant LAN use presents a safety issue.

Table 59. Treatment-emergent adverse events by preferred term and concomitant use of LAN from randomization to study termination (safety analysis set); incidence ≥ 2.0% in any ranolazine group

Preferred Term	LAN user		Non-LAN user	
	Placebo (N=123) n (%N)	Ranolazine (N=130) n (%N)	Placebo (N=160) n (%N)	Ranolazine (N=151) n (%N)
Infection	10 (8.1)	5 (3.8)	7 (4.4)	3 (2.0)
Peripheral Edema	0	7 (5.4)	8 (5.0)	9 (6.0)
Constipation	1 (0.8)	13 (10.0)	4 (2.5)	12. (7.9)
Dizziness	2 (1.6)	3 (2.3)	5 (3.1)	8 (5.3)
Hyperglycemia	1 (0.8)	2 (1.5)	6 (3.8)	3 (2.0)

Reviewer: No safety signal is noted with concomitant LAN use.

Adverse Events by Gender: Among ranolazine-treated patients, 44/80 (55%) of women and 68/201 (33.8%) of men reported at least one adverse event. In this subgroup analysis, women on ranolazine reported the highest incidence of infection, headache, constipation and peripheral edema.

Table 60. Treatment-emergent adverse events by preferred term and gender (Randomization to study termination; Safety analysis set): incidence > 4% in any ranolazine subgroup

Preferred Term	Female		Male	
	Placebo (N=77)	Ranolazine (N=80)	Placebo (N=206)	Ranolazine (N=201)
Infection	6 (7.8)	7 (8.8)	11 (5.3)	1 (0.5)
Headache	4 (5.2)	6 (7.5)	3 (1.5)	2 (1.0)

Peripheral edema	4 (5.2)	6 (7.5)	4 (1.9)	10 (5.0)
Constipation	3 (3.9)	12 (15)	2 (1.0)	13 (6.5)
Dizziness	3 (3.9)	2 (2.5)	4 (1.9)	9 (4.5)

Adverse events by Age:

Elderly patients on ranolazine reported higher rates of constipation and peripheral edema.

Table 61. Treatment-emergent adverse events by preferred term and age subgroup (Randomization to study termination; Safety analysis set): incidence > 4% in any ranolazine subgroup

	Under 65 years		65 years and over	
Preferred term	Placebo (n=167)	Ranolazine (n=164)	Placebo (n=116)	Ranolazine (n=117)
Peripheral edema	4 (2.4)	6 (3.7)	4 (3.4)	10 (8.5)
Constipation	1 (0.6)	9 (5.5)	4 (3.4)	16 (13.7)
Dizziness	4 (2.4)	8 (4.9)	3 (2.6)	3 (2.6)

Adverse events by Race: Because the study population was almost exclusively Caucasian, no analysis of adverse events by race will be presented.

Laboratory Tests:
The submission included a shift table of baseline and termination laboratory values. Serum creatinine was the only laboratory test that showed an increased shift from normal (ranolazine vs. placebo):

Table 62. Serum creatinine shift table

	Termination							
Baseline	Placebo (N=283)				Ranolazine (N=281)			
	Low	Normal	High	Missing	Low	Normal	High	Missing
Low	4	9	1	0	1	14	0	1
Normal	5	204	**15**	3	3	178	**31**	3
High	1	22	**18**	1	0	21	**29**	0
Missing	0	0	0	0	0	0	0	0

Source: Table 14.8.1

The sponsor claims that this shift is due to a drug effect on inhibition of renal tubular secretion of creatinine. (**Reviewer**: A review of treatment-emergent adverse events revealed no signal under the term "increased creatinine" or "BUN increased").

Vital Signs:
In both ranolazine and placebo groups, there was a small mean decrease from baseline to Visit 5 in sitting heart rate (mean decrease 1.6-2.0 bpm) without a statistically significant difference between the two groups. For systolic and diastolic BP, there were also decreases from baseline to Visit 5 (systolic BP: 1.7-2 mm Hg decrease from baseline; diastolic BP: 0.6-1.0 mm Hg

decrease from baseline) without a statistically significant treatment effect. For standing systolic BP the mean change from baseline to endpoint was -2.9 mm Hg for ranolazine and -1.8 mm Hg for placebo (p=NS).
A review of postural vital signs (supine to standing) did not reveal a significant treatment effect.

ECG:
According to the sponsor, ECG abnormalities were collected by the site if they were considered significant and could preclude the patient's continued participation in the study. Such abnormalities were noted for 3 patients (1 placebo, 2 ranolazine). Patient #5710-7006 (ranolazine) had evidence of ischemia/infarction on an ECG on Day 0 (continued in the study); patient # 8604-7010 (placebo) had ventricular extrasystoles on Day 21 (withdrawn from double-blind study drug); an ECG for patient # 8624-7008 (ranolazine) showed ischemia/infarction at study termination (MI reported as SAE). Patient # 8618-7013 (ranolazine) had QT prolongation as an adverse event (the patient continued in the study through completion).

The sponsor also submitted available ECGs as follow-up in patients with cardiovascular events in study CVT 3037. Four ranolazine patients with cardiovascular AEs did not have available ECGs.
Reviewer: The ECGs are of adequate quality although several are missing grids (possibly due to the copy quality) for evaluation of conduction/repolarization. One patient (#8625-7006) was noted to have a QTc of 450 msec; atrial fibrillation (but not prolonged QTc) was coded.

Reviewer Comments/Conclusions:

1. This was a double-blind, placebo-controlled parallel-group study evaluating the effect of ranolazine 1000 mg bid on average weekly angina attacks (via patient diary).
2. Due to the presence of outliers, the study analysis was changed to a non-parametric analysis (changes reviewed by the Agency). The study met its primary endpoint.
3. Limitations of this study include:
    a. Patient-reporting: Unless the diary reporting is contemporaneous with the angina attack, reporting may be subject to differences in memory and recollection of events. In addition, patients may differ in their perceptions of angina attacks (some may interpret every pain as angina, whether or not cardiac in origin).
    b. Activity: Since level of activity is not controlled or tested in this trial, the weekly rate of angina attacks may be subject to varying levels of activity (as opposed to drug effect).
    c. Seattle Angina Questionnaire: While originally listed as a secondary endpoint, the SAQ has not been validated in the study population and will not be used by these reviewers in regulatory decision-making.

    Since the study was blinded and placebo-controlled, one would hope that the issues raised in points a. and b. will occur equally in both groups.
4. No significant treatment effect was seen in the female subgroup. The sponsor has noted that the female subgroup has a smaller sample size. While the sample size is smaller for the female subgroup, it is worth noting that the effect size for the primary endpoint is also smaller in females compared to the effect size in males.
5. A shift in creatinine was seen in the ranolazine group; however, no safety signal was seen in this study with regard to treatment-emergent or serious renal AE.

6. The following treatment-emergent AE were increased in the ranolazine group: constipation, nausea, peripheral edema, and dizziness. Slight increases were seen with regard to: dry mouth, dyspepsia, asthenia, and abdominal pain. No safety signals were seen with respect to discontinuations due to AE or serious/fatal AE.
7. Higher rates of constipation and peripheral edema were reported in the elderly.

10.2 Line-by-Line Labeling Review

Proposed Labeling

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20 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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Shari Targum
12/8/2005 02:02:09 PM
MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Secondary Review

NDA: 21-526 (Ranexa; ranolazine for angina)

Sponsor: CV Therapeutics

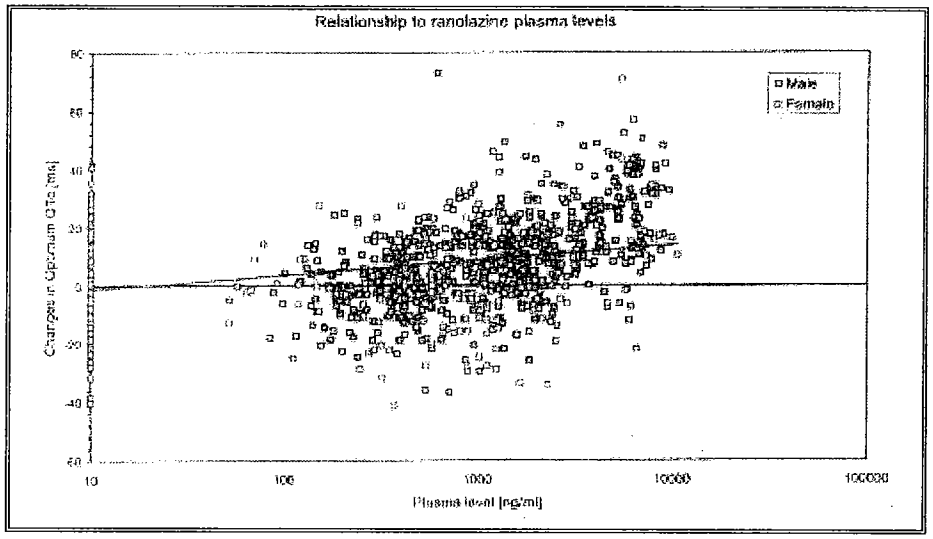
Review date: 7 November 2003

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Summary: This is an amendment to the secondary review of Ranexa, ranolazine for angina.

Distribution: NDA 21-526
HFD-110/Project Manager
HFD-860/Bhattaram/Gobburu

The original secondary review of ranolazine erroneously concludes that there is an escalating relationship between plasma level of ranolazine and QTc, based on this figure, taken from the sponsor's study report.



This figure is a plot of change in QTc vs. log of plasma level and the straight line is therefore a log-linear relationship, which is clearly inadequate to fit these data.

All of the available data from various studies are consistent with a linear relationship between plasma ranolazine levels and QTc.

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/s/

Norman Stockbridge
11/7/03 01:28:29 PM
MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Secondary Review

NDA: 21-526 (Ranexa; ranolazine for angina)

Sponsor: CV Therapeutics

Review date: 29 September 2003

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Summary: This is a secondary review of Ranexa, ranolazine for angina.

Distribution: NDA 21-526
HFD-110/Project Manager
HFD-110/Gordon/Hausner/Koerner/Targum
HFD-710/Freidlin/Hung
HFD-810/Chidambaram
HFD-860/Bhattaram/Hinderling/Nguyen

This secondary review is based on primary reviews of chemistry (Dr. Chidambaram, 15 September 2003), pharmacology and toxicology (Dr. Hausner, 2 September 2003; Dr. Koerner, 4 September 2003), clinical pharmacology and biopharmaceutics (Drs. Hinderling, Nguyen, and Bhattaram, 15 September 2003), clinical efficacy (Drs. Targum and Freidlin, 28 August 2003, 2 September 2003, and 12 September 2003), and clinical safety (Dr. Gordon, 31 July 2003).

An NDA amendment submitted on 13 September 2003 was considered by all primary reviewers and it was found not to make a material contribution to the issues raised by those reviewers.

From a manufacturing perspective, Ranexa should be considered approvable, pending (since 14 January 2003) the results of the inspection of the manufacturing facility.

The mechanism by which ranolazine may be antianginal is unclear. The sponsor's preclinical studies suggest it may be through inhibition of cardiac metabolism of fatty acids. Ranolazine and its metabolites interact with various cardiac ion channels, including IKr and IKs. Ranolazine prolongs the action potential duration in cardiac M-cells. In the ventricular wedge, ranolazine prolongs the transmural QT interval and slows the action potential upstroke, in the presence of hypokalemia, at concentrations similar to what may be effective in man. Early afterdepolarizations were not seen.[1]

Ranolazine produces embryotoxicity in rats and rabbits and skeletal malformations in fetal rats, at doses well below that shown to be effective in man.

Ranolazine is a racemate. The plasma level peaks 2 to 5 hours after multiple doses of the sustained-release formulation. Absorption is about 73% from an aqueous solution. Bioavailability of the tablet is 76% of that from a solution. Bioavailability of ranolazine is unaffected by food. As shown in Table 1, AUC increases somewhat more than linearly

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[1] *Dr. Koerner's review cites additional shortcomings of available preclinical data related to proarrhythmic risk. Ranolazine was not studied in the ventricular wedge preparation under conditions necessary to elicit cisapride's proarrhythmia. Metabolites have not been adequately studied. Ranolazine has also not been evaluated in the presence of other risk factors for proarrhythmia, including female gender, pacing with a pause or with an accelerating rhythm, with adrenergic stimulation, or with heart failure.*

after multiple doses. Variability is high; the CV is about 50 to 80% for estimates of Cmax and AUC. With repeated dosing, ranolazine levels increase by less than two-fold.

Table 1. Single- and multiple-dose pharmacokinetics[2]

	500 mg	1000 mg	1500 mg
AUC day 1	9615	21075	33779
AUC day 6	13720	32902	56134

There must be substantial binding of ranolazine in tissues, since binding to plasma protein and erythrocytes do not account for ranolazine's large volume of distribution (>80 L).

Ranolazine is extensively metabolized with pathways involving CYP 3A4, CYP 2D6, sulfatases, and glucuronidases. Four "major" circulating metabolites have AUCs 5 to 40% of the AUC for ranolazine. Elimination of radioactivity after oral administration of labeled ranolazine in solution is by urine (73%) and feces.

Ketoconazole increases plasma levels of ranolazine by about 3-fold. Common doses of diltiazem (up to 360 mg QD studied) increase ranolazine levels 2.8-fold. The 2D6 inhibitor paroxetine had relatively small effects. Digoxin levels increased 40 to 70% after to-be-marketed doses of ranolazine.

Of the 80-some studies reported, only two have been identified as useful to characterize the effectiveness of sustained-release ranolazine in angina.

The first such study is CVT3033, a randomized, double-blind, parallel, and placebo-controlled study. Active study groups received 750 or 1000 mg BID for 12 weeks. Exercise testing (treadmill with modified Bruce protocol) was performed at "peak" (4 hours after dosing) at weeks 2 and 12, and "at trough" at weeks 2, 6, and 12. A final assessment for "rebound" was conducted 48 hours after the last dose. Subjects in this study were on a background of amlodipine 5 mg QD or diltiazem 180 mg QD[3].

The principal measures of effectiveness are shown in Table 2 and Table 3 below.

Table 2. Effectiveness in CVT3033[4]

Change from baseline. placebo	750 mg BID		1000 mg BID	
	Peak	Trough	Peak	Trough
Total ETT (s)	34±11	24±11	26±11	24±11
Onset angina	38±12	30±12	38±13	26±12
1 mm ST depression	41±12	29±12	35±12	21±12

Table 3. Angina during CVT3033.

Angina/week	Placebo	750 mg	1000 mg
Baseline	4.6±0.4	4.4±0.3	4.4±0.3
Double-blind	3.3±0.3	2.5±0.2	2.1±0.2

The primary end point treatment effect at trough is only marginally significant (0.03 for each dose), so the statistical significance is quite sensitive to various robustness

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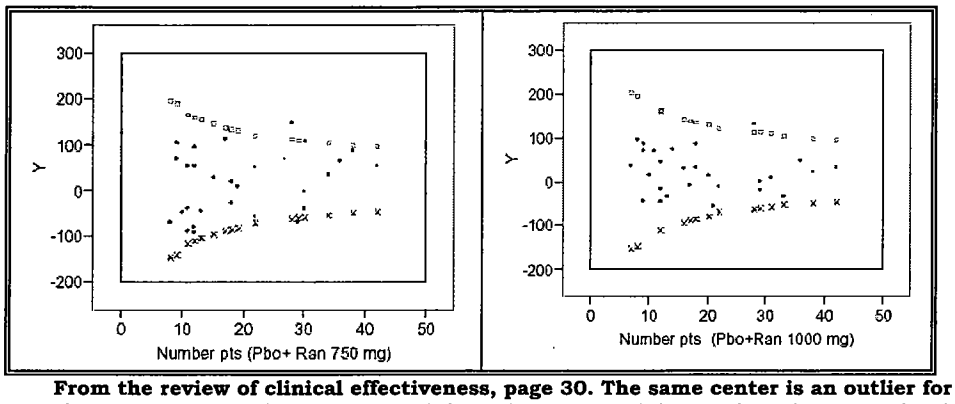
[2] *Adapted from the review of clinical pharmacology, page 120.*

[3] *Such a background cannot be considered responsive to the need to demonstrate effectiveness in a refractory population.*

[4] *Adapted from the review of effectiveness, page 8.*

exercises, such as exclusion of the "outlier" site in the funnel plot shown in the figure below.



From the review of clinical effectiveness, page 30. The same center is an outlier for the analysis of results on 750 mg (left) and 1000 mg (right), perhaps because what is discrepant is the placebo effect.

Drs. Targum and Freidlin also evaluated various subgroups within this study, but the marginal overall results doomed this effort.

While it remains unclear what combination of factors contributed to difficulties in obtaining a robust effect in CVT3033—effect size, inter-subject variability, inter-center variability, dosing interval—the two doses, producing, as they do, plasma levels that overlap considerably, support one another for the primary end point of total exercise time, for secondary end points of time to onset of angina and time to ST depression, and for the rate of angina attacks. Furthermore, effects on exercise time were, as would be expected, somewhat larger, and certainly statistically more robust when assessed nearer the time of peak plasma levels.

The second study supporting effectiveness is CVT3031, a randomized, double-blind study in which subjects not on background antianginal therapy received, in random order, one week on placebo and ranolazine 500, 1000, and 1500 mg BID. This study had one baseline assessment (ETT based on the modified Bruce protocol), and then single ETT assessments at the end of each crossover period. There was no washout between crossover periods.

Again, for reasons not well understood, the results are not very compelling. In addition to the sample-size issues raised by study CVT3033, CVT3031 adds concerns related to carryover effects (which, given the short half life, were not expected) and training effects.

Table 4. Effectiveness in study CVT3031[5]

	500 mg BID		1000 mg BID		1500 mg BID	
	Peak	**Trough**	**Peak**	**Trough**	**Peak**	**Trough**
Total ETT	29±7	23±8	52±7	35±9	56±8	46±9
Onset angina	34	31	57	35	70	60
1 mm ST	38	24	60	44	66	66

And, as in CVT3033, larger and more statistically significant results are seen in measurements of exercise near the time of peak plasma levels.

[5] *Adapted from sponsor's study report, vol 1.146, page 311ff. Time to onset of angina and time to ST depression were not reported in the primary review.*

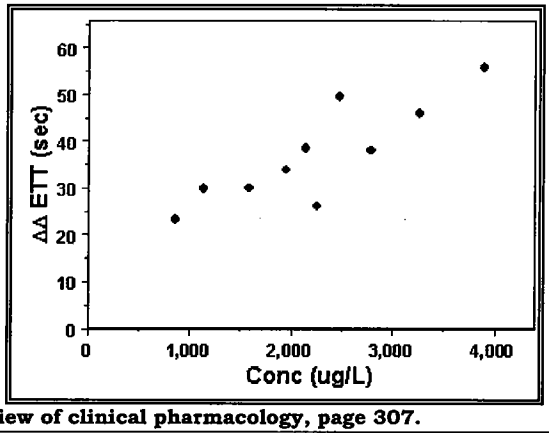
These studies—and there really are no others suitable for evaluating the effects of sustained-release ranolazine on exercise—are subject to some fair criticism. In particular, they failed to demonstrate a dose-response relationship, because the doses were close together and the intersubject variability in plasma levels was large within a dose group. Thus, one can consider at least adjacent dose groups within these studies as multiple looks at nearly the same dose. As such, the results are entirely internally consistent—active drug was always better than placebo on total exercise time and time to onset of angina and time to 1-mm ST depression, all true for measurements at the interdosing interval as well as "peak".

Some consideration has been given to whether the less impressive results at the interdosing interval were the result of getting the interdosing interval wrong. However, looking at the nominal trough-peak ratio for values shown in Table 2 and Table 4 reveals a fairly consistent estimate >0.5, as shown in Table 5[6].

Table 5. Nominal trough-peak ratios in studies CVT3033 and CVT3031.

	CVT3033		CVT3031		
	750 mg	**1000 mg**	**500 mg**	**1000 mg**	**1500 mg**
Total ETT	0.71	0.92	0.79	0.67	0.82
Onset angina	0.79	0.68	0.91	0.61	0.86
ST depression	0.49	0.60	0.63	0.73	1.00

Additional evidence of a relationship of ETT to dose comes from pharmacometric analyses of ETT by peak and trough plasma levels in these two studies, shown in the figure below.

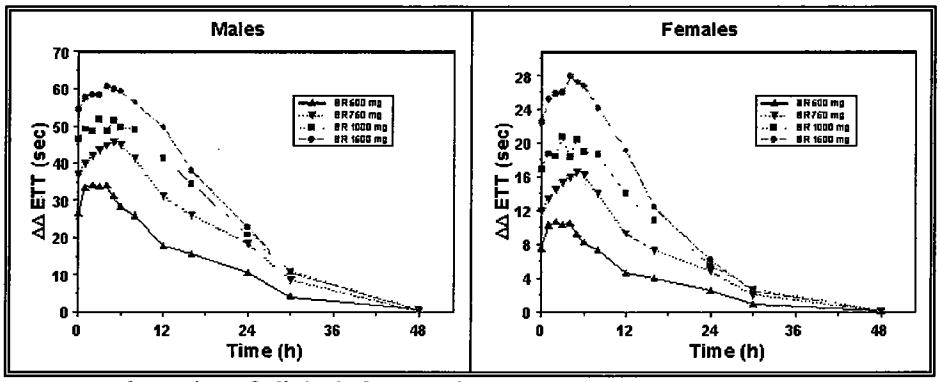


From the review of clinical pharmacology, page 307.

The pharmacometrics team modeled the relationship between plasma levels and ETT and the time course of plasma levels to obtain expected treatment effects as a function of time, as shown in the figure below[7].

[6] *However, it must be said that there are no data adequately describing the time course of treatment effect. In particular, the "peak" measurements were made earlier than the estimated time of peak plasma concentrations. The effect of underestimating the true peak effect is that the trough-peak ratios will be inflated.*

[7] *However, to be clear, there are no data for times other than "peak" and interdosing interval.*



From the review of clinical pharmacology, page 310.

Note that the effect in women follows the same time course as the effect in men, but that the effect size is about half as large. This difference is not the result of differences in pharmacokinetics.

The sponsor[8] has suggested that Study Ran-072[9] is supportive of a treatment effect in a refractory population. This was a randomized, double-blind, two-period crossover study in which subjects with chronic angina on beta-blockers (n=61, up to 100 mg QD of atenolol or metoprolol), calcium channel blocker (n=43, up to 60 mg QID of diltiazem), or both (n=50) received treadmill exercise tests 2.5 to 3 hours following placebo and single oral doses of ranolazine 10, 60, 120, or 240 mg. Some of the results of this study (abstracted from the clinical review) are shown in Table 6.

Table 6. Change in total ETT (Ran-072).

	Ranolazine + BB				Ranolazine + CCB				Both	
	10 N=14	60 N=15	120 N=17	240 N=15	10 N=10	60 N=11	120 N=12	240 N=10	10 N=24	60 N=26
ΔETT	7	21	5	39*	12	6	-8	34	10	14
*Nominal p=0.02										

The subjects in this study were not shown to be resistant to other therapy, nor was the other therapy optimized for each subject. The doses of ranolazine in this study were lower than those explored in later studies, so it is not surprising that no treatment effect is seen, even near the time of peak plasma levels of ranolazine—no evident dose-response and no statistically significant treatment effect after correction for 10 possible comparisons. This study does not support effectiveness of ranolazine in a resistant population.

In total, nearly 2700 subjects were exposed to ranolazine in more than 80 clinical studies. Much of this, however, was with short-term exposure, doses lower than are now believed to be effective, and with the immediate-release formulation. About 750 subjects received at least one dose of sustained-release ranolazine at a dose of 500 to 1500 mg BID for an average of about 10 weeks. Several hundred subjects received open-label ranolazine for more than one year.

During controlled studies, subjects receiving ranolazine were, compared to those receiving placebo, more likely to experience adverse events, more likely to have adverse

[8] *Personal communication.*

[9] *Medical/statistical review page 47.*

events considered severe, causing a reduction, interruption, or discontinuation of treatment, or associated with a fatal outcome.

Category	Number (%) of Subjects/Patients			
	ISS Database		Phase 2/3 SR Controlled Studies	
	Total Ranolazine (N = 2,682)	All Placebo (N = 1,529)	Total Ranolazine (N = 749)	Placebo (N = 455)
Mean Duration of Exposure (Days)	160	25	86	53
Any AE	1,465 (54.6)	418 (27.3)	275 (36.7)	101 (22.2)
Any SAE	255 (9.5)	30 (2.0)	51 (6.8)	16 (3.5)
Any Severe AE	286 (10.7)	47 (3.1)	46 (6.1)	14 (3.1)
Any Possibly/Probably Drug-Related AE	852 (31.8)	182 (11.9)	140 (18.7)	26 (5.7)
Any AE Leading to Death	23 (0.9)	3 (0.2)	4 (0.5)	3 (0.7)
Any AE Leading to Dose Reduction	48 (1.8)	1 (0.1)	0	0
Any AE Leading to Dose Interruption	70 (2.6)	8 (0.5)	23 (3.1)	3 (0.7)
Any AE Leading to Study Drug Discontinuation	210 (7.8)	28 (1.8)	60 (8.0)	17 (3.7)
Any AE Leading to Adding Concomitant Medication	646 (24.1)	136 (8.9)	112 (15.0)	45 (9.9)

AE = adverse event; SAE = serious adverse event

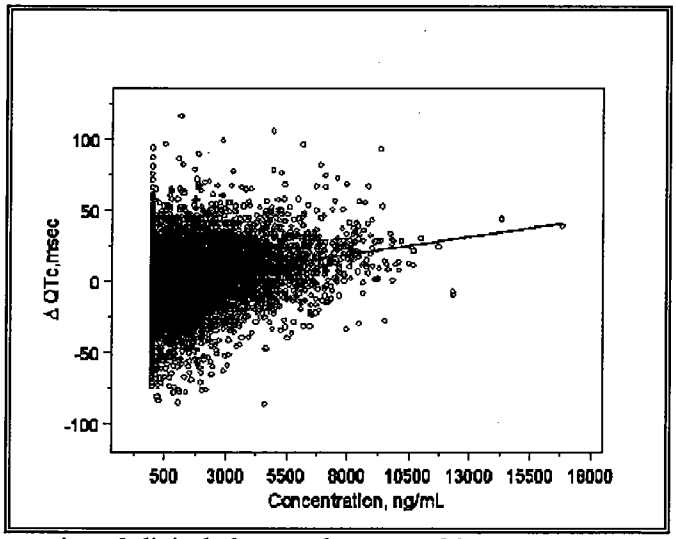
Abstracted from **Appendix III B Table E-1.1, Appendix V B Table E-1.3, Appendix III D Table G-1.1, and Appendix V D Table G-1.3.**

From the review of clinical safety, page 15.

During controlled studies, the most common adverse events, more common on ranolazine than placebo, were dizziness (8% vs. 1%), constipation (7% vs. <1%), and nausea (6% vs. <1%).

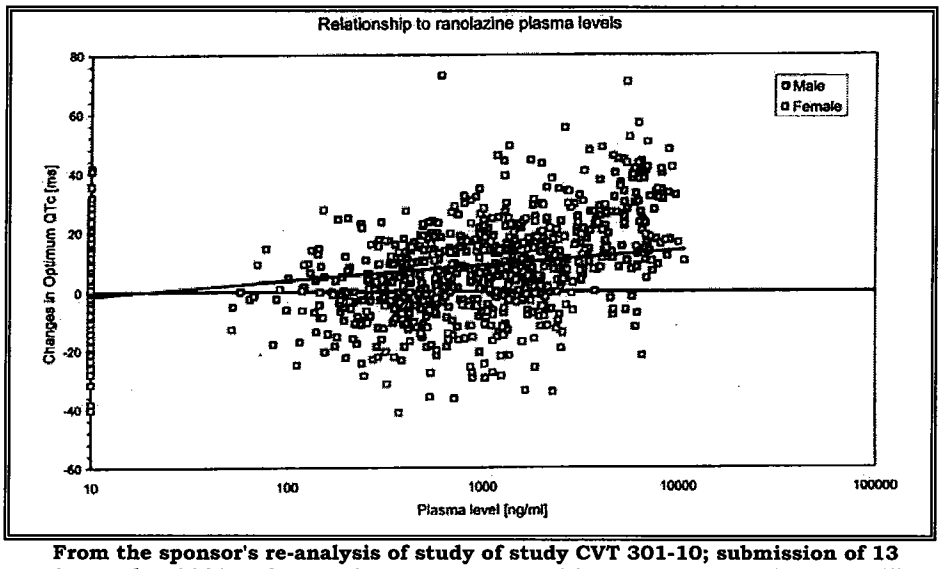
There were 37 deaths during the development program (33 on ranolazine). These were mostly cardiovascular, with some described only as sudden. Two subjects, both on ranolazine 1000 mg BID had sudden deaths long after reported QTc values >500 ms.

As shown in the figure below, the change in QTc was positively correlated with plasma levels of ranolazine.



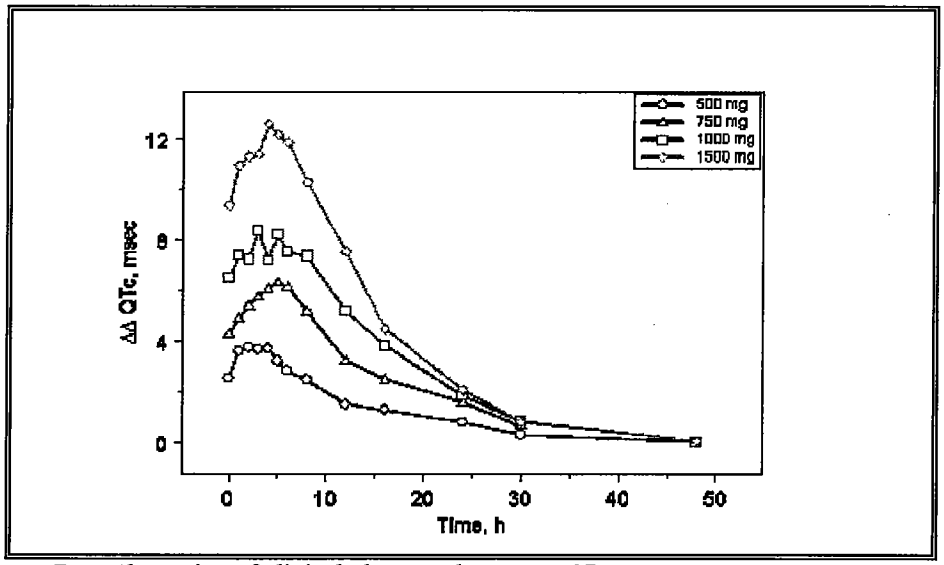
From the review of clinical pharmacology, page 34.

However the nonlinearity of the relationship between QT and dose and the steepness with which QTc increases with plasma levels >1000 ng/mL is better illustrated in data taken solely from the ketoconazole study.



From the sponsor's re-analysis of study of study CVT 301-10; submission of 13 September 2003, vol 8, section 8.3.1, page 11. The report asserts that a curvilinear fit to these data is not superior to a linear fit. However, the vast majority of data points at plasma levels >1000 ng/mL are above the fitted line, and the vast majority of points at plasma levels <1000 ng/mL are below the fitted line.

The (linear) model-based estimated time course of changes in QTc is shown in the figure below.



From the review of clinical pharmacology, page 35.

Ranolazine has no effect on heart rate. Effects of ranolazine on QTc were manifest in controlled studies[10], modeled in the figure above. The mean double difference from baseline and placebo was, at peak, about 4 ms at 500 mg BID, increasing monotonically

[10] *Values shown are Bazett-corrected QT. Where Fredericka-corrected data are available, the trends are similar.*

with dose, to about 12 ms at 1500 mg BID. At the highest dose, 6% of subjects reported changes from baseline >60 ms and 7.5% had QTc >500 ms[11].

The difference between the linear and nonlinear models is of little consequence for doses up to 1500 mg in the absence of metabolic inhibition. However, in the presence of metabolic inhibition, the linear model grossly underestimates the effect on the QTc near the time of peak plasma level.

Notched T waves were also more likely to be reported on drug than on placebo. The incidence increased with dose and, within dose, by plasma level. At 10,000 ng/mL, the likelihood of notched T-waves was about 75%. The clinical significance of this is not clear.

Ranolazine appears to be conventional with respect to its effects on angina, conventional in the nature of its benefits (symptomatic), conventional in the magnitude of its benefits (modest), and conventional with respect to most aspects of its safety profile.

Ranolazine's most distinguishing feature is its effect on ventricular repolarization, seen in preclinical assessments, mean effects on QTc, and outliers for QTc. Despite the less-than-linear increase in plasma levels with dose, effects on QT, unlike effects on ETT, were fairly easily distinguished by dose. This suggests that QT prolongation can be attenuated by keeping the dose below 1000 mg BID. However, large inter-subject variability in pharmacokinetics and drug interactions involving 3A4 inhibitors, 2D6 inhibitors, diltiazem, and digoxin will clearly undermine efforts to control the risks by limiting dose. Available clinical data do little to constrain the estimated rate of arrhythmias that may result from use of ranolazine; the clinical experience with long-term use is simply too small.

Under the circumstances, restriction of use to a population refractory to usual treatments is the only sensible option. If one understood enough about the mechanism of antianginal action of ranolazine, one might entertain approving this restricted use without a specific study in a refractory population. However, the mechanism is not well understood, and the pharmacodynamic interaction of ranolazine with other antianginal agents cannot be predicted with confidence. Ranolazine should be considered "approvable", pending demonstration of use in a refractory population.

Because of concerns about the effects of ranolazine on ventricular repolarization, at several points in the development program, the sponsor was encouraged to study its use in a population with refractory angina[12].

In a letter to Dr. Throckmorton, dated 5 September 2003, the sponsor reaches much the same conclusion:

> *"It therefore appears reasonable to allow a trial of ranolazine in those patients in whom the currently available agents have been demonstrated to be either inadequate or not tolerated. For those among them whose angina symptoms are decreased by ranolazine, the benefit will surely justify the risk, if any, of the small QT effect."*

This additional study may need to carry some additional burdens. At least, it needs to provide better characterization of the dose-response relationship. Some considerations should also be given to issues relating to effects in subgroups by gender.

Various review disciplines have commented on parts of the proposed label that would need amending. These comments can be gathered into a deficiencies letter, but a

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[11] *In the sponsor's re-analysis of data from two studies, lower rates of outliers are reported when the basis of study is only lead II, rather than all leads. The trend of an increased incidence with dose remains.*

[12] *See Dr. Targum's review of 12 September 2003 for a brief history of the formal interactions with the sponsor.*

complete labeling recommendation is not possible until the results of the missing study are known.

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/s/

Norman Stockbridge
9/29/03 10:55:42 AM
MEDICAL OFFICER

MEDICAL REVIEW OF SAFETY-AMENDMENT

NDA#21,526
Drug Name: ranolazine (Ranexa™)
Sponsor: CV Therapeutics, Inc.
Review date: September 26, 2003
Medical Reviewer: Maryann Gordon, M.D.

I have reviewed the amendment dated September 13, 2003. I do not agree that the sponsor has supplied information that changes my assessment of risk associated with ranolazine's effect on the QT interval. Therefore, no additional time is needed to review the application.

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/s/

Maryann Gordon
9/26/03 09:30:53 AM
MEDICAL OFFICER

Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852
Tel (301) 594-5377, FAX (301) 594-5494

Memorandum

DATE: September 25, 2003

FROM: Shari L. Targum, M.D.
TO: NDA 21-526

SUBJECT: Amendment: Additional Efficacy Data and Analysis
DATE RECEIVED BY REVIEWER: September 24, 2003

SPONSOR: CV Therapeutics

The sponsor has submitted additional efficacy subgroup analyses from studies CVT 3031 and CVT 3033. Treadmill exercise data were analyzed in: 1. An aggregate of patients with either reactive airway disease, CHF, diabetes or low BP, slow heart rate, or PR prolongation; 2. Patients with a prior myocardial infarction (MI); 3. Patients who have undergone a revascularization procedure. In addition, analyses of patient reported angina frequency and nitroglycerin use were conducted for each of the above subgroups.

Given the difficulties in interpreting the primary efficacy endpoint in CVT 3031, it is not clear to this reviewer how to interpret post-hoc subgroup analyses from CVT 3031.
The post-hoc subgroup analyses from CVT 3033 were also reviewed. It is concluded that these analyses do not add to or alter the conclusions of the efficacy review

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/s/

Shari Targum
9/25/03 10:55:13 AM
MEDICAL OFFICER

MEDICAL REVIEW OF SAFETY

NDA#21,526
Drug Name: ranolazine (Ranexa™)
Sponsor: CV Therapeutics, Inc.
Review start date: February, 2003
Medical Reviewer: Maryann Gordon, M.D.

Table of Contents

Summary of safety

This is an agent that was developed for chronic stable angina. The number of patients who were included in the database and received ranolazine is around 2700; approximately 280 subjects received the drug for at least 1 year. Several formulations were studied: immediate release (IR) with nearly 1300 subjects, sustained release (SR) with nearly 1360 subjects, and intravenous (IV) with less than 80 subjects. There were 3 placebo controlled SR angina clinical trials (designated as Phase 2/3 controlled angina) with a total of 749 ranolazine and 455 placebo subjects. One of these trials was a cross over with doses up to 1500 mg bid. The other trial was a parallel group, 12 weeks duration with the highest dose being 1000 mg bid. The third trial enrolled only 11 patients. Targeted SR dose range was 500 mg- 1500 mg bid.

QT interval prolongation and T wave morphology changes

The sponsor found out early in development that ranolazine increases the QT interval on ECG and changes the morphology of the T wave. The drug effect at peak concentration is greater than at trough. The mean changes by dose are shown below.

Mean change from baseline in QT[1]/QTc interval (msec) at peak

	Placebo N=432	Ranol 500 N=177	Ranol 750 N=269	Ranol 1000 N=428	Ranol 1500 N=170
Mean change from baseline	-3.7/-2.0	-1.0/3.3	7.3/3.5	6.7/5.0	8.5/11.0
Max mean change from baseline	0.9/1.1	-1.0/3.3	16.3/8.9	11.5/8.1	8.5/11.0

Table N-1.3.2.1vol 1.0376

The table below shows the number and percent of patients, by dose, who had selected QTc interval changes from baseline at endpoint at peak drug concentration.

No. and (percent) of patients

Change from baseline	Placebo N=433	Ranol 500 N=177	Ranol 750 N=271	Ranol 1000 N=433	Ranol 1500 N=170
0-30 msec	167 (38.6)	67 (37.9)	160 (59.0)	242 (55.9)	71 (41.8)
31-60 msec	21 (4.8)	20 (11.3)	6 (2.2)	29 (6.7)	28 (16.5)
≥61 msec	4 (0.9)	6 (3.4)	1 (0.4)	1 (0.2)	10 (5.9)

Table N-15.3.1 vol 1.0377

There also were changes in the morphology of the T-wave during ranolazine use. The frequencies of notched T waves are shown below by treatment group at peak and trough concentrations (study CVT 3031).

% of subjects with notched T waves

	Placebo	Ranol 500	Ranol 1000	Ranol 1500
peak	2	1	3	6
trough	<1	<1	5	5

There were more notched T waves were reported in the Ranolazine 1000 mg and 1500 mg doses than in the placebo and ranolazine 500 mg dose groups.

[1] From fax dated 6-27-03

The number and percent of patients in CVT 3033 with notched T waves at weeks 2 and 12 by drug group are shown below.

% of subjects with notched T waves (at peak)

Placebo		Ranolazine SR 750 mg		Ranolazine SR 1000 mg	
Week 2	Week 12	Week 2	Week 12	Week 2	Week 12
0.4	0	4.1	1.2	2.0	3.4

Genetic studies have shown that long-QT syndrome (LQTS) is a primary electrical disease caused by mutations in specific ion channels.[2] LQTS patients exhibit QT prolongation on the ECG and are at risk of arrhythmogenic syncope and sudden death. In addition to duration, T-wave morphology is often abnormal, and notched T waves have been included in diagnostic criteria.[3] This pattern has been associated with a poor prognosis.[4]

Drug interactions

CYP3A4 is a major determinant for ranolazine clearance. There was an average increase of plasma concentration of 3- to 4-fold in the presence of the potent CYP3A4 inhibitor ketoconazole (200 mg bid)[5]. The effect on QTc is shown below.

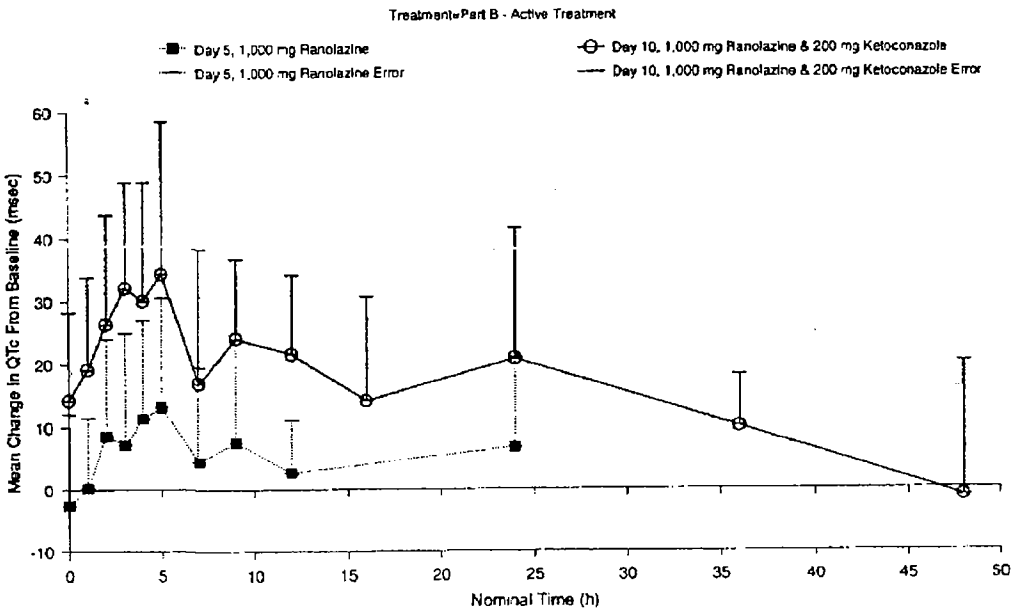
[2] Roden DM, Spooner PM. Inherited long QT syndromes: a paradigm for understanding arrhythmogenesis. J Cardiovasc Electrophysiol. 1999;
10: 1664-1683.

[3] Schwartz P1, Moss AJ, Vincent GM, and et al. Diagnostic criteria for the long QT syndrome: an update. Circulation. 1993; 88: 78-784.

[4] Malfatto G, Beria B, Sala S, et al. Quantitative analysis of T wave abnormalities and their prognostic implications in the idiopathic long QT syndrome. J Am Coll Cardiol. 1994; 23: 296-301.

[5] Study CVT 301-10

Figure 14.4.3.2 Mean Plots of Changes in QTc Interval From Baseline in Part A Following Twice Daily Administration of 1,000 mg Ranolazine/Placebo Alone (Day 5) and Co-administration of 200 mg Ketoconazole (Day 10)



Concomitant use with diltiazem resulted in increases in ranolazine plasma concentrations of 1.5- to 2.4-fold over the diltiazem total daily dose range (180-360 mg)[6]. Ranolazine 1,000 mg bid at steady-state caused a less than two-fold increase simvastatin exposure dosed at 80 mg qd[7].

Hepatic impairment
Subjects with moderate hepatic impairment had increases in AUC and Cmax. This resulted in increases in QTc.

Renal impairment
Subjects with creatinine clearance decreasing from 100 mL/min to 30 mL/min had increases in AUC and Cmax.

Adverse events
Commonly reported events in the SR controlled angina studies were dizziness (6.8% placebo subtracted), constipation (6.1%), and nausea (5.0%). Events reported mostly by subjects receiving 1500 mg bid included syncope, sweating, and vomiting. Syncope and assorted events that could be related to syncope were reported by 19.2% of the overall ranolazine population compared to the 4.4% of the placebo population. There is orthostatic hypotension reported with the higher doses[8].

[6] Studies CVT 3012, RANO121, and RANO6S
[7] Study CVT 3017
[8] Study RANS0201

The survival curves of chronic angina patients on ranolazine versus those on placebo over a 3 month period were similar. The Cox proportional hazards regression model rules out that ranolazine is more than 3.27 times worse than placebo or more than 8.2 times better than placebo. Changes in laboratory values were unremarkable and included small decreases in hematocrit/ hemoglobin and small increases BUN and serum creatinine.

1.0 Overall clinical program

Eighty-one clinical studies were conducted in support of the safety and efficacy of ranolazine. The studies sponsored by Syntex are identified in the NDA with the prefix "RAN" and those sponsored by CVT with the prefix "CVT." Clinical reports for studies sponsored by Syntex were also assigned a report number by Syntex that begins with the prefix "CL."

As agreed with the Division at the pre-NDA teleconference of 20 December 2001, 64 of the 81 studies are included in the Integrated Safety Summary (ISS) database. The 17 studies that were not integrated include 16 early, low-dose studies conducted by Syntex and 1 bioequivalence study (CVT 301-15). These studies were discussed in the narrative of the ISS, but the data were not integrated.

The safety data were generated with several formulations of ranolazine that were used throughout the course of the development program. All of these formulations resulted in systemic exposure to the same ranolazine moiety (i.e. ranolazine base). Ranolazine SR is the proposed commercial formulation.

The 64 studies that comprise the ISS database were categorized as follows:

•Thirteen Phase 2/3 controlled studies: 11 angina (3 SR, 8 IR), and 2 intermittent claudication studies (SR);

• Five Phase 2/3 uncontrolled open-label extension studies in angina (2 SR and 3 IR);

•Forty-six Phase 1 and clinical pharmacology studies, including two studies in CHF (one SR and one IV), one study in patients with renal failure (SR) and one study in patients with hepatic impairment (SR).

The overview of the program including sample sizes is shown below.

Table 4 Overview of the Ranolazine Development Program by Treatment Group

	Number of Subjects/Patients[a]					
	Ranolazine				Total Number Exposed	
Category	Immediate Release	Sustained Release	IV	Ranolazine[b]	Placebo	All Subjects/Patients[b]
ISS Database[c]	1,299	1,359	77	2,682	1,529	2,985
Bioequivalence Study CVT 301-15	0	36	0	36	0	36
16 Early Studies[d]	86	0	151	237	159	304
Overall Total	1,385	1,395	228	2,955	1,688	3325

[a] Number of subjects/patients reflects number of subjects/patients who received at least one dose of study drug.

[b] For studies with a crossover design, subjects/patients were only counted once in the overall total number of subjects/patients columns.

[c] Sixty-four studies; see **Appendix I**.

[d] Includes Studies RAN001, RAN002, RAN003, RAN003B, RAN004, RAN005, RAN006A, RAN007, RAN008, RAN010, RAN011, RAN012, RAN014, RAN055, RAN070, and RAN1789.

There were 1299 subjects who received the immediate release, 1359 received sustained release, and 77 received the IV formulations. Subjects could receive more than 1 formulation.

Of the 2985 patients in the ISS data base, 2682 received ranolazine (any formulation) and 1529 received placebo (some patients received both ranolazine and placebo, about 800 received only placebo or placebo first[9]). Of the 1529 placebo subjects, 947 received placebo IR, 13 received placebo IV, and 569 received placebo SR (vol 1.0343 page 3).

Duration of exposure ranged from single dose to more than 2 years of treatment. Doses ranged from 10 mg once daily to 2000 mg bid. More than 45% (1359/2985) of the patients in the ISS data base received the SR formulation. The mean duration of exposure for patients receiving open label ranolazine SR as of the cut off date is 448 days.

"All" subjects (ISS data base)
A total of 2985 patients from 64 studies are included in this database. The formulations used were IR and SR. Two studies are still ongoing: CVT 3032 and CVT 3034, both are uncontrolled follow up studies.

The mean duration of exposure, the number and percent of the ISS patients who discontinued early and reasons for the discontinuations are shown below.

[9] Correspondence with sponsor

Table 6 Subject/Patient Disposition and Reason for Discontinuation—ISS Database

Category	Number of Subjects/Patients	
	Total Ranolazine N = 2,682	Total Placebo N = 1,529
Mean Duration of Exposure [Days]	160	25
Discontinuation, n (%)	492 (18.3)	63 (4.2)
Reason for Discontinuation		
Unacceptable AE	212 (7.9)	28 (1.8)
Inappropriate Enrollment	7 (0.3)	0
Non-compliance (drug/protocol)	31 (1.2)	5 (0.3)
Need for Prohibited Medication	2 (< 0.1)	0
Lost to Followup	7 (0.3)	0
Elective Withdrawal	31 (1.2)	5 (0.3)
Death[a]	27 (1.0)	2 (0.1)
Study Termination by Sponsor	75 (2.8)	3 (0.2)
Other	100 (3.7)	20 (1.3)

[a] Four additional deaths occurred which were not included in the ISS database. See **ISS Section 8** for additional information.

Abstracted from **Appendix III A Table D-3.1** and **Appendix III B Table E-1.1.**

Mean duration of exposure was 160 days for ranolazine and 25 days for placebo. Overall, more than 4 times as many ranolazine patients discontinued treatment compared to placebo patients (18.3% vs. 4.2%). Of the 492 ranolazine patients who discontinued, 212 (7.9%) did so because of an adverse event, 31 (1.2%) for non-compliance, 31 chose to withdraw, 27 (1.0%) died (plus 4 not included in list), 75 (2.8%) were stopped because of the sponsor, and 100 (3.7%) discontinued for other reasons.

Controlled trials

There were 11 studies with 2103 angina patients receiving either the IR or the SR formulations. A list of the Phase 2/3 controlled angina studies by individual study number and number of subjects by dose is shown below.

RANOLAZINE ISS
PHASE II/III CONTROLLED STUDIES

TABLE D-1.2 (PAGE 1 OF 2)
Patients Enrolled by Study

Protocol	Placebo N (%)	Ranolazine (mg) IR (Immediate Release) 10 QD 30 TID 60 QD 60 TID N (%)	120 QD 120 TID 180 TID N (%)	240 QD 240 TID 267 TID N (%)	400 BID 400 TID N (%)	SR (Sustained Release) 500 BID N (%)	750 BID N (%)	1000 BID N (%)	1500 BID N (%)	Total Ranolazine N (%)
Total Number of Patients in Summary	1266	245	264	454	470	181	279	459	187	1737
CVT3031	179(14.1)	0	0	0	0	181(100)	0	180(39.2)	187(100)	191(11.0)
CVT3033	269(21.2)	0	0	0	0	0	279(100)	275(59.9)	0	554(31.9)
RAN015	11(0.9)	0	11(4.2)	0	0	0	0	0	0	11(0.6)
RAN020	25(2.0)	25(10.2)	26(9.8)	0	0	0	0	0	0	26(1.5)
RAN054	123(9.7)	0	120(45.5)	124(27.3)	0	0	0	0	0	127(7.3)
RAN072	106(8.4)	50(20.4)	29(11.0)	27(5.9)	0	0	0	0	0	106(6.1)
RAN080	154(12.2)	0	0	0	155(33.0)	0	0	0	0	155(8.9)
RAN1490	4(0.3)	8(3.3)	0	0	0	0	0	0	0	8(0.5)
RAN1513	79(6.2)	162(66.1)	78(29.5)	0	0	0	0	0	0	240(13.8)

RANOLAZINE ISS
PHASE II/III CONTROLLED STUDIES

TABLE D-1.2 (PAGE 2 OF 2)
Patients Enrolled by Study

Protocol	Placebo N (%)	Ranolazine (mg) IR (Immediate Release) 10 QD 30 TID 60 QD 60 TID N (%)	120 QD 120 TID 180 TID N (%)	240 QD 240 TID 267 TID N (%)	400 BID 400 TID N (%)	SR (Sustained Release) 500 BID N (%)	750 BID N (%)	1000 BID N (%)	1500 BID N (%)	Total Ranolazine N (%)
Total Number of Patients in Summary	1266	245	264	454	470	181	279	459	187	1737
RAN1514	309(24.4)	0	0	303(66.7)	315(67.0)	0	0	0	0	315(18.1)
RAN2240	7(0.6)	0	0	0	0	0	0	4(0.9)	0	4(0.2)

IR doses ranged from 10 mg qd to 400 mg tid. SR doses ranged from 500 mg bid to 1500 mg bid. The 2 major studies that used the SR formulation were CVT 3031 and CVT 3033. These studies together enrolled 1102 ranolazine subjects (63.4% of the ranolazine population).

Controlled SR angina trials

A total of 1025 patients were treated in Phase 2/3 SR controlled angina studies. Of these patients, 749 received ranolazine (570 patients received only ranolazine SR and 179 received both ranolazine SR and placebo) and 276 received only placebo[10].

The table below shows the mean duration of exposure and the patient disposition for this selected patient population, by dose.

[10] Total 455 includes 276 placebo only plus 179 placebo and ranolazine

Table 7 Patient Disposition and Reason for Discontinuation—Phase 2/3 SR Controlled Angina Studies Population

	Number of Subjects/Patients					
	Ranolazine SR b.i.d.					
Category	Total SR N = 749	500 mg N = 181	750 mg N = 279	1,000 mg N = 459	1,500 mg N = 187	Placebo N = 455
Mean Duration of Exposure [Days]	66	8	82	50	8	53
Discontinuation [n (%)]	91 (12.1)	4 (2.2)	29 (10.4)	44 (9.6)	14 (7.5)	35 (7.7)
Reason for Discontinuation						
Unacceptable AE	59 (7.9)	1 (0.6)	20 (7.2)	27 (5.9)	11 (5.9)	15 (3.3)
Inappropriate Enrollment	1 (0.1)	0	0	1 (0.2)	0	0
Non-compliance (Drug/Protocol)	2 (0.3)	0	2 (0.7)	0	0	2 (0.4)
Lost to Followup	1 (0.1)	0	0	1 (0.2)	0	0
Elective Withdrawal	10 (1.3)	1 (0.6)	1 (0.4)	5 (1.1)	3 (1.6)	4 (0.9)
Death	4 (0.5)	1 (0.6)	2 (0.7)	1 (0.2)	0	2 (0.4)
Study Termination by Sponsor	0	0	0	0	0	1 (0.2)
Other	14 (1.9)	1 (0.6)	4 (1.4)	9 (2.0)	0	11 (2.4)

Abstracted from **Appendix V A Table D-3.3** and **Appendix V B Table E-1.3.**

The mean durations of exposure were 66 days for the total SR population (n=749) and 53 days for placebo (n=455). The dose of ranolazine with the largest number of patients is 1000 mg bid (459 patients). Discontinuation rates for any reason was 12.1% for any dose of ranolazine compared to 7.7% for placebo. The reason with the largest percent of discontinuations in the total SR group was for an adverse event (7.9%). There is no obvious dose response for noncompleters but sample sizes and length of exposure are unequal.

Long term, open label trials

CVT 3032 and CVT 3034

Of the 550 patients enrolled in these studies[11], 440 are still ongoing and 110 (20%) were discontinued. Of the patients who discontinued, 58 did so because of an adverse event. In addition, there were 262 subjects who received the IR formulation during one of 5 uncontrolled IR studies.

The disposition of these subjects (and IR patients from earlier trials) is shown in the table below.

[11] cut off date 10-15-01

TABLE D-2.3 (PAGE 1 OF 1)
Patient Disposition

Disposition	IR (Immediate Release)	SR (Sustained Release)
Total Number of Patients in Summary	262	550
Normal Completion	97(37.0)	0
Ongoing	0	440(80.0)
Early Termination	165(63.0)	110(20.0)
Unacceptable Adverse Event	34(13.0)	58(10.5)
Inappropriate Enrollment	2(0.8)	0
Non-compliance (drug/protocol)	3(1.1)	4(0.7)
Lost to Follow up	0	3(0.5)
Elective Withdrawal	0	16(2.9)
Death	6(2.3)	16(2.9)
Study Termination by Sponsor	66(25.2)	0
Other	54(20.6)	13(2.4)

Twenty percent of long term subjects withdrew early from ranolazine treatment. More than half of these withdrew for unacceptable adverse events.

Other populations
There were 6 studies with patient populations with diseases other than angina. These include CHF (2 studies, 96 patients), intermittent claudication (2 studies, 48 patients), renal impairment (1 study, 29 subjects), hepatic impairment (1 study, 32 subjects). Data from these populations were integrated into the ISS database.

Extent of exposure

"All" subjects (ISS data base)
The numbers of subjects who received treatment (ranolazine, placebo, or both) for a specified amount of time are shown below.

Table 8 Extent of Exposure for All Treated Subjects/Patients—ISS Database

Exposure	Number (%) of Subjects/Patients[a]	
	Total Ranolazine N = 2,682	Total Placebo N = 1,529
≤ 1 Day	196 (7.3)	213 (13.9)
2–6 Days	371 (13.8)	137 (9.0)
7–13 Days	295 (11.0)	560 (36.6)
14–27 Days	187 (7.0)	152 (9.9)
28–41 Days	477 (17.8)	205 (13.4)
42–55 Days	26 (1.0)	10 (0.7)
56–83 Days	172 (6.4)	21 (1.4)
≥ 84 Days	958 (35.7)	231 (15.1)
Average Duration (Days)	160	25

[a] This is not a cumulative count. A patient was only counted in the cell corresponding to the longest period of exposure and was not counted in any other cells.

Abstracted from **Appendix III B Table E-1.1**.

The mean duration of exposure was 160 days for ranolazine compared to 25 days for placebo.

Phase 2/3 SR controlled angina studies

Extent of exposure for this subpopulation is shown below.

Table 9 Extent of Exposure for All Treated Subjects/Patients—Phase 2/3 SR Controlled Angina Studies Population

Category	Number (%) of Subjects/Patients[a]					
	Ranolazine SR (b.i.d.)					
	500 mg N = 181	750 mg N = 279	1,000 mg N = 459	1,500 mg N = 187	Total SR N = 749	Placebo N = 455
≤ 1 day	0	0	0	0	0	1 (0.2)
2–6 days	8 (4.4)	4 (1.4)	14 (3.1)	19 (10.2)	12 (1.6)	18 (4.0)
7–13 days	170 (93.9)	1 (0.4)	186 (40.5)	165 (88.2)	26 (3.5)	168 (36.9)
14–27 days	3 (1.7)	8 (2.9)	10 (2.2)	3 (1.6)	179 (23.9)	14 (3.1)
28–41 days	0	4 (1.4)	3 (0.7)	0	24 (3.2)	1 (0.2)
42–55 days	0	3 (1.1)	4 (0.9)	0	7 (0.9)	2 (0.4)
56–83 days	0	37 (13.3)	48 (10.5)	0	85 (11.3)	20 (4.4)
≥ 84 days[b]	0	222 (79.6)	194 (42.3)	0	416 (55.5)	231 (50.8)
Average Duration (Days)	8	82	50	8	66	53

[a] This is not a cumulative count. A patient was only counted in the cell corresponding to the longest period of exposure and was not counted in any other cells.

[b] Maximum period of exposure for any patient in Studies CVT 3033 and RAN2240 was 103 days, see CSR **Item 8, Section 8. 16**

Abstracted from **Appendix V B Table E-1.3**.

The average duration of exposure for all ranolazine was 66 days compared to 53 days for placebo. The 750 mg dose had the longest average duration of exposure (82 days).

Long term, open label studies

CVT 3032 and CVT 3034

The mean duration of exposure to ranolazine SR in uncontrolled studies was 448 days. A total of 276 patients received the drug for at least one year and 101 received it for at least 2 years.

Adequacy of clinical experience

The development program was excessively large in number but had only a limited number of clinical trials that were helpful in assessing safety. That said, there are enough patients studied under controlled conditions to comfortably determine the major safety effects of ranolazine.

Case report forms were submitted and spot checked for subjects who died or were withdrawn for adverse event.

2.0 Demographics

The table below shows demographic and baseline characteristics for the ISS database population and the Phase 2/3 SR controlled studies.

Table 10 Demographic and Baseline Characteristics—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations

	Number (%) of Patients					
	ISS Database Population			Phase 2/3 SR Controlled Studies		
Category	Ranolazine N = 2,682	Placebo N = 1,529	Total N = 2,985	Ranolazine N = 749	Placebo N = 455	Total N = 1,025
Gender						
Male	2,170 (80.9)	1,207 (78.9)	2,400 (80.4)	580 (77.4)	341 (74.9)	788 (76.9)
Female	512 (19.1)	322 (21.1)	585 (19.6)	169 (22.6)	114 (25.1)	237 (23.1)
Age						
< 65 years	1,753 (65.4)	965 (63.1)	1,935 (64.8)	370 (49.4)	220 (48.4)	504 (49.2)
65 to < 75 years	751 (28.0)	465 (30.4)	847 (28.4)	287 (38.3)	189 (41.5)	405 (39.5)
≥ 75 years	178 (6.6)	99 (6.5)	203 (6.8)	92 (12.3)	46 (10.1)	116 (11.3)
Race						
Caucasian	2,306 (86.0)	1,347 (88.1)	2,569 (86.1)	715 (95.5)	434 (95.4)	986 (96.2)
Non-Caucasian	376 (14.0)	182 (11.9)	416 (13.9)	34 (4.5)	21 (4.6)	39 (3.8)
Underlying Disease						
Diabetes Mellitus	383 (14.3)	217 (14.2)	436 (14.6)	179 (23.9)	102 (22.4)	238 (23.2)
CHF	331 (12.3)	150 (9.8)	407 (13.6)	197 (26.3)	107 (23.5)	274 (26.7)
CAD	1,869 (69.7)	1,217 (79.6)	2,106 (70.6)	749 (100)	455 (100)	1,025 (100)
Prior Unstable Angina	223 (8.3)	104 (6.8)	241 (8.1)	160 (21.4)	89 (19.6)	215 (21.0)
Previous MI	990 (36.9)	634 (41.5)	1,133 (38.0)	427 (57.0)	247 (54.3)	580 (56.6)

Table 10 Demographic and Baseline Characteristics—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations (Cont'd)

Category	Number (%) of Patients					
	ISS Database Population			Phase 2/3 SR Controlled Studies		
	Ranolazine N = 2,682	Placebo N = 1,529	Total N = 2,985	Ranolazine N = 749	Placebo N = 455	Total N = 1,025
Ventricular Arrhythmias	254 (9.5)	173 (11.3)	289 (9.7)	78 (10.4)	44 (9.7)	97 (9.5)
Valvular Heart Disease	111 (4.1)	59 (3.9)	132 (4.4)	40 (5.3)	23 (5.1)	60 (5.9)
Prior Cardiac Arrest	15 (0.6)	14 (0.9)	22 (0.7)	10 (1.3)	9 (2.0)	16 (1.6)
Hypertension	1,039 (38.7)	627 (41.0)	1,218 (40.8)	479 (64.0)	291 (64.0)	657 (64.1)
Prior Stroke	80 (3.0)	43 (2.8)	95 (3.2)	39 (5.2)	19 (4.2)	50 (4.9)
Angioplasty (including PTCA)	371 (13.8)	243 (15.9)	4021 (13.5)	164 (21.9)	115 (25.3)	220 (21.5)
Cardiac Revascularization	431 (16.1)	261 (17.1)	471 (15.8)	162 (21.6)	88 (19.3)	199 (19.4)
Concomitant Medications						
ACE Inhibitors	501 (18.7)	264 (17.3)	—	279 (37.2)	172 (37.8)	—
Alpha and Beta Blockers	704 (26.2)	325 (21.3)	—	265 (35.4)	135 (29.7)	—
AT1 Angiotensin II Antagonists	59 (2.2)	21 (1.4)	—	26 (3.5)	19 (4.2)	—
Calcium Channel Blockers	771 (28.7)	385 (25.2)	—	324 (43.3)	159 (34.9)	—

Table 10 Demographic and Baseline Characteristics—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations (Cont'd)

Category	Number (%) of Patients					
	ISS Database Population			Phase 2/3 SR Controlled Studies		
	Ranolazine N = 2,682	Placebo N = 1,529	Total N = 2,985	Ranolazine N = 749	Placebo N = 455	Total N = 1,025
Fibrates	141 (5.3)	88 (5.8)	—	38 (5.1)	25 (5.5)	—
HMG CoA Reductase Inhibitors	670 (25.0)	349 (22.8)	—	348 (46.5)	218 (47.9)	—
Platelet Aggregation Inhibitors	162 (6.0)	96 (6.3)	—	50 (6.7)	34 (7.5)	—

AT = angiotensin; ACE = angiotensin-converting enzyme; CHF = congestive heart failure; CAD = coronary artery disease; HMG CoA = hydroxymethyl glutaryl coenzyme A; PTCA = percutaneous transluminal coronary angioplasty; MI = myocardial infarction; NA = not available.

Abstracted from **Appendix III A Table D-4.1, Appendix III A Table D-4.1.1, Appendix III A Table D-5.1, Appendix V A Table D-4.3,** and **Appendix V A Table D-5.3.**

"All" subjects (ISS data base)

The 2 treatment groups were well balanced. The majority of subjects were male, less than 65 years of age, and white. Less than 7% of subjects were 75 years of age or older.

Overall, around 14% of subjects had diabetes mellitus and about 14% had congestive heart failure. The majority had coronary artery disease, around 8% had prior unstable angina, and around 40% had had a previous myocardial infarction. About 10% had ventricular arrhythmias, about 4% had valvular heart disease, less than 1% had had a prior cardiac arrest, about 40% had hypertension, about 3% had had a prior stroke, about 14% had had angioplasty and about 16% had had cardiac revascularization.

Commonly used concomitant medication includes ACE inhibitors, alpha/beta blockers, calcium channel blockers, and HMG CoA reductase inhibitors..

Phase 2/3 SR controlled angina studies

The majority of subjects was male, less than 75 years of age, and mostly white.
About 11% of subjects were at least 75 years of age. The 2 treatment groups were well balanced.

Around 23% of subjects had diabetes mellitus and about 25% had congestive heart failure. All had coronary artery disease, around 20% had prior unstable angina, and around 55% had had a previous myocardial infarction. About 10% had ventricular arrhythmias, about 5% had valvular heart disease, around 2% had had a prior cardiac arrest, 64% had hypertension, about 5% had had a prior stroke, less than 25% had had angioplasty and about 20% had had cardiac revascularization. The 2 treatment groups were well balanced.

Commonly used concomitant medication includes ACE inhibitors, alpha/beta blockers, calcium channel blockers, and HMG CoA reductase inhibitors. The 2 treatment groups were well balanced.

Exclusion criteria
The list below outlines the patients who were excluded from the 2 of the largest placebo controlled efficacy trials (CVT 3033 and 3031).

-presence of electrocardiographic or other factors that might interfere with ECG interpretation or may cause a false positive stress test
- New York Heart Association Class III-IV CHF;
-Clinically significant valvular heart disease or congenital cardiac defects;
-Unstable angina pectoris within the 2 months prior to study entry;
-Second or third degree atrio-ventricular block or uncontrolled clinically significant cardiac arrhythmias or a history of life-threatening ventricular arrhythmias unassociated with acute MI;
-Corrected QT interval (QTc) > 0.50 sec at Visit 1;
-Required medications known to prolong the QT interval;
-Required medications that inhibit or induce cytochrome P450 3A4,
-Unwillingness to refrain from grapefruit/grapefruit juice consumption for the duration of the study
-Requirement for digoxin;
-MI, CABG, PTCA, or other catheter-based revascularization procedures within 2 months before study entry;
-Active acute myocarditis or pericarditis;
-Hypertrophic cardiomyopathy;
-Uncontrolled hypertension;
-Systolic BP< 100 mmHg;

3.0 All adverse events
Methodology
According to the sponsor, adverse event data were collected by routine monitoring and reporting while the patient was on-study. An adverse event was defined as any unfavorable or unintended sign (including laboratory values), symptom, or disease that appeared or worsened during the clinical trial, whether or not deemed causally associated with the study drug. Investigators identified and graded adverse events by direct observation, questioning, and spontaneous reports from patients. Investigators identified the action taken regarding the adverse event, and they assigned a causality descriptor. An adverse event could result in the patient's premature discontinuation from the study. Adverse events were reported as verbatim terms in the case report forms (CRFs); these terms were subsequently mapped (using a COSTART thesaurus) to a preferred term and body system.

The table below shows the reporting of all adverse events in the ISS database and the Phase 2/3 SR controlled angina studies.

Table 11 Incidence of Treatment-Emergent Adverse Events by Category and by Treatment—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations

Category	Number (%) of Subjects/Patients			
	ISS Database		Phase 2/3 SR Controlled Studies	
	Total Ranolazine (N = 2,682)	All Placebo (N = 1,529)	Total Ranolazine (N = 749)	Placebo (N = 455)
Mean Duration of Exposure (Days)	160	25	66	53
Any AE	1,465 (54.6)	418 (27.3)	275 (36.7)	101 (22.2)
Any SAE	255 (9.5)	30 (2.0)	51 (6.8)	16 (3.5)
Any Severe AE	286 (10.7)	47 (3.1)	46 (6.1)	14 (3.1)
Any Possibly/Probably Drug-Related AE	852 (31.8)	182 (11.9)	140 (18.7)	26 (5.7)
Any AE Leading to Death	23 (0.9)	3 (0.2)	4 (0.5)	3 (0.7)
Any AE Leading to Dose Reduction	48 (1.8)	1 (0.1)	0	0
Any AE Leading to Dose Interruption	70 (2.6)	8 (0.5)	23 (3.1)	3 (0.7)
Any AE Leading to Study Drug Discontinuation	210 (7.8)	28 (1.8)	60 (8.0)	17 (3.7)
Any AE Leading to Adding Concomitant Medication	646 (24.1)	136 (8.9)	112 (15.0)	45 (9.9)

AE = adverse event; SAE = serious adverse event

Abstracted from **Appendix III B Table E-1.1, Appendix V B Table E-1.3, Appendix III D Table G-1.1,** and **Appendix V D Table G-1.3.**

"All" subjects (ISS data base)

The mean duration of exposure is more than 4 times for the ranolazine treatment group than the placebo group (25 days vs. 160 days, respectively). Therefore, it is not unusual that the group with the longer exposure (ranolazine, in this case) would have a higher reporting rate. The usefulness of conclusions drawn from these data is questionable.

Phase 2/3 SR controlled angina studies

The mean duration of exposure was similar for the 2 treatment groups (66 days and 53 days for ranolazine and placebo, respectively). There were more reports of any adverse event for the ranolazine group (36.7%) compared to placebo (22.2%), and the ranolazine group reported more serious events (6.8% vs. 3.5%), and more events resulting in treatment interruption (3.1% vs. 0.7%)/discontinuation (8.0% vs. 3.7%).

Individual adverse events

The table below shows the reporting of adverse events that were reported by at least 2% of the subjects in the ISS database on any treatment.

Table 12 Treatment-Emergent Adverse Events Reported for ≥ 2% of Subjects/Patients—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations

Body System Preferred Term	Number (%) of Patients[a]			
	ISS Database		Phase 2/3 SR Controlled Studies	
	Total Ranolazine (N = 2,682)	Total Placebo (N = 1,529)	Total Ranolazine (N = 749)	Placebo (N = 455)
Mean Duration of Exposure (Days)	160	25	66	53
Total Patients with Any AEs	1,465 (54.6)	418 (27.3)	275 (36.7)	101 (22.2)
Body as a Whole				
Abdominal Pain	101 (3.8)	18 (1.2)	13 (1.7)	3 (0.7)
Asthenia	265 (9.9)	51 (3.3)	31 (4.1)	10 (2.2)
Back Pain	56 (2.1)	14 (0.9)	1 (0.1)	3 (0.7)
Chest Pain	87 (3.2)	17 (1.1)	2 (0.3)	2 (0.4)
Headache	359 (13.3)	90 (5.9)	22 (2.9)	9 (2.0)
Infection	56 (2.1)	6 (0.4)	9 (1.2)	4 (0.9)
Pain	83 (3.1)	23 (1.5)	11 (1.5)	3 (0.7)
Cardiovascular System				
Angina Pectoris	177 (6.6)	32 (2.1)	34 (4.5)	21 (4.6)
Palpitation	65 (2.4)	16 (1.0)	7 (0.9)	5 (1.1)
Peripheral Edema	59 (2.2)	8 (0.5)	4 (0.5)	3 (0.7)

Table 12 Treatment-Emergent Adverse Events Reported for ≥ 2% of Subjects/Patients—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations (Cont'd)

Body System Preferred Term	Number (%) of Patients[a]			
	ISS Database		Phase 2/3 SR Controlled Studies	
	Total Ranolazine (N = 2,682)	Total Placebo (N = 1,529)	Total Ranolazine (N = 749)	Placebo (N = 455)
Digestive System				
Constipation	149 (5.6)	4 (0.3)	49 (6.5)	2 (0.4)
Diarrhea	61 (2.3)	16 (1.0)	5 (0.7)	7 (1.5)
Dyspepsia	132 (4.9)	28 (1.8)	16 (2.1)	4 (0.9)
Nausea	200 (7.5)	16 (1.0)	43 (5.7)	3 (0.7)
Nervous System				
Dizziness	354 (13.2)	44 (2.9)	61 (8.1)	6 (1.3)
Respiratory System				
Cough Increased	53 (2.0)	13 (0.9)	8 (1.1)	1 (0.2)
Dyspnea	76 (2.8)	20 (1.3)	14 (1.9)	6 (1.3)
Pharyngitis	64 (2.4)	17 (1.1)	3 (0.4)	2 (0.4)
Rhinitis	71 (2.6)	11 (0.7)	1 (0.1)	0
Skin and Appendages				
Rash	72 (2.7)	13 (0.9)	3 (0.4)	3 (0.7)

[a] Some patients may have been treated at more than one dose level.
AE = adverse event
Abstracted from **Appendix III B Table E-1.1, Appendix V B Table E-1.3, Appendix III D Table G-2.1,** and **Appendix V D Table G-2.3.**

"All" subjects (ISS data base)
Since the duration of use was more than 6 times longer in the ranolazine group compared to the placebo group, the usefulness of examining the individual events in the ISS data base is questionable.

Phase 2/3 SR controlled angina studies
The numbers and percents of patients in the Phase 2/3 controlled angina studies who reported an adverse event (limited to those events reported by more than 1% of the total ranolazine group and reported more in the ranolazine group than the placebo group) are shown in the table below, by treatment group. The placebo subtracted rate is also shown.

No. and (percent) of patients

event	Total ranolazine N=749	Total placebo N=455	Placebo subtracted %
Any event	275 (36.7)	101 (22.2)	14.5
Dizziness	61 (8.1)	6 (1.3)	6.8
Constipation	49 (6.5)	2 (0.4)	6.1
Nausea	43 (5.7)	3 (0.7)	5.0
Asthenia	31 (4.1)	10 (2.2)	1.9
Dyspepsia	16 (2.1)	4 (0.9)	1.2
Abdominal pain	13 (1.7)	3 (0.7)	1.0
Cough increased	8 (1.1)	1 (0.2)	0.9
Headache	22 (2.9)	9 (2.0)	0.9
Pain	11 (1.5)	3 (0.7)	0.8
Dyspnea	14 (1.9)	6 (1.3)	0.6
Infection	9 (1.2)	4 (0.9)	0.3
Rhinitis	1 (0.1)	0	0.1

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The placebo subtracted rate for reporting any adverse event was 14.5%. Those events with placebo subtracted rates greater than 2% includes dizziness (6.8%), constipation (6.1%), and nausea (5.0%).

Dose response
Events possibly associated with dose are shown in the table below for the SR formulation, by dose.

No. and (percent) of patients reporting events

	Ranol 500 mg N=181	Ranol 750 mg N=279	Ranol 1000 mg N=459	Ranol 1500 mg N=187
Any event	28 (15.5)	87 (31.2)	134 (29.2)	63 (33.7)
Dizziness	2 (1.1)	10 (3.6)	29 (6.3)	22 (11.8)
Asthenia	0	5 (1.8)	16 (3.5)	11 (5.9)
Nausea	1 (0.6)	9 (3.2)	17 (3.7)	16 (8.6)
Syncope	0	0	5 (1.1)	3 (1.6)
Sweating	0	3 (1.1)	5 (1.1)	5 (2.7)
Vomiting	0	2 (0.7)	5 (1.1)	4 (2.1)

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Unfortunately, the sample sizes for the SR formulation are small. However, the most convincing dose related adverse events are shown above. For example, syncope was only reported with doses 1000 mg and above.

4.0 Serious safety

Methodology

According to the sponsor, a serious adverse event (SAE) was characterized by one of the following criteria: resulted in death, was life threatening, required hospitalization or prolongation of an existing hospitalization, resulted in persistent or significant disability or incapacity, caused congenital anomaly or birth defect, and/or was considered medically significant by the investigator. Prior to 1997, the criteria for an SAE also included cancer and drug overdose. For some older (Syntex) studies, SAEs were not identified on the case report forms. Consequently, for those studies, SAEs were identified by medical monitors after review of the safety database. Summary tables regarding SAEs included: the type of SAE, concomitant medications received, action taken, outcome, and treatment assignment. All treatment-emergent SAEs were included in the summary tables, regardless of their severity or relationship to the study drug. SAEs occurring in the run-in period were excluded.

Deaths

There were 37 reported deaths (33 ranolazine and 4 placebo) in all 81 ranolazine studies[12]. For the total ranolazine group (including IR, SR, and IV formulations), the mortality rate was 1.2% (33/2682). The controlled trials randomized 749 subjects to ranolazine with a mortality rate of 0.7% (5/749) and 455 subjects to placebo also with a mortality rate of 0.7% (3/455).

Subject ID	Dose SR bid and IR tid/duration (days)	Cause of death
Controlled studies		
3031/133-1017	Dosing schedule: Ranol SR 1000 mg for 9 days, placebo for 7 days, ranol 500 mg for 3 days	V fib/collapsed at home
3033/177-9027	Ranol SR 750 mg/33	Acute MI
3033/704-7600	Ranol SR 750 mg/18	Sudden death
3033/706-9575	Ranol SR 1000 mg/13	Sudden death
3033/710-7631	Placebo/18	Sudden death (elevated ethanol level)

[12] as of 10-15-01

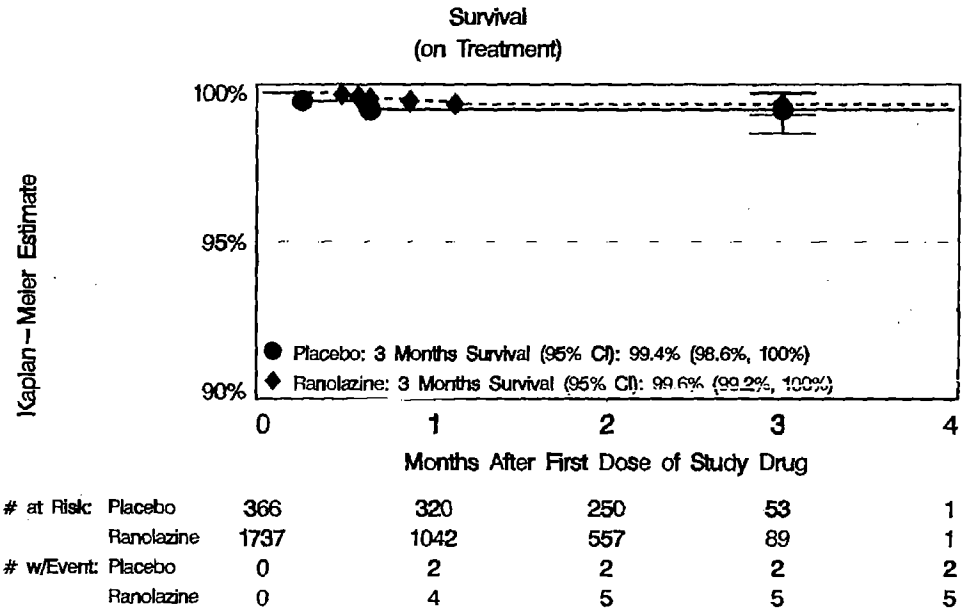
3033/717-8668	Placebo/6	Sudden death while driving
3033/751-9386	Placebo/95	Dissection of coronary arteries followed by cardiac arrest during elective PTCA
054/6858-414	Ranol IR 120 mg/41	MI
Uncontrolled studies		
054/6858/415+	Dosing schedule: ranol IR 240 mg for 28 days, placebo for 28 days, ranol IR 120 mg for 28 days.	Sudden death (died 2 days after last dose)
1513/3073-4609	Ranol IR 30 mg/died 45 days after last dose	Pulmonary embolism
3032/133-1018	Ranol SR 1000 mg/26	Malignant melanoma
3032/133-1019	Ranol SR 1000 mg/24	Lung carcinoma
3032/149-1193	Dosing schedule: Ranol SR 750 mg for 70 days, 1000 mg for 261 days	Sudden death. Developed a fib/flutter earlier, QTc was increased to 525 msec on day 173. QTc was 386 msec about 6 weeks prior to death
3032/153-1249	Ranol SR 750 mg/86	Esophageal carcinoma
3032/162-1281	Ranol SR 1000 mg/19	Sudden death. QTc interval up to 533 msec. Had complaints of dyspnea and chest pain immediately prior to death
3032/180-1462	Ranol SR 750 mg/366	CVA
3032/182-1458	Ranol SR 750 mg/210	Sudden death
3032/501-1441	Ranol SR 750 mg/167	CHF
3032/512-1366	Ranol SR 750 mg/256	AMI
3032/515-1392	Ranol SR 750 mg/342	Cardiovascular insufficiency S/P revascularization
3034-181-8445	Ranol SR 1000 mg/84	AMI with arrhythmia
3034/182-9269	Ranol SR 500 mg/428	Sudden death
3034/185-8374	Ranol SR 1000 mg/176	Sudden death
3034/190-8007	Ranol SR 1000 mg/298	Sudden death proceeded by complaints of angina and dyspnea
3034/195-8051	Ranol SR 750 mg/315	Sudden death (heart arrest)
3034/204-9024	Ranol SR 1000 mg/224	Sudden death (VF)
3034/236-8480	Ranol SR 750 mg/8	MI
3034/510-8353	Ranol SR 1000 mg/53	Pulmonary embolism proceeded by nausea and vomiting
3034/562-9186	Ranol SR 750 mg/332	unknown
081/6810/181	Ranol IR 400 mg/325	MI
1515/3838/2210	Ranol IR 120 mg/1319	MI
1515/3435/3702	Ranol IR 60 mg/187	Smoke inhalation
2074/3953/7001	Ranol IR 400 mg/526	Sudden death
2074/3971/15008	Ranol IR 400 mg/168	Died while undergoing CABG with balloon pump support
2074/1807/28002	Ranol IR 400 mg/364	Ruptured aortic aneurysm
1789/3645/2302^	Placebo IV/13	Complication of PTCA

+not included in clinical data base
^not included in ISS

Many causes of death were reported as sudden or other cardiovascular related; such deaths are not unexpected in this patient population.

Survival curve: all patients from Phase 2/3 controlled angina studies

Figure 1 **Survival of Chronic Angina Patients on Ranolazine: All Patients from Phase 2/3 Controlle Angina Studies**



# at Risk:	Placebo	366	320	250	53	1
	Ranolazine	1737	1042	557	89	1
# w/Event:	Placebo	0	2	2	2	2
	Ranolazine	0	4	5	5	5

Patient RAN054_6858415 death was captured in safety report, not in database.
SOURCE: GSURV_RAN_VS_PLA (07AUG2002 16:53) GSURV_RAN_VS_PLA_TRT_ALL.CGM

There was no difference in the survival curves between the placebo and ranolazine groups. Also, there was no difference between the groups when patients who received <120 mg ranolazine were removed from the analysis.

The survival data were analyzed using a Cox proportional hazards regression model[13] with a single effect for treatment. The hazard ratio and the 95% two sided confidence interval are shown in the table below.

Table 1 **Ranolazine ISS Phase 2/3 Controlled Studies – Cox Regression Analysis of Survival Time**

Hazard Ratio	*95% Confidence Interval*	*p-Value*
0.633	(0.122, 3.27)	0.58

Source: GSURV RAN_VS_PLA (30JUN2003 18:30)

[13] from fax sent 7-1-03

The estimated hazard ratio of 0.633 corresponds to a 36.7% reduction in the risk of death in the ranolazine treatment group. However, this estimate is highly variable because of the small number of events in the dataset. Therefore, the confidence interval for the hazard ratio is very wide. The analysis rules out that ranolazine is more than 3.27 times worse than placebo, or more than 8.2 times better than placebo, with regard to patient survival.

Long term, open label trials

CVT 3032 and CVT 3034

Of the 550 patients enrolled in these studies[14], 440 are still ongoing and 110 (20%) were discontinued. Of the patients who discontinued, 58 did so because of an adverse event. In addition, there were 262 subjects who received the IR formulation during one of 5 uncontrolled IR studies.

There were 25 deaths (table F-1.3 vol. 1.0378). Causes of death are shown below.

Cause of death	Number of subjects
Cancer	2
AMI	5
Sudden death	7
CVA	1
Congestive heart failure	2
V fib/tach	1
Cardiac arrest	2
Pul embolism	1
Unknown	2
House fire	1
AAA rupture	1
total	25

Table F-1.3 vol 1.0378

Causes of death included 7 sudden deaths, 1 ventricular fibrillation, and 5 acute myocardial infarctions.

Withdrawals for adverse events

The table below shows the numbers and percents of subjects who withdrew from a study because of an adverse event.

[14] cut off date 10-15-01

Table 24 Number (%) of Subjects/Patients Who Discontinued Study Medication Due to Treatment-Emergent Adverse Events by Category and Treatment—All Treated Subjects/Patients

Category	Ranolazine		Placebo	
	Total N	Number (%) of Subjects/Patients[a]	Total N	Number (%) of Subjects/Patients[a]
All Treated Subjects/Patients	2,955	240 (8.1)	1,688	38 (2.3)
ISS Database	2,682	237 (8.8)	1,529	35 (2.3)
Phase 2/3 SR Controlled Angina Studies	749	63 (8.4)	455	18 (4.0)
16 Early Studies not in the ISS Database	237	3 (1.3)	159	3 (1.9)
Bioequivalence Study (CVT 301-15)[b]	36	0	0	0

[a] Number of subjects/patients reflects number of subjects/patients who received at least one dose of study drug. See **Table 4**.

[b] See **ISS Section 23** for a summary of safety data.

Abstracted from **End-of-Text Table-1, Appendix III A, Table D-4.1, Appendix III F Table I-1.1, Appendix IV A Table D-4.2, Appendix V A Table D-4.3, Appendix V F Table I-1.3, Appendix VI A Table D-4.4, Appendix III G Table J-1.1, Appendix V G Table J-1.3, Study Report CVT 301-15**, and **Item 8, Section 8.15.**

The percents of dropouts for adverse events in all but the smallest categories were at least twice as high in the ranolazine group compared to placebo. One explanation is that the mean duration of exposure is much higher for the treated compared to the placebo groups (in the ISS database the ranolazine and placebo groups mean duration of exposure were 160 days and 25 days, respectively). However, in the Phase 2/3 controlled angina trials where the mean duration were similar (ranolazine 66 days and placebo 53 days), the dropout rate was more than 2 times higher in the ranolazine group (8.4%) compared to placebo (4.0%).

ISS database

The table below shows the adverse events leading to discontinuation in at least 0.5% of subjects in the ranolazine group and reported more often in the ranolazine group than the placebo group.

No. and (percent) of patients

Event	Placebo N=1529	Ranolazine N=2682	Placebo subtracted
Any event	31 (2.0)	226 (8.4)	6.4
Dizziness	1 (0.1)	30 (1.1)	1.0
Nausea	1 (0.1)	26 (1.0)	0.9
Angina	11 (0.7)	36 (1.3)	0.6
Asthenia	0	13 (0.5)	0.5
Headache	1 (0.1)	17 (0.6)	0.5
Myocardial infarct	0	14 (0.5)	0.5
Constipation	0	14 (0.5)	0.5

Table G-6.1

The adverse events leading most often to discontinuation in the ranolazine group compared to placebo included dizziness, nausea, and angina.

Phase 2/3 controlled trials
The table below shows the adverse events leading to discontinuation in at least 0.5% of subjects in the ranolazine group and reported more often in the ranolazine group than the placebo group.

No. and (percent) of patients

Event	Placebo N=455	Ranolazine N=749	Placebo subtracted
Any event	18 (4.0)	62 (8.3)	4.3
Dizziness	1 (0.2)	13 (1.7)	1.5
Nausea	0	10 (1.3)	1.3
Headache	0	6 (0.8)	0.8
Constipation	0	6 (0.8)	0.8
Asthenia	0	5 (0.7)	0.7
Myocardial infarct	0	4 (0.5)	0.5
Syncope	0	4 (0.5)	0.5
Vomiting	0	4 (0.5)	0.5

Table G-6.3

A total of 62 (8.3%) subjects discontinued ranolazine compared to 18 (4.0%) placebo subjects. The adverse events leading most often to discontinuation in the ranolazine group compared to placebo included dizziness, nausea, headache, and constipation.

By dose
Specific adverse events that led to discontinuation and are suggestive of a dose response are shown in the table below.

No. and (percent) of patients

	Ranol 500 mg N=181	Ranol 750 mg N=279	Ranol 1000 mg N=459	Ranol 1500 mg N=187
Any event	2 (1.1)	22 (7.9)	28 (6.1)	10 (5.3)
Dizziness	0	2 (0.7)	8 (1.7)	3 (1.6)
Nausea	0	1 (0.4)	5 (1.1)	4 (2.1)
Headache	0	1 (0.4)	2 (0.4)	3 (1.6)
Constipation	0	2 (0.7)	2 (0.4)	2 (1.1)
Vomiting	0	1 (0.4)	1 (0.2)	2 (1.1)
Syncope	0	0	3 (0.7)	1 (0.5)
Asthenia	0	1 (0.4)	3 (0.7)	1 (0.5)

Table J-1.3 vol 1.0366

Although the sample sizes are relatively small, the highest ranolazine group (1500 mg) had the highest reporting rates for these events.

Serious adverse events
The numbers and percents of patients reporting serious events in the 81 ranolazine studies are shown below.

Table 18 Incidence of Serious Adverse Events by Category and Treatment—All Treated Subjects/Patients

Category	Ranolazine		Placebo	
	Total N	Number (%) of Subjects/ Patients with Any SAEs	Total N	Number (%) of Subjects/ Patients with Any SAEs
All Treated Subjects/Patients (all studies)	2,955	268 (9.1)	1,688	36 (2.1)
ISS Database (64 studies)	2,682	255 (9.5)	1,529	30 (2.0)
Phase 2/3 SR Controlled Angina Studies	749	51 (6.8)	455	16 (3.5)
16 Early Studies not in the ISS Database	237	13(5.5)	159	6 (3.8)
Bioequivalence Study CVT 301-15	36	0	0	0

Abstracted from **Appendix III A Table D-4.1, Appendix III F Table I-1.1, Appendix IV A Table D-4.2, Appendix V A Table D-4.3, Appendix V F Table I-1.3, Appendix VI A Table D-4.4,** Final Study Reports of 16 Early Studies not in the ISS database **(Item 8, Section 8.15)**, and Study CVT 301-15 **(Item 8, Section 8.15)**.

In all cases except the 16 early studies, the percents of ranolazine patients reporting serious events were at least twice as high compared to placebo patients.

Phase 2/3 SR controlled angina studies

Only angina was identified as a serious adverse event that was reported by at least 1% of subjects in any treatment group. Out of 749 ranolazine subjects in the controlled angina studies, 1.7% reported angina compared to 1.8% in the placebo group.

Syncope

The number and percent of subjects reporting adverse events of syncope or suggestive of syncope or pre syncope are shown below from the ISS data base.

S Database

TABLE K-1 (PAGE 1 OF 1)
Summary of Potential Syncope Related Adverse Events*

Preferred Term	Placebo IR N (%)	Ranolazine IR N (%)	Placebo IV N (%)	Ranolazine IV N (%)	Placebo SR N (%)	Ranolazine SR N (%)	Total Placebo N (%)	Total Ranolazine N (%)
tal Number of Patients in Summary	947	1299	13	77	569	1359	1529	2682
tal Patients With Any AEs	35(3.7)	201(15.5)	2(15.4)	33(42.9)	31(5.4)	284(20.9)	68(4.4)	516(19.2)
DY AS A WHOLE	35(3.7)	201(15.5)	2(15.4)	33(42.9)	31(5.4)	284(20.9)	68(4.4)	516(19.2)
ABNORMAL VISION	0	4(0.3)	0	2(2.6)	0	12(0.9)	0	18(0.7)
BLACKOUT	0	2(0.2)	0	0	0	0	0	2(0.1)
COLLAPSE	1(0.1)	1(0.1)	0	0	0	1(0.1)	1(0.1)	2(0.1)
DIPLOPIA**	0	1(0.1)	0	5(6.5)	0	4(0.3)	0	10(0.4)
DIZZINESS**	11(1.2)	75(5.8)	2(15.4)	24(31.2)	12(2.1)	123(9.1)	25(1.6)	220(8.2)
FAINT	3(0.3)	9(0.7)	1(7.7)	1(1.3)	2(0.4)	6(0.4)	6(0.4)	16(0.6)
HYPOTENSION	0	8(0.6)	0	1(1.3)	3(0.5)	25(1.8)	3(0.2)	34(1.3)
LIGHT HEADED	9(1.0)	45(3.5)	0	5(6.5)	7(1.2)	58(4.3)	16(1.0)	108(4.0)
LOSS OF CONSCIOUSNESS	0	0	0	0	0	1(0.1)	0	1(0.0)
NAUSEA AND VOMITING**	0	3(0.2)	0	0	0	3(0.2)	0	6(0.2)
NAUSEA**	13(1.2)	73(5.5)	0	19(24.7)	5(0.8)	110(8.1)	18(1.0)	202(7.5)
PRE/NEAR SYNCOPE/SYNCOPAL	0	0	0	0	0	3(0.2)	0	3(0.1)
SYNCOPE/SYNCOPAL	0	4(0.3)	0	2(2.6)	1(0.2)	13(1.0)	1(0.1)	19(0.7)
VASOVAGAL	0	4(0.3)	0	2(2.6)	0	2(0.1)	0	8(0.3)
VERTIGO**	1(0.1)	5(0.4)	0	0	1(0.2)	16(1.2)	2(0.1)	21(0.8)
VOMITING**	6(0.6)	11(0.8)	0	3(3.9)	3(0.5)	31(2.3)	9(0.6)	45(1.7)

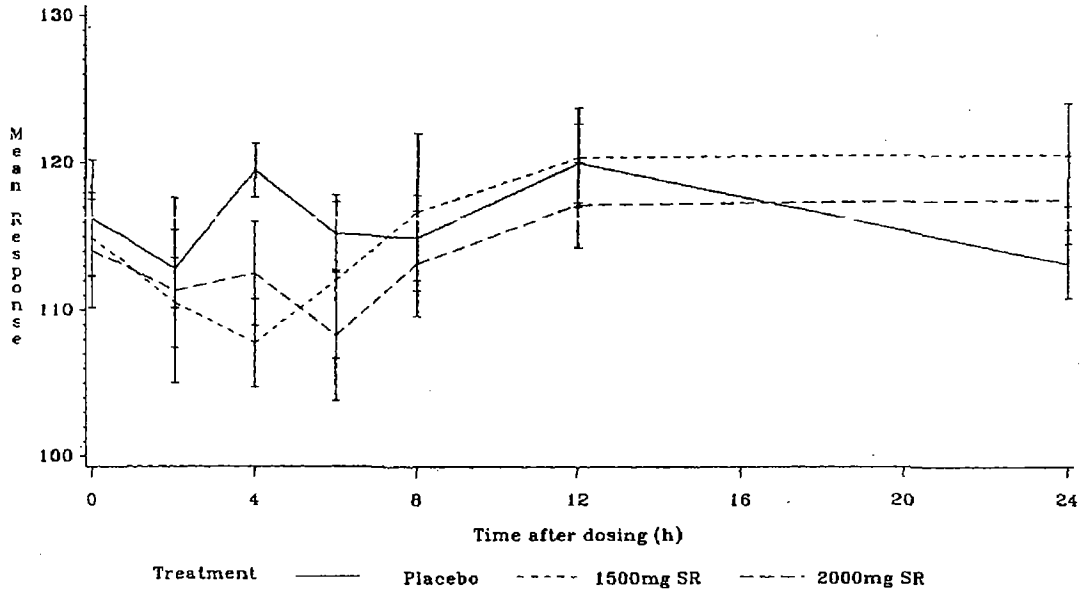
Verbatim and Preferred Terms are used in this Table
Preferred Terms also Appear in G, H, I, J Series Tables
URCE: TAE_S1 (25OCT2002 17:14) CVT-303\ISS\STATISTICS\MODULE0\TABLE_GRAPH\TAE_S1.RTF

The percent of total ranolazine subjects reporting one or more of these events was 19.2%, this is more than 4 times the percent of placebo patients reporting the same events (4.4%). The percents of subjects reporting syncope and/or near syncope were 0.1% (1) for placebo and 0.8% (21) for ranolazine. Reports of dizziness and light headed were also more common with ranolazine.

Doses associated with syncope (orthostatic changes)

There were 10 reports of syncope (called syncopal episode, vasovagal episode, loss of consciousness, collapse) in the Phase 2/3 controlled trials. The doses being used at the time the event was reported were 1500 mg SR (3), 5 at 1000 mg SR (5), 120 tid IR (1), and placebo (1). In study RANSO201, doses of 1500 and 2000 mg bid produced significant mean orthostatic changes (-9.8 mmHg and -8.4 mmHg, respectively, compared to placebo) at 4-6 hours after dosing. Some of the subjects could not have their erect blood pressures recorded because of these changes. The figure below shows the mean erect systolic blood pressures profiles by dose.

RANS0201 Figure 8
Haemodynamic Data: Mean values (+/- standard error)
Erect Systolic Blood Pressure (mmHg): Day 5



Erect systolic blood pressure decreased from baseline at around 4 hours after dose intake, the time of peak drug concentration. The drop was greater for the 2000 mg dose. Three subjects could not undergo erect blood pressure recordings because of symptoms of lightheadedness.

5.0 ECG

Methodology

All ECGs from CVT-conducted multiple dose studies were read by a central Core ECG Laboratory (St. Louis University Core ECG Laboratory). The parameters summarized are the ECG intervals as measured in msec: PR, QRS, QT, and the corrected QT (QTc).

Each QT value from CVT-conducted multiple dose studies is the maximum QT value among the 12 leads in that ECG, corrected as indicated for heart rate.

ECG intervals

ISS database

Mean changes from baseline at endpoint for ECG intervals are shown below. The ECG recordings were not necessarily obtained at peak effect.

Table 36 Summary of Mean Overall Change From Baseline by Treatment Group in ECG Intervals—ISS Database

	Ranolazine SR	Placebo SR	Total Ranolazine	Total Placebo
PR Interval				
N	1,277	550	2,276	1,316
Mean Change from Baseline (msec)[a]	1.1	-1.1	0.2	-1.5
SD	14.0	13.8	23.8	28.6
QRS Interval				
N	1,287	553	2,342	1,322
Mean Change from Baseline (msec)[a]	0.2	-0.2	0.5	-0.1
SD	8.5	8.1	14.1	13.4
QT Interval				
N	1,276	552	2,327	1,317
Mean Change from Baseline (msec)[a]	3.6	-3.8	2.7	-1.5
SD	22.6	20.6	25.3	26.9
QT_cB Interval				
N	1,276	552	2,333	1,320
Mean Change from Baseline (msec)[a]	2.0	-1.6	1.5	-1.2
SD	16.3	18.3	24.5	28.7

[a] Mean changes were calculated over the duration of treatment and were not correlated to peak/trough measurements.

Abstracted from **Appendix III J Table N-1.1.**

Compared to placebo, there were larger changes from baseline for all of the ECG intervals listed above. The changes from baseline for the QT and QTc intervals for the ranolazine SR group were 3.6 msec and 2.0 msec, respectively, and 2.7 msec and 1.5 msec, respectively, for total ranolazine. Comparative changes for the placebo groups were negative. These measurements are independent of time of last dose so results are underestimates of the true effect.

Shift tables

The following table shows the number and percent of subjects who received either placebo or ranolazine SR only (in the ISS database) and had a normal QT/QTc interval at baseline that became abnormal at endpoint.

No. and (percent) of subjects

	Placebo SR N=569	Ranolazine SR N=1359
Normal QT at baseline abnormal QT at endpoint	49 (8.6)	210 (15.5)+
Normal QTc at baseline abnormal QTc at endpoint	28 (4.9)	70 (5.2)^

+includes 2 subjects whose abnormal QT interval was judged not to be clinically significant
^includes 65 subjects whose abnormal QTc interval was judged not to be clinically significant
Table N 8.1 vol1.0363 pg 379-380

Phase 2/3 SR controlled angina studies

The table below shows the mean changes from baseline for ECG intervals by dose.

Table 37 Summary of the Mean Changes From Baseline by Dose in ECG Parameters for the Phase 2/3 SR Controlled Angina Studies Population

		Ranolazine (mg)				
	Placebo	500 b.i.d.	750 b.i.d.	1,000 b.i.d.	1,500 b.i.d.	Total Ranolazine SR
PR Interval						
N	438	177	269	434	172	706
Mean Change from Baseline (msec)[a]	-0.5	0.6	1.6	2.1	5.7	1.7
SD	14.1	14.0	13.8	14.5	14.5	13.9
QRS Interval						
N	440	177	271	438	172	712
Mean Change from Baseline (msec)[a]	-0.1	0.4	0.7	1.2	1.8	1.0
SD	8.6	9.9	8.6	9.4	10.5	8.8
QT Interval						
N	439	177	269	434	173	706
Mean Change from Baseline (msec)[a]	-3.1	1.3	7.0	6.6	10.5	6.7
SD	21.0	23.1	23.7	22.2	24.9	22.3
QT_cB Interval						
N	439	177	269	434	173	706
Mean Change from Baseline (msec)[a]	-2.0	2.1	3.7	4.6	8.7	4.6
SD	19.1	24.7	13.6	17.2	25.9	15.7

[a] Mean changes were calculated over the duration of treatment and were not correlated with peak/trough measurements.

There were dose related increases in all of the ECG intervals and these changes were greater than those for placebo. Mean increases from baseline for QT/QTc were 1.3/2.1 msec for the 500 mg dose and 10.5/8.7 msec for the 1500 mg dose.

Maximum mean QT changes were 11.4, 9.9, 25.7, 20.5, and 18.4 msec for placebo, ranolazine 500 mg, 750 mg, 1000 mg, and 1500 mg, respectively (table N-1.3.1 vol 1.0376).

The measurements discussed above are independent of time of last dose (and peak effect is greater than trough effect) so they are underestimates of the true effect.

Peak effect
Mean change from baseline in QTc interval (msec) at peak

	Placebo 455	Ranol 500 N=177	Ranol 750 N=269	Ranol 1000 N=428	Ranol 1500 N=170
Mean change from baseline	-2.0	3.3	3.5	5.0	11.0
Max mean change from baseline	1.1	3.3	8.9	8.1	11.0

Table N-1.3.2.1vol 1.0376

Effects of ranolazine on QTc interval are greater when measured at peak drug concentration than effects measured at trough (or at random).

The shift table below shows the number and percent of patients, by dose, who had a normal QTc interval at baseline and an abnormal one at endpoint. ECG measurements were made at peak drug concentration.

No. and (percent) of patients

	Placebo N=455	Ranol 500 N=181	Ranol 750 N=279	Ranol 1000 N=459	Ranol 1500 N=187
Normal at baseline and abnormal+ at endpoint	24 (5.3)	18 (9.9)	10 (3.6)	28 (6.1)	40 (21.4)

+includes those that the sponsor identified as not clinically significant.
Table N-8.3.2.1 vol 1.0377

A total of 40 subjects (21.4%) of subjects who received the 1500 mg dose of ranolazine developed an abnormal QTc interval that was "normal" at baseline.

The table below shows the number and percent of patients, by dose, who had selected QTc interval changes from baseline at endpoint at peak drug concentration.

No. and (percent) of patients

Change from baseline	Placebo N=433	Ranol 500 N=177	Ranol 750 N=271	Ranol 1000 N=433	Ranol 1500 N=170
0-30 msec	167 (38.6)	67 (37.9)	160 (59.0)	242 (55.9)	71 (41.8)
31-60 msec	21 (4.8)	20 (11.3)	6 (2.2)	29 (6.7)	28 (16.5)
≥61 msec	4 (0.9)	6 (3.4)	1 (0.4)	1 (0.2)	10 (5.9)

Table N-15.3.1 vol 1.0377

Major placebo controlled trials and their follow up studies
A total of 980 patients were randomized into Studies CVT 3031 or CVT 3033 and had baseline and at least one post-randomization ECG. Of these patients, 550 also elected to continue ranolazine treatment in the respective open-label studies, Studies CVT 3032 or CVT 3034 as of the NDA cut-off date (October 15, 2001). Of this selected group, those with either an increase from baseline ≥ 60 msec in the QTc interval or a QTc value > 500 msec using Bazett's correction are summarized by treatment in the table below.

Table 39 Summary of Bazett QT_c Outliers by Treatment in Studies CVT 3031, CVT 3032, CVT 3033, and CVT 3034

Treatment	Number of Patients Treated	Number (%) of Patients with a QT_c Increase ≥ 60 msec from Baseline	Number (%) of Patients with a QT_c > 500 msec	Either	Both
Placebo	436	7 (1.6%)	7 (1.6%)	11 (2.5%)	3 (0.7%)
Placebo (Rebound Phase)	245	0 (0%)	1 (0.4%)	1 (0.4%)	0 (0%)
Ranolazine 500 mg b.i.d.	500	12 (2.4%)	11 (2.2%)	17 (3.4%)	6 (1.2%)
Ranolazine 750 mg b.i.d.	611	9 (1.5%)	2 (0.3%)	10 (1.6%)	1 (0.2%)
Ranolazine 1,000 mg b.i.d.	528	9 (1.7%)	15 (3.0%)	22 (4.2%)	3 (0.6%)
Ranolazine 1,500 mg b.i.d.	173	11 (6.9%)	13 (7.5%)	21 (12.1%)	4 (2.3%)
Off-Treatment	112	0	1 (0.9%)	1 (0.9%)	0

Abstracted from Appendix VII F Table N-23, and Appendix VII F Table N-28.1.

Overall, the effect of ranolazine on the QTc interval was worse compared to placebo. For patients receiving the highest dose, 2.3% had both an increase in QTc of at least 60 msec over baseline and had QTc >500 msec compared to 0.7% of placebo patients. Again, this is probably an underestimate because the effect of ranolazine is worse at peak concentration.

The sponsor states that the Fridericia correction is "better [because it] eliminates the relationship between QT and heart rate as well as reduces variability." The table below shows the number and percent of QT outliers using Fridericia's correction.

Table 41 Summary of Fridericia QT_c Outliers by Treatment in Studies CVT 3031, CVT 3032, CVT 3033, and CVT 3034

Treatment	Number of Patients Treated	Number (%) of Patients with a QT_c Increase ≥ 60 msec from Baseline	Number (%) of Patients with a QT_c > 500 msec	Either	Both
Placebo	436	1 (0.2%)	2 (0.5%)	3 (0.7%)	0 (0%)
Placebo (Rebound Phase)	245	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ranolazine 500 mg b.i.d.	500	7 (1.2%)	4 (0.8%)	9 (1.6%)	2 (0.4%)
Ranolazine 750 mg b.i.d.	611	6 (1.0%)	1 (0.2%)	7 (1.2%)	0 (0%)
Ranolazine 1,000 mg b.i.d.	528	9 (1.7%)	5 (0.9%)	13 (2.5%)	1 (0.2%)
Ranolazine 1,500 mg b.i.d.	173	7 (4.6%)	7 (4.1%)	10 (6.4%)	4 (2.3%)
Off-Treatment	112	0	1 (0.9%)	1 (0.9%)	0

Abstracted from **Appendix VII F Table N-23**, and **Appendix VII F Table N-28.2**.

Regardless of the correction used, ranolazine has been shown to prolong the QT interval.

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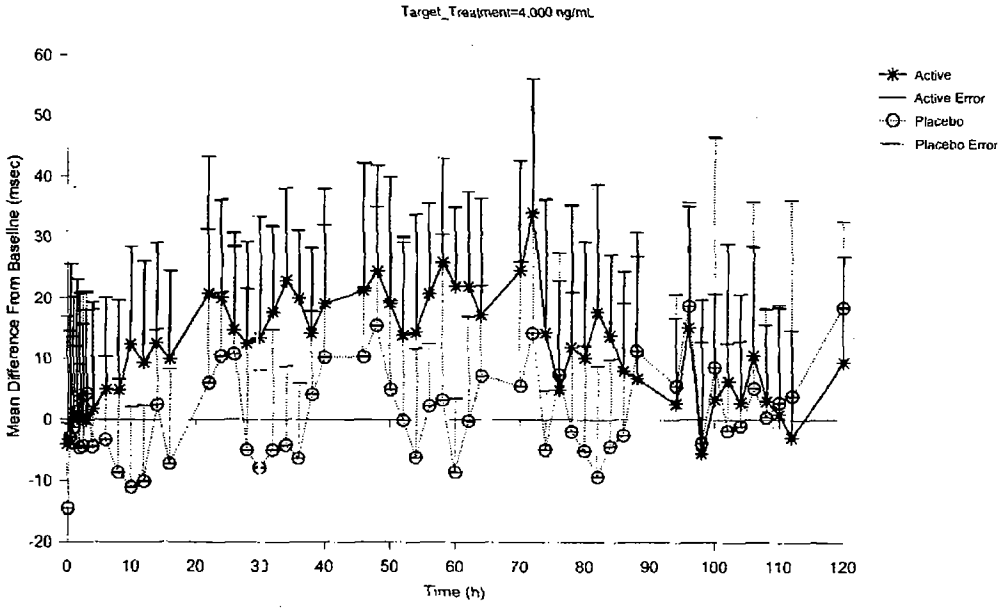
Plasma concentration and QT effect

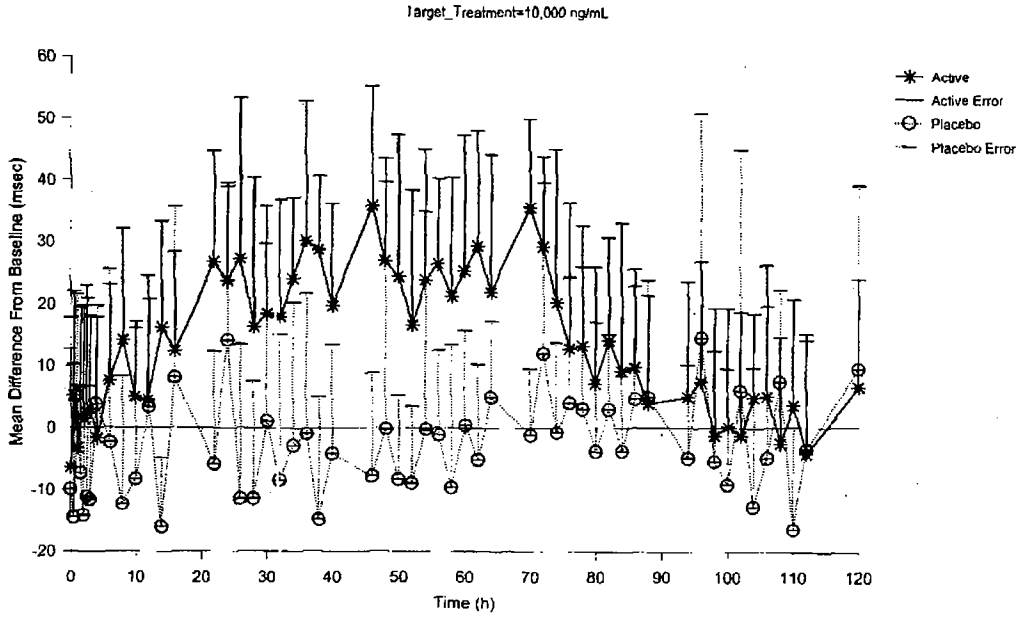
Study CVT 3111 was designed to characterize the relationship between the plasma ranolazine concentration and the effect of ranolazine (and its major metabolites) on the QTc interval by achieving plasma ranolazine concentrations higher than those typically generated.

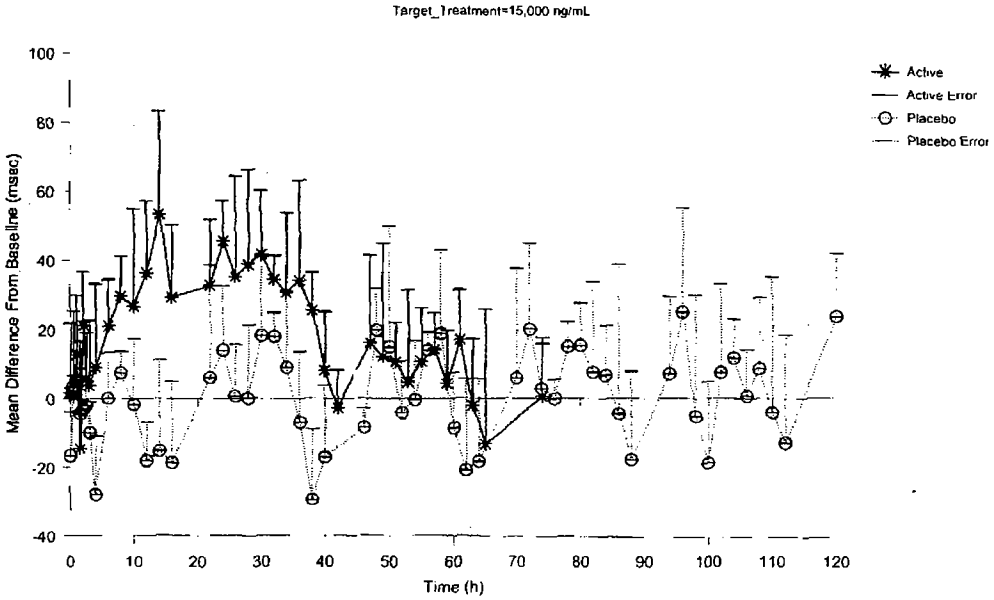
This was a randomized, placebo-controlled, single IV infusion, dose escalation, 4 period study involving 30 female and male healthy subjects. Period I consisted of a 2 hour IV infusion of ranolazine aiming for a target peak plasma ranolazine concentration of 2,000 ng/mL. Period 2 consisted of a 72 hour IV infusion of ranolazine/placebo aiming for a target peak plasma ranolazine concentration of 4,000 ng/mL. Period 3 consisted of a 72 hour IV infusion of ranolazine/placebo aiming for a target peak plasma ranolazine concentration of 10,000 ng/mL. Period 4 consisted of a 72 hour IV infusion of ranolazine/placebo aiming for a target peak plasma ranolazine concentration of 15,000 ng/mL. In each period the infusion of ranolazine/placebo was preceded by a 24 hour placebo infusion.

The figures below show the mean difference from baseline in QTc versus time for each target plasma concentration.

Figure 12.3.3 Mean (+SD) Difference From Baseline in QTc Interval of Subjects Receiving Ranolazine or Placebo for Each Target Treatment (Bazett)







Only 1 subject completed the ranolazine infusion in period 4.

A linear relationship between ranolazine plasma concentration and change in QTc interval from baseline was estimated to have an average slope of 2.29 msec per 1000 ng/mL. Three subjects were discontinued prematurely because of the attainment of protocol specified stopping rule of a greater than 30% increase in QTc from baseline or a value >500 msec.

There was no delay between QTc interval change and the achievement of steady-state ranolazine concentration. Therefore, it is likely that QTc changes are related to ranolazine and not its metabolites.

Higher oral dose
Subjects in Study RAN0201 received the highest single dose of oral ranolazine administered (ranolazine SR 2,000 mg b.i.d.). These doses resulted in significant orthostatic changes in systolic blood pressure compared to placebo 4 to 6 hours post-dosing (about 10 mmHg drop in standing systolic blood pressure). The mean plasma ranolazine concentration at the same time points ranged from 7,223 to 6,328 ng/mL in those receiving 2,000 mg bid. Three of eight volunteers administered ranolazine SR developed severe symptoms of lightheadedness upon standing.

PR Interval: the mean value was higher with ranolazine with a statistically significant increase over placebo of 8.8 msec at 2 hr post-dose on Day 5 with the 2000 mg dose ($p = 0.024$). This difference disappeared by 24 h after the final dose.

QT Interval: by Day 5 QT interval tended to be prolonged with both doses of ranolazine compared to placebo at all time points. The statistically significant increases seen with the 2000 mg dose were at 2 h post-dose (+ 14.2 msec), 4 h post-dose (+ 19.2 msec), and 6 h post-dose (+ 18.2 msec) on Day 5.

The mean QTc/QT intervals and mean differences from baseline profiles at steady state are shown below.

RANS0201
Table 49
ECG DATA
QT Interval (msec)
Mean Values and Treatment Comparisons : Day 5

Treatment		Time						
		Pre-dose	2 h	4 h	6 h	8 h	12 h	24 h
1500 mg SR	mean	407.6	409.1	412.1	388.1	405.1	388.1	404.6
	se	8.8	8.8	8.8	8.8	8.8	8.8	8.8
	n	8	8	8	8	8	8	8
2000 mg SR	mean	417.0	416.0	419.0	396.0	406.0	393.5	405.0
	se	8.8	8.8	8.8	8.8	8.8	8.8	8.8
	n	8	8	8	8	8	8	8
Placebo	mean	409.9	401.9	399.9	377.9	397.9	377.4	397.4
	se	8.7	8.7	8.7	8.7	8.7	8.7	8.7
	n	8	8	8	8	8	8	8
1500 mg SR - Placebo	mean difference	-2.3	7.2	12.2	8.2	7.2	10.7	7.2
	sed	6.3	6.3	6.3	6.3	6.3	6.3	6.3
	P	0.713	0.261	0.058	0.201	0.261	0.099	0.261
	95% CI	(-14.9,10.2)	(-5.4,19.7)	(-0.4,24.7)	(-4.4,20.7)	(-5.4,19.7)	(-1.9,23.2)	(-5.4,19.7)
2000 mg SR - Placebo	mean difference	7.2	14.2*	19.2**	18.2**	8.2	6.2	7.7
	sed	6.2	6.2	6.2	6.2	6.2	6.2	6.2
	P	0.253	0.025	0.003	0.004	0.193	0.325	0.221
	95% CI	(-5.2,19.5)	(1.8,26.5)	(6.8,31.5)	(5.8,30.5)	(-4.2,20.5)	(-6.2,18.5)	(-4.7,20.0)

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

Changes in QT were large (up to 19.2 msec) and statistically different from placebo at hours 2, 4, and 6 (for the 2000 mg dose), the time of peak drug concentrations.

RANS0201
Table 52
ECG DATA
QT, interval (msec)
Mean Values and Treatment Comparisons : Day 5

Treatment		Time						
		Pre-dose	2 h	4 h	6 h	8 h	12 h	24 h
1500 mg SR	mean	412.6	410.2	408.8	418.1	410.9	415.8	406.6
	se	6.3	6.3	6.3	6.3	6.3	6.3	6.3
	n	8	8	8	8	8	8	8
2000 mg SR	mean	415.0	415.0	416.4	414.4	411.5	415.4	402.1
	se	6.3	6.3	6.3	6.3	6.3	6.3	6.3
	n	8	8	8	8	8	8	8
Placebo	mean	396.4	393.6	388.2	400.2	390.4	402.4	395.4
	se	6.2	6.2	6.2	6.2	6.2	6.2	6.2
	n	8	8	8	8	8	8	8
1500 mg SR - Placebo	mean difference	16.1**	16.6**	20.6***	17.9**	20.5***	13.4*	11.1*
	sed	5.4	5.4	5.4	5.4	5.4	5.4	5.4
	P	0.004	0.003	<0.001	0.001	<0.001	0.015	0.043
	95% CI	(5.4,26.9)	(5.9,27.4)	(9.9,31.4)	(7.1,28.6)	(9.7,31.2)	(2.6,24.1)	(0.4,21.9)
2000 mg SR - Placebo	mean difference	18.6***	21.4***	28.2***	14.2**	21.1***	12.9*	6.7
	sed	5.2	5.2	5.2	5.2	5.2	5.2	5.2
	P	<0.001	<0.001	<0.001	0.007	<0.001	0.014	0.201
	95% CI	(8.3,28.9)	(11.1,31.8)	(17.9,38.5)	(3.9,24.5)	(10.8,31.4)	(2.6,23.3)	(-3.6,17.0)

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

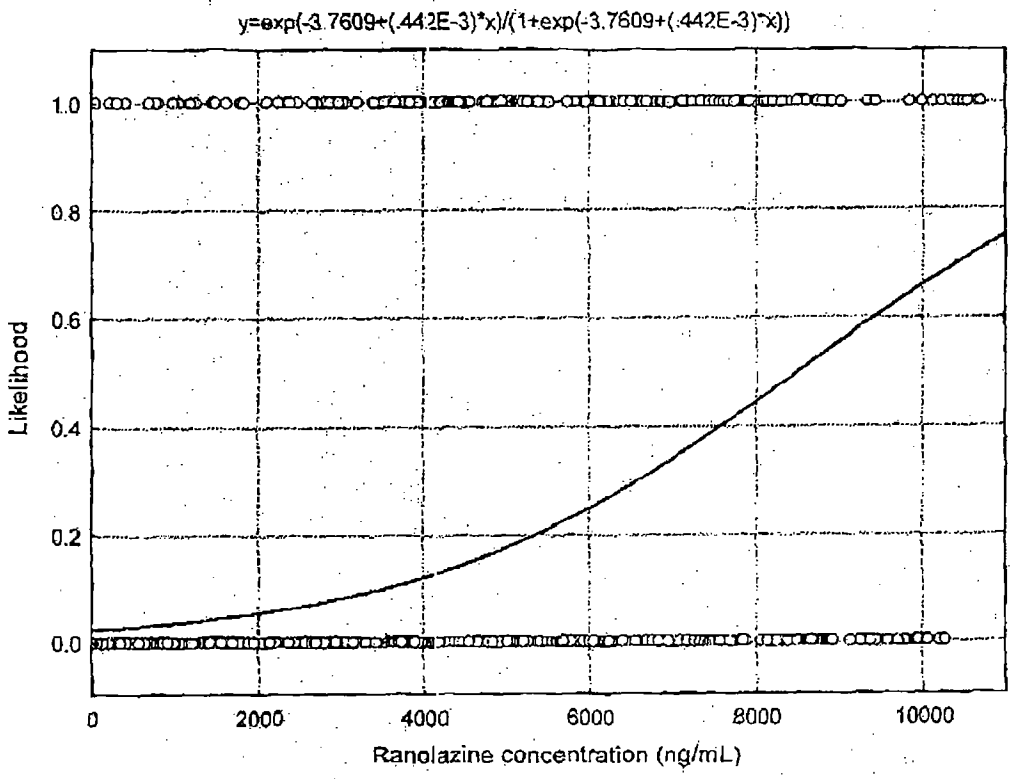
Substantial differences between active and placebo treatment n the mean QTc intervals were evident on Day 5, with statistical significant differences from placebo at every time point with both doses of ranolazine, except at 24 h after the final dose of 2000 mg. The maximum mean differences seen were at 4 h post-dose, when the mean value for the 1500 mg treatment was 20.6 msec greater than for placebo and the mean value for the 2000 mg treatment was 28.2 msec greater than for placebo.

T wave Morphology: repolarization abnormalities, represented by blunting or notching of the T wave, were detected in 1/8 subjects during placebo treatment, 5/8 subjects during treatment with 1500 mg ranolazine and 7/8 subjects during treatment with 2000 mg ranolazine SR. The only subject without any observed changes in T wave morphology also had the lowest plasma ranolazine concentrations.

T wave morphology
Along with QT interval changes, there were changes in T-wave morphology. These changes include both a reduction in amplitude as well as change in its configuration. The T-waves were classified by the Core EGG Laboratory according to the following system: amplitude (positive, negative, flat) and configuration (biphasic +/-, biphasic -/+, and notched).

The figure below shows the logistic regression function fitted to all data from active treatment to determine the likelihood of a notched T-wave at various ranolazine concentrations.

Figure 8.6-18 Likelihood of Observing a Notched T-wave in Study CVT 3111 at Different Ranolazine Plasma Concentrations



A decrease in amplitude was seen up to a concentration of approximately 3,000 ng/mL. Of the 109 ECGs with reported T wave notching, the average ranolazine concentration was 3,020 ng/mL (SD 2,310). The remaining ECGs (about 5700) with no T wave notching reported, the average ranolazine concentration was 1,360 ng/mL (SD 1583).

There were 3 episodes of syncope, one was considered to be serious and 2 that occurred during standing for blood pressure measurements. These episodes tended to be preceded by nausea, dizziness, sinus bradycardia (despite hypotension), blurring of vision, diplopia.

There were 3 withdrawals for QTc greater than 500 msec.

In total, 10 out of the 15 subjects who reached plasma ranolazine concentrations higher than 8,000 ng/mL in any of the dosing periods had their dosing interrupted because of CNS-related AEs, including visual disturbances and altered sensation. One additional subject also had dosing interrupted because of adverse event at a plasma ranolazine concentration of 5,510 ng/mL. None of the subjects' ECGs showed signs of cardiac arrhythmia.

In study CVT 3031, there were changes in the morphology of the T-wave during ranolazine use. These changes include both a reduction in amplitude (positive, negative, flat) as well as changes in its configuration (biphasic +/-, biphasic -/+, and notched).

The frequency of notched T waves is shown below by treatment group at peak and trough concentrations.

% of subjects with notched T waves

	Placebo	Ranol 500	Ranol 1000	Ranol 1500
peak	2%	1%	3%	6%
trough	<1%	<1%	5%	5%

There were more notched T waves were reported in the Ranolazine 1000 mg and 1500 mg doses than in the placebo and ranolazine 500 mg dose groups.

Genetic studies have shown that long-QT syndrome (LQTS) is a primary electrical disease caused by mutations in specific ion channels.[15] LQTS patients exhibit QT prolongation on the ECG and are at risk of arrhythmogenic syncope and sudden death. In addition to duration, T-wave morphology is often abnormal, and notched T waves have been included in diagnostic criteria.[16] This pattern has been associated with a poor prognosis.[17]

6.0 Vital signs

The tables below show the mean change from baseline for vital signs at trough and peak drug concentration. The data are grouped into ISS database, Phase 2/3 SR controlled trials, and open labeled studies.

Table 33 Summary of Mean Change from Baseline to Endpoint in Vital Sign Parameters in the ISS Database or Phase 2/3 SR Controlled Angina Studies Populations

Parameter	ISS Database		Phase 2/3 SR Controlled Studies		Open-Label Studies	
	Total Ranolazine	Total Placebo	Total Ranolazine	Placebo	Ranolazine	
					12-24 months	>24 months
	At Trough					
Systolic BP (mm Hg)						
N	2,044	944	716	442	220	93
Change from Baseline [n (%)]	-0.3 (0.6)	0.6 (1.1)	-0.2 (0.8)	0.3 (0.9)	-1.7	-3.0
SD[a]	16.0	14.6	16.9	14.8	16.7	17.2
Diastolic BP (mm Hg)						
N	2,044	944	716	442	220	93
Change from Baseline [n (%)]	-0.8 (0.0)	-0.3 (0.1)	0.1 (0.8)	0.3 (1.0)	-1.8	-3.5
SD[a]	9.5	9.1	9.1	9.0	9.0	10.2
Heart Rate (bpm)						
N	1,886	794	717	444	220	93
Change from Baseline [n (%)]	-0.2 (1.7)	1.2 (3.5)	-1.6 (-0.4)	-0.4 (1.2)	-6.3	-10.6
SD[a]	13.7	13.6	11.8	12.8	14.0	14.4

[15] Roden DM, Spooner PM. Inherited long QT syndromes: a paradigm for understanding arrhythmogenesis. J Cardiovasc Electrophysiol. 1999;
10: 1664-1683.

[16] Schwartz P1, Moss AJ, Vincent GM,et aI. Diagnostic criteria for the long QT syndrome: an update. Circulation. 1993; 88: 78-784.

[17] Malfatto G, Beria B, Sala S, et al. Quantitative analysis of T wave abnormalities and their prognostic implications in the idiopathic long QT syndrome. J Am Coll Cardiol. 1994; 23: 296-301.

Table 33 Summary of Mean Change from Baseline to Endpoint in Vital Sign Parameters by Dose in the ISS Database or Phase 2/3 SR Controlled Angina Studies Population (Cont'd)

Parameter	ISS Database		Phase 2/3 SR Controlled Studies		Open-Label Studies	
					Ranolazine	
	Total Ranolazine	Total Placebo	Total Ranolazine	Placebo	12-24 months	>24 months
			At Peak			
Systolic BP (mm Hg)						
N	1,382	908	707	432	NA	NA
Change from Baseline [n (%)]	-4.2 (-2.5)	-3.3 (-1.8)	-6.1 (-3.8)	-4.1 (-2.3)	NA	NA
SD[a]	15.6	14.6	16.1	15.9	NA	NA
Diastolic BP (mm Hg)						
N	1,382	908	707	432	NA	NA
Change from Baseline [n (%)]	-2.1 (-2.1)	-0.5 (-0.1)	-3.2 (-3.5)	-0.8 (-0.4)	NA	NA
SD[a]	9.1	8.2	9.3	8.5	NA	NA
Heart Rate (bpm)						
N	1,223	756	707	432	NA	NA
Change from Baseline [n (%)]	-1.0 (-0.1)	0.5 (1.8)	-0.6 (0.6)	1.1 (2.9)	NA	NA
SD[a]	11.5	11.0	11.6	11.9	NA	NA

[a] The standard deviation presented is associated with the mean change from baseline data.

BP = blood pressure; bpm = beats per minute; mm Hg = millimeters of mercury; NA = not available; SD = standard deviation.

Abstracted from **Appendix III Table M-1.1**, **Appendix V Table M-1.3.1**, and **Appendix VI M-7.1**.

Phase 2/3 SR controlled angina studies

The tables below shows mean changes in pre-exercise standing vital signs at peak and trough drug concentrations, by dose.

Table 34 Summary of Mean Change from Baseline to Endpoint in Pre-Exercise Standing Vital Sign Parameters by Dose—Phase 2/3 SR Controlled Angina Studies Population

Parameter	Placebo	Ranolazine SR (mg)				Total Ranolazine
		500 b.i.d	750 b.i.d.	1,000 b.i.d.	1,500 b.i.d.	
			At Trough			
Systolic BP (mm Hg)						
N[a]	437	177	272	438	172	713
Change from Baseline [n (%)]	1.0 (1.5)	-3.1 (-1.7)	3.2 (3.1)	-0.2 (0.7)	-2.9 (-1.4)	0.9 (1.5)
SD[b]	13.1	14.8	12.3	14.8	17.3	13.2
Diastolic BP (mm Hg)						
N[a]	437	177	272	438	172	713
Change from Baseline [n (%)]	1.1 (2.0)	-0.4 (0.3)	1.4 (2.5)	0.4 (1.2)	-0.2 (0.2)	0.7 (1.6)
SD[b]	7.9	8.7	6.8	8.1	8.2	7.2
Heart Rate (bpm)						
N[a]	437	177	272	438	172	713
Change from Baseline [n (%)]	0.1 (1.8)	-0.8 (0.1)	-0.8 (0.7)	-1.6 (-0.5)	-3.6 (-3.1)	-1.2 (0.1)
SD[b]	11.7	11.1	10.5	10.9	11.4	10.4

7.0 Laboratory values

Methodology

Laboratory assessments collected at baseline and the end visit of each study phase were used. Laboratory parameters were in three panels:

- Hematology: white cell count, red cell count, hemoglobin, hematocrit, platelets, granulocytes, lymphocytes, and monocytes;

- Chemistry: BUN, creatinine, sodium chloride, total carbon dioxide, potassium, glucose, SGOT, SGPT, alkaline phosphatase, total bilirubin, creatinine kinase (OK), CK-MB isoenzymes;

- Urinalysis: color, pH, protein, glucose, ketones, bilirubin, urobilinogen, and nitrates.

- Adrenocorticotropic hormone (ACTH) stimulation testing was performed in some studies.

Laboratory parameters were evaluated for abnormalities in the 64 studies in the ISS data base as well as in the Phase 2/3 SR controlled angina studies plus their long term follow up studies. Only data from the controlled angina are presented in this review, although the results in the ISS data base were examined.

Hematology

The table below shows the mean changes from baseline for selected hematology parameters for the Phase 2/3 SR formulation, by dose (numbers of patients are approximates). The parameters were selected for the table if they appeared to be consistently different from placebo.

Mean change from baseline

	Placebo N=260	Ranol 500 mg N=41	Ranol 750 mg N=237	Ranol 1000 mg n=264	Ranol 1500 mg n=52
Eosinophils %	0	1.1	0	0.2	1.1
Hematocrit %	-0.1	-1.5	-0.9	-1.2	-1.0
Hemoglobin g/dL	-0.1	-0.5	-0.5	-0.6	-0.4
Lymphocytes %	0.3	-1.7	-1.5	-1.4	-1.1
RBC 10^6/ul	-0.1	-0.2	-0.2	-0.3	-0.1

Appendix V B table L-1.3 vol 1.0367

Compared to placebo, there are small mean increases from baseline in eosinophils and small mean decreases in hematocrit/hemoglobin and lymphocytes. These changes were not dose related. The sponsor states that there was no evidence of occult blood loss. (vol 340 page 11).

Shift changes for these parameters are shown below.

Table 28 Shifts of Selected Parameters from Baseline to Endpoint by Dose—Phase 2/3 SR Controlled Angina Studies

		Total Placebo	500 mg b.i.d.	750 mg b.i.d.	1000 mg b.i.d.	1500 mg b.i.d.	Total RAN
Eosinophils N(%)							
	N	260	41	237	264	52	593
Normal	Normal	253 (97.3)	30 (73.2)	226 (95.4)	237 (89.8)	36 (69.2)	528 (89.0)
	High	3 (1.2)	10 (24.4)	4 (1.7)	14 (5.3)	8 (15.4)	36 (6.1)
Red Blood Cells N(%)							
	N	260	41	237	264	52	593
Normal	Normal	237 (91.2)	36 (87.8)	212 (89.5)	238 (90.2)	47 (90.4)	532 (89.7)
	Low	8 (3.1)	3 (7.3)	14 (5.9)	21 (8.0)	2 (3.8)	40 (6.7)
Low	Normal	5 (1.9)	1 (2.4)	3 (1.3)	0	0	4 (0.7)
	Low	10 (3.8)	1 (2.4)	7 (3.0)	5 (1.9)	3 (5.8)	16 (2.7)
Hematocrit N(%)							
	N	259	41	230	261	51	582
Normal	Normal	226 (87.3)	34 (82.9)	208 (90.4)	235 (90.0)	40 (78.4)	516 (88.7)
	Low	8 (3.1)	3 (7.3)	8 (3.5)	13 (5.0)	2 (3.9)	26 (4.5)
Low	Normal	7 (2.7)	0	4 (1.7)	2 (0.8)	4 (7.8)	10 (1.7)
	Low	12 (4.6)	4 (9.8)	5 (2.2)	9 (3.4)	5 (9.8)	23 (4.0)
Occult Blood N(%)							
	N	299	40	258	297	54	649
Normal	Normal	272 (91.0)	35 (87.5)	236 (91.5)	269 (90.6)	49 (90.7)	589 (90.8)
	Abnormal	10 (3.3)	1 (2.5)	9 (3.5)	7 (2.4)	1 (1.9)	18 (2.8)

RAN = Ranolazine

Abstracted from **Appendix V H Table L-8.3.**

These changes are small and seemingly unrelated to dose.

The summary of mean changes for selected hematology values for the ISS data base, the Phase 2/3 SR controlled studies (all doses combined), and the open label studies.

Table 27 Summary of Mean Changes From Baseline in Eosinophils, Red Blood Cells, and Hematocrit Values

	ISS Database		Phase 2/3 SR Controlled Angina Studies		Open-Label Studies				
			Total		Ranolazine SR				
Laboratory Parameter	Ranolazine SR	Placebo	Ranolazine SR	Placebo	6–12 weeks	12 wks–6 months	6–12 months	12–24 months	>24 months
Mean Duration of Exposure (days)	200	44	66	53			448		
Eosinophils (%) Normal range: 0 to 6%									
N[a]	1,251[a]	371[a]	651[a]	301[a]	278	492	426	221	98
Mean Value[b]	2.9[b]	2.7[b]	2.8[b]	2.7[b]	2.6	2.4	2.5	2.3	2.4
Mean Difference from Baseline	0.0	0.1	0.2	0.0	–0.2	–0.3	–0.2	–0.5	–0.8
Red Blood Cells ($10^6/\mu L$) Normal range: 3.8 to 6.4 x $10^6/\mu L$									
N[a]	1.271[a]	376[a]	651[a]	301[a]	278	492	426	221	98
Mean Value[b]	4.8[b]	4.8[b]	4.8[b]	4.7[b]	4.6	4.5	4.5	4.5	4.5
Mean Difference from Baseline	–0.2	–0.1	–0.3	–0.1	–0.2	–0.2	–0.2	–0.2	–0.2
Hematocrit (%) Normal range: 34 to 52%									
N[a]	1,233[a]	376[a]	643[a]	301[a]	278	491	426	221	98
Mean Value[b]	42.8[b]	42.4[b]	42.8[b]	42.3[b]	41.6	41.7	41.4	41.2	41.2
Mean Difference from Baseline	–1.0	–0.5	–1.1	–0.1	–1.1	–0.7	–1.2	–1.6	2.1

[a] Number of patients at baseline **Appendix V H Table L-1.3**

[b] End point value for ISS database and Phase 2/3 SR controlled Angina Studies, Mean Value at each time point otherwise.

Mean difference from baseline = mean change from baseline to end of treatment

Abstracted from **Appendix III B Table E-1.1, Appendix V B Table E-1.3, Appendix III H Table L-1.1 and Appendix VI H Table L-7.**

In the ranolazine group[18], there was 1 withdrawal for anemia in the ranolazine group (IR formulation), 2 withdrawals for leukopenia (1 each IR and SR formulations). There were no placebo patients dropping out for these reasons.

Regarding serious adverse events, there were 3 reports of anemia (1 IR formulation and 2 SR formulation. There was 1 serious report of leukopenia (SR formulation). There were no placebo patients with these reports.

Blood chemistries

The table below shows the mean changes from baseline for selected blood chemistries parameters from the Phase 2/3 SR formulation, by dose (numbers of patients are approximates). The parameters were selected for the table if they appeared to be consistently different from placebo.

Mean change from baseline

	Placebo N=300	Ranol 500 mg N=41	Ranol 750 mg N=262	Ranol 1000 mg n=301	Ranol 1500 mg n=55
BUN mg/dl	-0.1	0.5	1.0	1.2	2.5
Creatinine mg/dl	0	0.1	0.1	0.1	0.2
Chloride mEq/l	0	0	-0.7	-0.6	-1.7
Glucose mg/dl	0.1	4.3	2.6	1.1	8.3
Sodium	-0.1	-0.7	-0.6	-0.8	-1.8

Appendix V B table L-1.3

Compared to placebo there were small increases in mean changes from baseline for both BUN and creatinine.

In the ranolazine groups from the ISS database, there was 1 withdrawal for increased BUN (IR formulation).[19]

8.0 Special populations

Age, race, gender

There were no clinical trials specifically designed to determine if there are age, gender, and/or race differences in safety.

The frequencies of reported adverse events, serious adverse events, and adverse events leading to discontinuation are shown below for the overall ISS database and Phase 2/3 SR controlled angina studies population.

[18] from Table G-6.1 vol 1.0349
[19] from Table G-6.1 vol 1.0349

Table 60 Incidence of Treatment-Emergent Adverse Events, Serious Adverse Events, and Adverse Events Leading to Discontinuation by Treatment, Age, Gender, Race—ISS Database and Phase 2/3 SR Controlled Angina Studies

Subgroup	Number (%) of Patients[a]											
	Ranolazine						Placebo					
	N	Total AEs	N	Total SAEs	N	Total DC	N	Total AEs	N	Total SAEs	N	Total DC
ISS Database												
Age [Years]												
< 65	1,753	950 (54.2)	1,753	116 (6.6)	1,753	97 (5.5)	965	278 (28.8)	965	17 (1.8)	965	15 (1.6)
65–<74	751	397 (52.9)	751	103 (13.7)	751	87 (11.6)	465	108 (23.2)	465	11 (2.4)	465	13 (2.8)
≥ 75	178	118 (66.3)	178	36 (20.2)	178	42 (23.6)	99	32 (32.3)	99	2 (2.0)	99	3 (3.0)
Gender												
Female	512	299 (58.4)	512	59 (11.5)	512	70 (13.7)	322	90 (28.0)	322	4 (1.2)	322	5 (1.6)
Male	2,170	1,166 (53.7)	2,170	196 (9.0)	2,170	156 (7.2)	1,207	328 (27.2)	1,207	26 (2.2)	1,207	26 (2.2)
Race												
Caucasian	2,306	1,250 (54.2)	2,306	236 (10.2)	2,306	201 (8.7)	1,347	353 (26.2)	1,347	28 (2.1)	1,347	31 (2.3)
Non-Caucasian	197	133 (67.5)	197	18 (9.1)	197	24 (12.2)	111	37 (33.3)	111	2 (1.8)	111	0

The placebo subtracted incidence rates are shown below.

Percent of patients

	age			gender		race	
	<65	65-<74	≥75	Female	Male	White	Non white
Total aes	25.4	29.7	34.0	30.4	26.5	28.0	34.2
Serious aes	4.8	11.3	18.2	10.3	6.8	8.1	7.3
Discontinued	3.9	8.8	20.6	12.1	5.0	6.4	12.2

Although there are differences in incidence rates, it's difficult to know if they are just the result of sample size discrepancies.

Table 60 Incidence of Treatment-Emergent Adverse Events, Serious Adverse Events, and Adverse Events Leading to Discontinuation by Treatment, Age, Gender, Race—ISS Database and Phase 2/3 SR Controlled Angina Studies (Cont'd)

Subgroup	Number (%) of Patients[a]											
	Ranolazine						Placebo					
	N	Total AEs	N	Total SAEs	N	Total DC	N	Total AEs	N	Total SAEs	N	Total DC
Phase 2/3 SR Controlled Angina Studies												
Age [Years]												
< 65	370	112 (30.3)	370	23 (6.2)	370	19 (5.1)	220	48 (21.8)	220	8 (3.6)	220	8 (3.6)
65–<74	287	110 (38.3)	287	19 (6.6)	287	26 (9.1)	189	41 (21.7)	189	6 (3.2)	189	7 (3.7)
≥ 75	92	53 (57.6)	92	9 (9.8)	92	17 (18.5)	46	12 (26.1)	46	2 (4.3)	46	3 (6.5)
Gender												
Female	169	63 (37.3)	169	9 (5.3)	169	18 (10.7)	114	26 (22.8)	114	3 (2.6)	114	4 (3.5)
Male	580	212 (36.6)	580	42 (7.2)	580	44 (7.6)	341	75 (22.0)	341	13 (3.8)	341	14 (4.1)
Race												
Caucasian	715	253 (35.4)	715	47 (6.6)	715	57 (8.0)	434	96 (22.1)	434	16 (3.7)	434	18 (4.1)
Non-Caucasian	34	22 (64.7)	34	4 (11.8)	34	5 (14.7)	21	5 (23.8)	21	0	21	0

[a] Number of patients reflects the number of patients who received at least one dose of study drug.

AE = adverse event; DC = discontinuation due to an AE; SAE = serious adverse event.

Abstracted from **Appendix III D Table G-8.1, Appendix III D Table G-9.1, Appendix III D Table G-10.1, Appendix III F Table I-4.1, Appendix III F Table I-5.1, Appendix III F Table I-6.1, Appendix III G Table J-5.1, Appendix III G Table J-6.1, Appendix III G Table J-7.1, Appendix V D Table G-8.3, Appendix V D Table G-9.3, Appendix V D Table G-10.3, Appendix V F Table I-4.3, Appendix V F Table I-5.3, Appendix V F Table I-6.3, Appendix V G Table J-5.3, Appendix V G Table J-6.3, Appendix V G Table J-7.3.**

Placebo subtracted incidence rates-Phase 2/3 SR controlled angina data base are shown below.

Percent of patients-placebo subtracted

	age			gender		race	
	<65	65-<74	≥75	Female	Male	White	Non white
Total aes	8.5	16.6	31.5	14.5	14.6	13.3	40.9
Serious aes	2.6	3.4	5.5	2.7	3.4	2.9	11.8
Discontinued	1.5	5.4	12.0	7.2	3.5	3.9	14.7

As with the ISS database, it's difficult to know if the differences in incidence rates are just the result of sample size discrepancies.

Hepatic impairment
Subjects with moderate hepatic impairment had an AUC and Cmax that were 76% and 51% higher, respectively, compared to healthy volunteers[20], when receiving ranolazine 875 mg followed by 500 mg bid. Subjects with mild impairment were similar to their healthy counterparts. The sponsor advises that this drug should not be used in patients with Child-Pugh category B or worse hepatic impairment. The table below shows the increase in QT with increasing hepatic impairment.

12.4.2.2 Mean Change from Baseline in QTc Interval

Day / Timepoint		Mean Change from Baseline (msec)		
		Healthy (n=16)	Hepatic Impairment	
			Mild (n=8)	Moderate (n=8)
Day 1	Predose	-6.9	-12.3	-11.6
	1 h	-14.3	-11.1	-14.8
	2 h	-6.9	-5.1	3.5
	3 h	-2.5	1.3	11.6
	4 h	0.9	11.6	13.1
	5 h	7.9	3.1	14.4
	7 h	-3.2	5.8	13.9
	9 h	-5.9	-5.5	3.8
	12 h	-4.9	3.4	4.4
Day 3	Predose	-3.6	-1.9	2.5
	1 h	-10.9	-14.8	-13.4
	2 h	-10.4	2.5	14.4
	3 h	-3.1	9.8	7.6
	4 h	-0.5	7.8	14.1
	5 h	12.5	18.1	12.3
	7 h	-6.4	12.3	20.8
	9 h	-4.0	3.5	4.4
	12 h	0.7	0.9	1.0

Note: Data presented in this table is located in Table 14.5.2.2.
Baseline is defined as the corresponding timepoint on Day -1.

The subjects had larger than expected prolongation of QTc. This could be the result of small sample sizes.

[20] Study CVT 3018

Renal impairment
With creatinine clearance decreasing from 100 mL/min to 30 mL/min, the average increase in ranolazine AUC and Cmax was approximately 80%[21].

Congestive heart failure
Study CVT 3031 enrolled 85 subjects with stable NYHA class III or IV heart failure and an ejection fraction <35%. Study design was double blind, placebo controlled, and randomized with patients receiving placebo or ranolazine SR 750 mg bid with or without digoxin. There were no deaths. Seven subjects reported a total of 8 serious events: cerebral ischemia, neuropathy, heart failure (2), myocardial ischemia, syncope, atrial flutter, and ventricular tachycardia. Half of these events were reported by subjects not receiving ranolazine. There were 2 discontinuations for adverse events: myocardial ischemia and heart transplant surgery.

Hypotension and/or postural hypotension were reported by 10 patients (all randomized to ranolazine). There was no evidence in this small study that ranolazine 750 mg bid worsens heart failure in patients with advanced CHF.

Regarding the entire ISS database, only 0.2% (5/2682) reported congestive heart failure or heart failure as an event that resulted in study drug discontinuation. There were 0/1529 placebo patients dropping out for this reason (table G-6.1).

Other concomitant diseases[22]
Adverse events, laboratory abnormalities, ECG changes, and vital signs were inspected in patients with concomitant reactive airway disease (N=153), or diabetes (383), or low BP, low HR and/or prolonged AV conduction (N=381). No studies were conducted to determine if there were effects of these concomitant diseases in patients taking ranolazine. There is no indication that patients with one or more of these concomitant diseases taking ranolazine are at increased risk compared to patients without additional disease.

9.0 Drug-drug interactions
CYP3A4 is a major determinant for ranolazine clearance. There was an average increase of plasma concentration of 3- to 4-fold in the presence of the potent CYP3A4 inhibitor ketoconazole (200 mg bid)[23]. Concomitant use with diltiazem resulted in increases in ranolazine plasma concentrations of 1.5- to 2.4-fold over the diltiazem total daily dose range (180-360 mg)[24]. Ranolazine 1,000 mg bid at steady-state caused a less than two-fold increase simvastatin exposure dosed at 80 mg qd[25]. Concomitant use of ranolazine and drugs that inhibit as well as those that are metabolized by CYP3A4 should be contraindicated.

In study CVT 3021, ranolazine SR 1000 mg bid was taken by healthy volunteers in conjunction with either placebo, or diltiazem 180, 240, or 360 mg qd for 8 days. There were statistically significant increases in ranolazine Cmax and AUC_{0-12}.

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[21] Study CVT 3016
[22] Ns reflect number of ranolazine patients with concomitant disease in ISS database except for low BP/HR/increased PR interval (patient number from Phase 2/3 controlled angina studies)
[23] Study CVT 301-10
[24] Studies CVT 3012, RANO121, and RANO6S
[25] Study CVT 3017

Verapamil (120 mg t.i.d.) increased ranolazine average plasma concentrations 2.25-fold at steady-state[26]. The primary cause of this effect could be the inhibition of P-glycoprotein (P-gp) in the gut, increasing the bioavailability of ranolazine. Concomitant use of ranolazine and drugs that inhibit P glycoprotein in the gut should be contraindicated.

Digoxin concentrations increased by 1.2-1.6 fold when used with ranolazine.

10.0 Abrupt withdrawal
In study CVT 3033, a 2-day rebound assessment for possible increase in anginal events, as measured by exercise treadmill test duration, was included in the study design. Ranolazine patients were discontinued from doses of 750 mg twice a day or 1000 mg twice a day compared to patients who were maintained on placebo during a 12 week treatment period. Trough exercise testing was obtained in all patients.

No patients were withdrawn from the study during the 2-day assessment phase and there were no deaths. There were 2 serious adverse events (myocardial infarction and myocardial ischemia) in patients randomized to ranolazine SR 750 mg with diltiazem as the concomitant medication.

11.0 Safety update
The 4-month safety update summarizes data collected from CVT's two ongoing open-label studies (CVT 3032 and CVT 3034) during the period of 15 October 2001 to 31 October 2002. It includes data from 194 new patients enrolled in CVT 3034, and additional data from 440 patients whose participation was ongoing as of the 15 October 2001 NDA data cut-off date. This safety update does not include any new information from controlled clinical studies.

As agreed with the Agency, the data presented in this submission includes updated information on the following:

- deaths;
- serious adverse events (SAEs);
- withdrawals due to adverse events (AEs); and
- electrocardiogram (ECG) data.

With this update, the total exposure has increased from 1171 to 1714 subject/patient years. The ongoing studies used the ranolazine SR formulation in doses ranging from 500 mg bid to 1000 mg bid. Currently, 219 patients have been exposed to ranolazine for 6-12 months, 402 for 12-24 months, and 293 for more than 24 months. Mean duration of exposure for the ISS data base is now 321 days; for the phase 2/3 controlled angina studies, it is now 612 days.

[26] Study CVT 301-1 1

Table 4R Overview of the Ranolazine Development Program by Treatment Group

	Number of Subjects/Patients[a] in Original Submission					
	Ranolazine			Total Number Exposed		
Category	Immediate Release	Sustained Release	IV	Ranolazine[b]	Placebo	All Subjects/Patients[b]
ISS Database[c]	1,299	1,359	77	2,682	1,529	2,985
Bioequivalence Study CVT 301-15	0	36	0	36	0	36
16 Early Studies[d]	86	0	151	237	159	304
Overall Total	1,385	1,395	228	2,955	1,688	3,325
	Number of Subjects/Patients[a] in 4-month Update					
	Ranolazine			Total Number Exposed		
Category	Immediate Release	Sustained Release	IV	Ranolazine[b]	Placebo	All Subjects/Patients[b]
ISS Database[c]	1,299	1,460	77	2,783	1,529	3,021
Bioequivalence Study CVT 301-15	0	Included in ISS database number	0	Included in ISS database number	0	Included in ISS database number
16 Early Studies[d]	86	0	151	237	159	304
Overall Total	1,385	1,460	228	3,020	1,688	3,325

[a] Number of subjects/patients reflects number of subjects/patients who received at least one dose of study drug.
[b] For studies with a crossover design, subjects/patients were only counted once in the overall total number of subjects/patients columns but may appear in more than one treatment column.
[c] 64 studies in the original NDA, 65 in the 4-month safety update with addition of Study CVT 301-15 to the ISS database population.
[d] Includes Studies RAN001, RAN002, RAN003, RAN003B, RAN004, RAN005, RAN006A, RAN007, RAN008, RAN010, RAN011, RAN012, RAN014, RAN055, RAN070, and RAN1789.

Abstracted from **Appendix III A Table D-4.1, Appendix III A Table D-4.1.1, Appendix IV A Table D-4.2, Appendix IV A Table D-4.2.1, Appendix V A Table D-4.3, Appendix V A Table D-4.3.1, Appendix VI A Table D-4.4, Appendix VI A Table D-4.4.1, Appendix VIII A Table D-4.5,** and Study Reports for the 16 early studies.

Patient disposition

Appears This Way
On Original

Table 6R Subject/Patient Disposition and Reason for Discontinuation—ISS Database

Category	Number of Subjects/Patients		
	Original Submission		4-Month Update
	Total Ranolazine N = 2,682	Total Placebo N = 1,529	Total Ranolazine N = 2,783
Mean Duration of Exposure [Days]	160	24	225
Discontinuation, n (%)	492 (18.3)	63 (4.2)	569 (20.4)
Reason for Discontinuation			
Unacceptable AE	212 (7.9)	28 (1.8)	233 (8.4)
Inappropriate Enrollment	7 (0.3)	0	7 (0.3)
Non-compliance (drug/protocol)	31 (1.2)	5 (0.3)	31 (1.1)
Need for Prohibited Medication	2 (< 0.1)	0	2 (<0.1)
Lost to Follow-up	7 (0.3)	0	9 (0.3)
Elective Withdrawal	31 (1.2)	5 (0.3)	64 (2.3)
Death	27 (1.0)	2 (0.1)	45 (1.6)
Study Termination by Sponsor	75 (2.8)	3 (0.2)	75 (2.7)
Other	100 (3.7)	20 (1.3)	103 (3.7)

Abstracted from **Appendix III A Table D-3.1 and Appendix III B Table E-1.1.**

Serious adverse events

There were 74 additional patients reporting a serious adverse event with submission of the safety update. The reports were mostly angina and myocardial infarction.

Table 19R Incidence of Treatment-Emergent Serious Adverse Events Reported for ≥ 1% of Subjects/Patients in Any Treatment Group by Body System—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations

Body System Preferred Term	Number (%) of Subjects/Patients				
	ISS Database			Phase 2/3 SR Controlled Studies	
	Original Submission		4-Month Update	Original Submission	
	Total Ranolazine N = 2,682	Total Placebo N = 1,529	Total Ranolazine N = 2,783	Total Ranolazine N = 749	Total Placebo N = 455
Mean Duration of Exposure (Days)	160	24	225	66	53
Total Patients With any SAEs	255 (9.5)	30 (2.0)	329 (11.8)	51 (6.8)	16 (3.5)
Cardiovascular System					
Angina Pectoris	77 (2.9)	15 (1.0)	99 (3.6)	13 (1.7)	8 (1.8)
Myocardial Infarct	23 (0.9)	1 (0.1)	40 (1.4)	6 (0.8)	0

SAE = serious adverse event.

Abstracted from **Appendix III B Table E-1.1, Appendix III F Table I-1.1, Appendix V B Table E-1.3, and Appendix V F Table I-1.3.**

Patient 3034/180/ 180 8213 was discontinued for elevated BUN (64 mg/dl), serum creatinine (2.0 mg/dl) , and serum uric acid (9.5 mg/dl). Drug was discontinued and the abnormalities started to resolve.

Deaths

There were reports of 21 additional deaths for this reporting period.

Table 22R Summary of Demographic Characteristics and Cause of Death—Phase 2/3 Controlled Angina Studies and Long-Term Open-Label Uncontrolled Studies Populations

	Frequency Count of Patients Who Died					
	Phase 2/3 Controlled Angina Studies[a]		Open-Label Angina Studies[a]			
	Original Submission		Original Submission		4-Month Update[c]	
	Ranolazine	Placebo[b]	Ranolazine	Off Treatment	Ranolazine	Off Treatment
Demographic Characteristics						
Mean Age (years)	62.6	56.0	71.3	65.6	68.4	65.0
Gender						
Male	6	3	14	9	25	16
Female	1	0	1	2	2	3
Cause of Death						
Sudden	2	1	6	1	8	4
VT/VF/CA	2	1	1	3	2	3
MI	2	0	3	4	7	7
Other CV	0	1	3	0	4	1
Other	1	0	1	3	5	4
Unknown	0	0	1	0	1	0

[a] Includes both ranolazine IR and ranolazine SR patients.

[b] Does not include 1 non-ISS population patient, a 70-year-old male patient (RAN 1789_2302) who died of multiple organ failure after treatment with placebo.

[c] Includes only patients exposed to ranolazine SR in Studies CVT 3032 and CVT 3034.

Abstracted from **Appendix II A, Appendix IV C Table F-1.1, and Appendix VI C Table F-1.3.**

Most of the causes of the newly reported deaths were cardiovascular in nature.

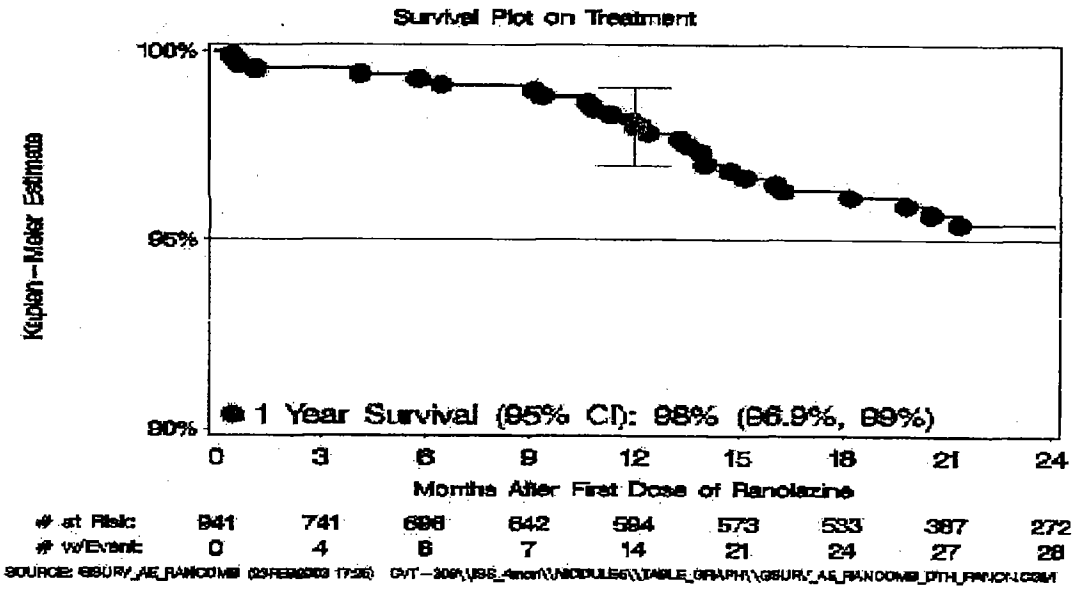
Deaths

Subject ID	Dose SR bid /duration (days)	Cause of death
3032/129/129 1082	1000 mg/1107	Liver carcinoma and sepsis
3032/505/505 1510+	1000 mg/1281	Non-Hodgkin's lymphoma
3032/506/506 1449	1000 mg/1159	Myocardial infarction
3034/141/141 8124	1000 mg/374	Elevated LFTs, jaundice, sepsis with biliary obstruction and probable cholangio-carcinoma
3034/182/182 9079	750 mg/740	Sudden death
3034/183/183 8354	750 mg/489	MI
3034/190/190 8006	1000 mg/864	Sudden death
3034/204/204 7021*	1000 mg/744	GI carcinoma, MI, UTI
3034/224/224 7300	1000 mg/650	Sudden death
3034/493/493 9516	1000 mg/83^	Collapse, prostatic carcinoma
3034/502/502 8117	750 mg/634	Sudden death
3034/512/512 8243	500 mg/666	MI
3034/519/519 9211	1000 mg/344	Angina, MI
3034/525/525 8258	750 mg/324	Sudden death
3034/706/706 8645	750 mg/178	Pulmonary embolism, endometrial carcinoma
3034/707/707 9604	1000 mg/176	Osteosarcoma
3034/710/710 9608	750 mg/202	MI
3034/712/712 7613	500 mg/117	Sudden death, Myocardial ischemia
3034/718/718 7643	1000 mg/46	Acute coronary syndrome
3034/721/721 9636	750 mg/192	Sudden death, hemopericardium
3034/728/728 9686	1000 mg/49	MI

+died after cut off date of 31 Oct 2002
*previous submitted, material updated
^ drug discontinued; patient died 44 days later

Survival curve
The updated version is shown below.

Figure 4R Survival of Chronic Angina Patients on Ranolazine SR; Studies CVT 3031–3034, on Treatment



Discontinuations for adverse events

An additional 30 patients were discontinued from treatment because of an adverse event, an increase of 0.8% compared to the original NDA.

Table 24R Number (%) of Subjects/Patients Who Discontinued Study Medication Due to Treatment-Emergent Adverse Events by Category and Treatment—All Treated Subjects/Patients

Category	Ranolazine				Placebo	
	Original Submission		4-Month Update		Original Submission	
	Total N	Number (%) of Subjects/ Patients[a]	Total N	Number (%) of Subjects/ Patients[a]	Total N	Number (%) of Subjects/ Patients[a]
All Treated Subjects/ Patients	2,955	240 (8.1)	3,020	270 (8.9)	1,688	38 (2.3)
ISS Database	2,682	237 (8.8)	2,783	267 (9.6)	1,529	35 (2.3)
Phase 2/3 SR Controlled Angina Studies	749	63 (8.4)	749	63 (8.4)	455	18 (4.0)
16 Early Studies not in the ISS Database	237	3 (1.3)	237	3 (1.3)	159	3 (1.9)
Bioequivalence Study (CVT 301-15)	36	0	Included in ISS database number	0	0	0

[a] Number of subjects/patients reflects number of subjects/patients who received at least one dose of study drug. See **Table 4R**.

Abstracted from **End-of-Text Table-1, Appendix III A, Table D-4.1, Appendix III F Table I-1.1, Appendix IV A Table D-4.2, Appendix V A Table D-4.3, Appendix V F Table I-1.3, Appendix VI A Table D-4.4, Appendix III G Table J-1.1, Appendix V G Table J-1.3.**

The adverse events most commonly resulting in discontinuation are shown below.

Table 25R Incidence of Most Common Treatment-Emergent Adverse Events Resulting in Discontinuation Reported for ≥ 1% of Subjects/Patients—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations

	Number (%) of Subjects/Patients				
	ISS Database			Phase 2/3 SR Controlled Studies	
	Original Submission		4-Month Update	Original Submission	
Category	Ranolazine (N = 2,682)	Placebo (N = 1,529)	Ranolazine (N = 2,783)	Ranolazine (N = 749)	Placebo (N = 455)
Mean Duration of Exposure (Days)	160	24	225	66	53
Total Subjects/ Patients Who Discontinued Due to AEs	226 (8.4)	31 (2.0)	256 (9.2)	62 (8.3)	18 (4.0)
Cardiovascular System					
Angina Pectoris	36 (1.3)	11 (0.7)	41 (1.5)	10 (1.3)	6 (1.3)
Digestive System					
Nausea	26 (1.0)	1 (0.1)	27 (1.0)	10 (1.3)	0
Nervous System					
Dizziness	30 (1.1)	1 (0.1)	30 (1.1)	13 (1.7)	1 (0.2)

Abstracted from **Appendix III B Table E-1.1, Appendix V B Table E-1.3, Appendix III G Table J-1.1, and Appendix V G Table J-1.3**.

This is similar to what was previously reported.

ECG

There is no new information about the effect of ranolazine on QT interval prolongation and T wave morphology changes. The summary of QTc outliers is shown below.

Table 39R **Summary of Bazett QT_c Outliers by Treatment in Studies CVT 3031, CVT 3032, CVT 3033, and CVT 3034**

Treatment	Number of Patients Treated		Number (%) of Patients with a QT_c Increase ≥ 60 msec from Baseline		Number (%) of Patients with a QT_c > 500 msec		Either QT_c Increase > 60msec from baseline or QT_c > 500msec		Both QT_c Increase > 60msec from baseline and QT_c > 500msec	
	Original Submission	4-Month Update	Original Submission	4-Month Update	Original Submission	4-Month Update	Original Submission	4-Month Update	Original Submission	4-Month Update
Placebo	436	436	7 (1.6)	7 (1.6)	7 (1.6)	7 (1.6)	11 (2.5)	11 (2.5)	3 (0.7)	3 (0.7)
Placebo (Rebound Phase)	245	245	0	0	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0
Ranolazine 500 mg b.i.d.	500	694	12 (2.4)	11 (1.6)	11 (2.2)	11 (1.6)	17 (3.4)	16 (2.3)	6 (1.2)	6 (0.9)
Ranolazine 750 mg b.i.d.	611	720	9 (1.5)	12 (1.7)	2 (0.3)	3 (0.4)	10 (1.6)	13 (1.8)	1 (0.2)	2 (0.3)
Ranolazine 1000 mg b.i.d.	528	620	9 (1.7)	13 (2.1)	15 (3.0)	16 (2.6)	22 (4.2)	25 (4.0)	3 (0.6)	4 (0.6)
Ranolazine 1500 mg b.i.d.	173	173	11 (6.9)	12 (6.9)	13 (7.5)	13 (7.5)	21 (12.1)	21 (12.1)	4 (2.3)	4 (2.3)
Off-Treatment	112	85	0	0	1 (0.9)	0	1 (0.9)	0	0	0

Abstracted from **Appendix VII F Table N-23, and Appendix VII F Table N-28.1.**

There is a dose related increase in the incidence rate of QTc outliers.

Protocol CVT 3031

A Double-Blind, Placebo-Controlled, 4-Period Cross Over, Multiple-Dose Study of Ranolazine SR as Monotherapy for Chronic Stable Angina Pectoris at Doses of 500 mg bid, 1000 mg bid, and 1500 mg bid.

The primary objective of this study was to determine the effect of ranolazine SR monotherapy compared to placebo in patients with chronic stable angina on exercise treadmill test duration at the time of trough ranolazine plasma levels (12 hours post dose) when given at the following doses 500 mg bid, 1000 mg bid and 1500 mg bid. There was no washout phase between doses.

Demographics

Panel 11A
Demographic and Background Characteristics - Safety Population

			Treatment Sequence				Comparison
Characteristic	Statistic	Total	ABCD	BDAC	CADB	DCBA	p-value
Total Number of Patients in Safety Population	N	191	47	49	50	45	
Gender:	n	191	47	49	50	45	0.050*
Male	n (%)	140 (73)	39 (83)	40 (82)	32 (64)	29 (64)	
Female	n (%)	51 (27)	8 (17)	9 (18)	18 (36)	16 (36)	
Mean Age (years)		64.3	64.7	65.0	64.0	63.2	0.807
Age Category:		191	47	49	50	45	0.817
<65 years	n (%)	90 (47)	23 (49)	20 (41)	24 (48)	23 (51)	
≥65 years	n (%)	101 (53)	24 (51)	29 (59)	26 (52)	22 (49)	
Race:	n	191	47	49	50	45	0.242
Caucasian	n (%)	174 (91)	45 (96)	46 (94)	43 (86)	40 (89)	
Black	n (%)	10 (5)	2 (4)	2 (4)	4 (8)	2 (4)	
Asian	n (%)	4 (2)	0	0	2 (4)	2 (4)	
Hispanic	n (%)	2 (1)	0	1 (2)	1 (2)	0	
Other	n (%)	1 (<1)	0	0	0	1 (2)	
Mean Weight	(kg)	83.3	85.3	86.8	80.7	80.2	0.076
Mean Height	(cm)	171.5	173.0	172.9	169.3	171.0	0.119

*0.010 < p-value ≤ 0.050; ** p-value ≤ 0.010.
Note: Treatment sequence comparison p-values for continuous variables are from an ANOVA with effects for treatment sequence and pooled site.
Note: Treatment sequence comparison p-values for categorical variables are based on a CMH test with pooled sites as strata.
Note: The treatment sequence comparison for race is for Caucasian versus Non-Caucasian.
Note: A = 500 mg bid; B = 1000 mg bid; C = 1500 mg bid; D = placebo.
Note: Percentages are based on the row totals for that category.
Data Source: Table 1.7.0

The majority of subjects were male, mean age was about 64 years, and most were white. Approximately half of the subjects were at least 65 years of age.

Study completion

Panel 10B
Patient Premature Discontinuation by Dose

			Treatment[2]			
	Statistic	Total[1]	Placebo	Ran SR 500mg	Ran SR 1000 mg	Ran SR 1500 mg
Total Number of Patients	N	191	179	181	180	187
Number of Patients Who Discontinued the Study Prematurely	n	23 (12%)	3	6	1	13
Primary Reason for Premature Discontinuation						
Unacceptable Adverse Event	n (%)	15 (8)	2 (67)	1 (17)	1 (100)	11 (85)
Inappropriate Enrollment	n (%)	1 (<1)	1 (33)	0	0	0
Non-compliance	n (%)	0	0	0	0	0
Elective Withdrawal	n (%)	4 (2)	0	2 (33)	0	2 (15)
Lost to Follow-up	n (%)	0	0	0	0	0
Death	n (%)	1 (<1)	0	1 (17)	0	0
Other	n (%)	2 (1)	0	2 (33)	0	0

[1] Percentages are based on the total number of patients randomized.
[2] Percentages are based on the total number of patients who discontinued the study prematurely.
Data Source: Table 1.2.0 and 1.2.1

There were 3 (1.7%) placebo subjects discontinued prematurely compared to 6 (3.3%) of the ranolazine 500 mg, 1 (0.5%) in the ranolazine 1000 mg, and 13 (7.0%) in the ranolazine 1500 mg groups.
Most of the discontinuations were the result of an adverse event.

Panel 10A (cont'd)
Patient Disposition

	Statistic	Total	Treatment Sequence ABCD	BDAC	CADB	DCBA
Primary Reason for Premature Discontinuation						
Unacceptable Adverse Event	n (%)	15 (8)	6 (13)	3 (6)	4 (8)	2 (4)
Inappropriate Enrollment	n (%)	1 (<1)	0	1 (2)	0	0
Non-compliance	n (%)	0	0	0	0	0
Elective Withdrawal	n (%)	4 (2)	1 (2)	0	2 (4)	1 (2)
Lost to Follow-up	n (%)	0	0	0	0	0
Death	n (%)	1 (<1)	0	1 (2)	0	0
Other	n (%)	2 (1)	0	0	1 (2)	1 (2)

[1]Defined as all randomized patients with evaluable efficacy measurements at baseline and for at least 3 of the 4 double-blind periods, irrespective of protocol violations.
[2]Defined as all randomized patients with evaluable efficacy measurements at baseline and for at least 1 double-blind treatment period, irrespective of protocol violations.
[3]Defined as all randomized patients with evaluable efficacy measurements at baseline and from the first double-blind period, irrespective of protocol violations.
[4]Defined as all randomized patients with an evaluable efficacy measurement at baseline and with at least 3 out of 4 treatment periods completed in accordance with the protocol.
[5]Defined as all randomized patients who receive at least 1 dose of double-blind study drug.
Note: Percentages are based on total number of patients randomized.
Note: A = 500 mg bid; B = 1000 mg bid; C = 1500 mg bid; D = placebo.
Data Source: Tables 1.0.0 and 1.2.0

All adverse events

Because of the cross over design of the study, it is very difficult to associate adverse event and dose. The following The table below shows the most common adverse events using the first period analysis (the analysis counting an AE in the period in which it occurred unless it worsened).

Panel 12C
Common Adverse Events*

	Statistic	Placebo (n=179)	500 mg Ran SR (n=181)	1000 mg Ran SR (n=180)	1500 mg Ran SR (n=187)
Total Number of Patients with at Least 1 AE	n (%)	26 (15)	28 (15)	37 (21)	62 (32)
Adverse Events:					
Dizziness	n (%)	1 (<1)	2 (1)	9 (5)	22 (12)
Nausea	n (%)	0	1 (<1)	2 (1)	16 (9)
Asthenia	n (%)	3 (2)	0	3 (2)	11 (6)
Angina Pectoris	n (%)	8 (4)	8 (4)	2 (1)	6 (3)

* Counting an AE only in the first period it occurred unless it worsened.
Data Source: Table 3.0.1

All of the reported events except angina pectoris were more frequent in the ranolazine 1500 mg group compare to lower dose groups and placebo.

Serious safety

Death

There was one death, the cause reported as ventricular fibrillation (sudden death), and the patient was on study drug for 17 days. He was taking ranolazine 500 mg at the time of death and in the previous weeks had received ranolazine 1000 mg and placebo in that order.

Serious adverse events

There were 12 patients who reported adverse events. The details of these events are shown below.

Panel 12H
Listing of Patients with Serious Adverse Events -
Safety Population

Site	Patient Number	Treatment Sequence	Treatment at Which SAE Occurred	SAE	Age/Sex/Race	Time From Baseline to Event (days)	Event Duration (days)	Frequency	Severity	Relation to Study Drug	Effect on Study Drug	Treatment	Outcome
124	1241034	ABCD	D	Atrial Fibrillation	76/M/C	28	1	Intermittent	Severe	Probably	Discontinued	Medication	Resolved
133	1331017	BDAC	A*	Ventricular Fibrillation	60/M/C	17	1	Single Episode	Severe	Possibly	None	None	Died
	1331018	CADB	C	Allergic Reaction	80/M/C	6	2	Single Episode	Severe	Probably Not	None	Medication	Resolved
137	1371132	BDAC	C**	Accidental Injury	71/M/B	37	2	Constant	Moderate	Probably Not	Discontinued	Other	Resolved
154	1541222	CADB	B	Shock	44/M/C	25		Constant	Severe	Probably Not	Discontinued	Medication	Ongoing
157	1571242	CADB	C	Postural Hypotension	63/M/C	8	1	Constant	Severe	Possibly	Interrupted	Other	Resolved
170	1701469	ABCD	C	Angina Pectoris	75/M/C	19	5	Intermittent	Moderate	Probably Not	None	Medication	Resolved
177	1771465	ABCD	C#	Syncope	76/F/C	20		Intermittent	Moderate	Probably Not	Discontinued	Other	Ongoing

* Patient 1331017 was dispensed drug for period 3 and died 2 days later. Information on tablets taken for that period is unknown.
**Patient 1371132 was dispensed drug for period 4, fractured his pelvis 10 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
Patient 1771465 was dispensed drug for period 3, experienced an SAE 4 days later, and withdrew from the study.
##Patient 1851529 experienced an SAE 4 days after completing period 4, the final visit in the double-blind treatment phase, and was no longer on study drug.
Note: For Race: C = Caucasian, B = Black, A = Asian, H = Hispanic, O = Other; For Sex: M = Male, F = Female.
Note: Ran SR = Ranolazine SR; A = 500 mg bid; B = 1000 mg bid; C = 1500 mg bid; D = Placebo
Note: SAE = Serious adverse event.
Note: One SAE not included in the table above is for patient 1551226, who had laboratory screening on [redacted]. He experienced chest pain on [redacted] and was hospitalized for observation. He stabilized, had Visit 1 on [redacted] and was subsequently randomized into the study.
Data Source: Table 3.1.1

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Panel 12H (cont'd)
Listing of Patients with Serious Adverse Events -
Safety Population

Site	Patient Number	Treatment Sequence	Treatment at Which SAE Occurred	SAE	Age/Sex/Race	Time From Baseline to Event (days)	Event Duration (days)	Frequency	Severity	Relation to Study Drug	Effect on Study Drug	Treatment	Outcome
185	1851529	DCBA	A##	Coronary Artery Disorder	50/M/C	32	2	Single Episode	Severe	Probably Not	None	Other	Resolved
512	5121315	CADB	C	Angina Pectoris	58/F/C	3	4	Intermittent	Moderate	Probably Not	Discontinued	Medication	Controlled
519	5191362	BDAC	C	Dizziness	65/M/C	25	1	Single Episode	Severe	Possibly	Discontinued	Medication	Resolved
				Headache		25	1	Single Episode	Severe	Possibly	Discontinued	Medication	Resolved
				Vertigo		25	1	Single Episode	Severe	Possibly	Discontinued	Medication	Resolved
520	5201341	ABCD	A	Angina Pectoris	45/M/C	3	2	Intermittent	Moderate	Possibly	Discontinued	Medication	Controlled

* Patient 1331017 was dispensed drug for period 3 and died 2 days later. Information on tablets taken for that period is unknown.
**Patient 1371132 was dispensed drug for period 4, fractured his pelvis 10 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
Patient 1771465 was dispensed drug for period 3, experienced an SAE 4 days later, and withdrew from the study.
##Patient 1851529 experienced an SAE 4 days after completing period 4, the final visit in the double-blind treatment phase, and was no longer on study drug.
Note: For Race: C = Caucasian, B = Black, A = Asian, H = Hispanic, O = Other; For Sex: M = Male, F = Female.
Note: Ran SR = Ranolazine SR; A = 500 mg bid; B = 1000 mg bid; C = 1500 mg bid; D = Placebo.
Note: SAE = Serious adverse event.
Note: One SAE not included in the table above is for patient 1551226, who had laboratory screening on [redacted]. He experienced chest pain on [redacted] and was hospitalized for observation. He stabilized, had Visit 1 on [redacted] and was subsequently randomized into the study.
Data Source: Table 3.1.1

Serious events were reported more often in the ranolazine 1500 mg group (7/191, 4%), compared to placebo (1/191, <1%), ranolazine 500 mg (3/191, 2%), and ranolazine 1000 mg (1/191, <1%). The events reported in the 1500 mg group include allergic reaction (post flu shot), accidental injury (occupation related), postural hypotension, angina (2), syncope, and dizziness (and headache and vertigo).

Withdrawals for adverse events

There were 15 subjects who withdrew from the study because of an adverse event.

Panel 12I
Listing of Patients Who Withdrew from the Study Due to Adverse Events - Safety Population

Site	Patient Number	Treatment Sequence	Treatment at Which SAE Occurred	AE	Age/ Sex/ Race	Time From Baseline to Event (days)	Event Duration (days)	Frequency	Severity	Relation to Study Drug	Effect on Study Drug	Treatment	Outcome
124	1241034	ABCD	D	Atrial Fibrillation	76/M/C	28	1	Intermittent	Severe	Probably	Discontinued	Medication	Resolved
			D	Supraventricular Extrasystoles		28	1	Intermittent	Moderate	Possibly	Discontinued	Medication	Resolved
127	1271119	ABCD	D	Arrhythmia	76/M/C	25	5	Intermittent	Moderate	Probably	Discontinued	None	Resolved
128	1281076	CADB	C	Increased Salivation	67/F/H	4	10	Intermittent	Moderate	Probably	Discontinued	None	Resolved
			C	Nausea		3	13	Intermittent	Moderate	Probably	Discontinued	None	Resolved
			C	Paresthesia		7	2	Intermittent	Moderate	Possibly	Discontinued	None	Resolved
			C	Thirst		4	10	Intermittent	Moderate	Possibly	Discontinued	None	Resolved
			C	Urine Abnormality		6	8	Intermittent	Moderate	Possibly	Discontinued	None	Resolved
			C	Vomiting		4	10	Intermittent	Moderate	Probably	Discontinued	None	Resolved
133	1331024	DCBA	C	Hematuria	80/F/C	9	4	Constant	Moderate	Possibly	Discontinued	Medication	Resolved
			C	Nausea		10	6	Constant	Moderate	Possibly	Discontinued	Medication	Resolved
137	1371132	BDAC	C*	Accidental Injury	71/M/B	37	2	Constant	Moderate	Probably Not	Discontinued	Other	Resolved
140	1401138	ABCD	A	Tremor	77/M/C	6	16	Constant	Moderate	Probably Not	Discontinued	Medication	Controlled
154	1541222	CADB	B	Congestive Heart Failure	44/M/C	25	1	Single Episode	Moderate	Probably Not	Discontinued	Medication	Resolved
			B	Shock		25		Constant	Severe	Probably Not	Discontinued	Medication	Ongoing

* Patient 1371132 was dispensed drug for period 4, fractured his pelvis 10 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
** Patient 1771465 was dispensed drug for period 3, began experiencing an SAE 4 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
Note: For Race: C = Caucasian, B = Black, A – Asian, H = Hispanic, O = Other; (Specify) For Sex: M = Male, F = Female.
Note: Ran SR = Ranolazine SR; A = 500 mg bid; B = 1000 mg bid; C – 1500 mg bid; D = Placebo.
Note: AE = Adverse event
Data Source: Table 3.1.2

Panel 12I (cont'd)
Listing of Patients Who Withdrew From the Study Due to Adverse Events - Safety Population

Site	Patient Number	Treatment Sequence	Treatment at Which SAE Occurred	AE	Age/ Sex/ Race	Time From Baseline to Event (days)	Event Duration (days)	Frequency	Severity	Relation to Study Drug	Effect on Study Drug	Treatment	Outcome
155	1551225	CADB	C	Abnormal Vision	68/F/C	2	1	Single Episode	Mild	Probably Not	Discontinued	Other	Resolved
			C	Constipation		4	6	Constant	Moderate	Probably Not	Discontinued	Other	Resolved
			C	Hypesthesia		5	5	Intermittent	Mild	Probably Not	Discontinued	Other	Resolved
			C	Hypesthesia		5	5	Intermittent	Mild	Probably Not	Discontinued	Other	Resolved
			C	Nausea		5	9	Constant	Moderate	Probably Not	Discontinued	Other	Resolved
			C	Vomiting		6	1	Single Episode	Mild	Probably Not	Discontinued	Other	Resolved
	1551227	DCBA	C	Abnormal Gait	78/F/C	10	3	Intermittent	Moderate	Possibly	Discontinued	None	Resolved
			C	Confusion		10	3	Intermittent	Mild	Possibly	Discontinued	None	Resolved
			C	Constipation		10	4	Constant	Moderate	Possibly	Discontinued	None	Resolved
			C	Headache		11	1	Constant	Severe	Possibly	Discontinued	None	Resolved
			C	Myasthenia		11	3	Intermittent	Severe	Possibly	Discontinued	None	Resolved
			C	Twitching		11	1	Single Episode	Moderate	Possibly	Discontinued	None	Resolved
170	1701469	ABCD	C	Asthenia	75/M/C	13	2	Constant	Moderate	Probably	Discontinued	None	Resolved
			C	Dizziness		13	27	Constant	Severe	Probably	Discontinued	None	Resolved

* Patient 1371132 was dispensed drug for period 4, fractured his pelvis 10 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
** Patient 1771465 was dispensed drug for period 3, began experiencing an SAE 4 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
Note: For Race: C = Caucasian, B = Black, A = Asian, H = Hispanic, O – Other; (Specify) For Sex: M = Male, F = Female.
Note: Ran SR = Ranolazine SR; A = 500 mg bid; B = 1000 mg bid; C = 1500 mg bid; D = Placebo.
Note: AE = Adverse event
Data Source: Table 3.1.2

Panel 12I (cont'd)
Listing of Patients Who Withdrew From the Study Due to Adverse Events - Safety Population

Site	Patient Number	Treatment Sequence	Treatment at Which SAE Occurred	AE	Age/ Sex/ Race	Time From Baseline to Event (days)	Event Duration (days)	Frequency	Severity	Relation to Study Drug	Effect on Study Drug	Treatment	Outcome
177	1771465	ABCD	C**	Syncope	76/F/C	20		Intermittent	Moderate	Probably Not	Discontinued	Other	Ongoing
			C**	Congestive Heart Failure		26	5	Single Episode	Moderate	Probably Not	Discontinued	Medication	Resolved
512	5121315	CADB	C	Angina Pectoris	58/F/C	3	4	Intermittent	Moderate	Probably Not	Discontinued	Medication	Controlled
	5121365	BDAC	C	Dizziness	49/M/C	23	2	Intermittent	Moderate	Probably	Discontinued	None	Resolved
			C	Headache		23	2	Constant	Moderate	Probably	Discontinued	None	Resolved
			C	Nausea		23	2	Single Episode	Mild	Probably	Discontinued	None	Resolved
519	5191362	BDAC	C	BUN Increased	65/M/C	25	6	Constant	Severe	Possibly	Discontinued	Medication	Resolved
			C	Dizziness		25	1	Single Episode	Severe	Possibly	Discontinued	Medication	Resolved
			C	Headache		25	1	Single Episode	Severe	Possibly	Discontinued	Medication	Resolved
			C	Vertigo		25	1	Single Episode	Severe	Possibly	Discontinued	Medication	Resolved
520	5201341	ABCD	A	Angina Pectoris	45/M/C	3	2	Intermittent	Moderate	Possibly	Discontinued	Medication	Controlled

* Patient 1371132 was dispensed drug for period 4, fractured his pelvis 10 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
** Patient 1771465 was dispensed drug for period 3, began experiencing an SAE 4 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
Note: For Race: C = Caucasian, B = Black, A = Asian, H = Hispanic, O = Other; (Specify) For Sex: M = Male, F = Female.
Note: Ran SR = Ranolazine SR; A = 500 mg bid; B = 1000 mg bid; C = 1500 mg bid; D = Placebo.
Note: AE = Adverse event
Data Source: Table 3.1.2

Of the 15 patients who withdrew, 10 (5%) were receiving ranolazine 1500 mg, 1 (<1%) was receiving 1000 mg, 2 (1%) were receiving 500 mg, and 2 (1%) were receiving placebo. The 10 subjects on the highest ranolazine dose withdrew because of increased salivation (and nausea, paresthesia, thirst, urine abnormality, vomiting), hematuria (and nausea), abnormal vision (and constipation, hypesthesia, nausea, vomiting), abnormal gait (and confusion, constipation, headache, myasthenia, twitching), asthenia (and dizziness), syncope (and CHF), angina, dizziness (and headache, nausea), BUN increased (and dizziness, headache, vertigo).

QT/QTc intervals
The frequency of QTc interval changes are shown below.

Panel 12N
Frequency of QTc (Bazett) Change from Baseline to ≥60 msec and to >500 msec, n (%) of Patients

	Placebo	RAN SR 500 mg	RAN SR 1000 mg	RAN SR 1500 mg
Trough	1/176 (0.6)	2/177 (1.1)	2/178 (1.1)	2/171 (1.2)
Peak	0/177 (0)	4/177 (2.3)	0/177 (0)	4/169 (2.4)

There were 9 subjects with 15 ECGs that matched the criteria of ≥ 60 msec from baseline to values to >500 msec.

Pt number/dose	Baseline QTc (msec)	Highest QTc (msec)	Change (msec)
1231001/500 mg	461	543	82
1411161/500 mg	482	583	101
1411161/1500 mg	482	561	79
1491198/1000 mg	460	528	68
1561230/placebo	465	527	62
1561230/1500 mg	438	535	97
5011437/1000 mg	426	503	77
5011441/1500 mg	438	558	120
5071428/1500 mg	433	522	89
5101417/500 mg	446	539	93
5251309/500 mg	506	571	65

T wave morphology

The frequency of notched T waves is shown below by treatment group at peak and trough concentrations.

% of subjects with notched T waves

	Placebo	Ranol 500	Ranol 1000	Ranol 1500
peak	2%	1%	3%	6%
trough	<1%	<1%	5%	5%

More notched T waves were reported in the Ranolazine 1000 mg and 1500 mg doses than in the placebo and ranolazine 500 mg dose groups.

Vital signs

The table below shows the mean blood pressure and heart rate at rest.

Panel 12L
LS Mean (SE) Standing BP, HR, and RPP

	Placebo (N=179)		Ranolazine Treatment 500 mg bid (N=181)		1000 mg bid (N=180)		1500 mg bid (N=187)	
	Trough	Peak	Trough	Peak	Trough	Peak	Trough	Peak
At Rest								
Systolic blood pressure (mm Hg)	138.9 (0.9)	134.8 (0.8)	136.6 (0.9)	134.4 (0.8)	137.9 (0.8)	134.5 (0.8)	137.1 (0.9)	132.5 (0.8)*
Diastolic blood pressure (mm Hg)	80.3 (0.5)	79.2 (0.5)	79.9 (0.5)	78.2 (0.5)	80.4 (0.5)	78.8 (0.5)	80.2 (0.5)	77.7 (0.5)*
Heart rate (bpm)	81.2 (0.5)	84.2 (0.6)	81.6 (0.5)	84.5 (0.6)	79.7 (0.5)*	82.7 (0.6)	78.4 (0.5)**	81.6 (0.6)**
Rate pressure product (mm Hg x bpm)	11243.7 (96.0)	11326.7 (99.5)	11088.9 (95.6)	11339.3 (99.7)	10946.1 (94.8)*	11065.7 (98.7)	10717.0 (97.7)**	10783.1 (102.0)**

At doses less than 1500 mg, there were no statistically significant differences between ranolazine and placebo for changes in blood pressure. There were significant decreases for the 1500 mg dose at peak drug concentrations (reductions were in the order of 2-3 mmHg[27]).

Heart rate reductions were significant for the 1500 mg dose at both peak and trough drug concentrations. Mean reductions in heart rate were 3 bmp or less.

[27] See page 170 item 8 vol 146

Protocol CVT 3033

A Double-Blind, Randomized, Stratified, Placebo-Controlled, Parallel Study of Ranolazine SR at Doses of 750 mg Twice a Day and 1000 mg Twice a Day in Combination with Other Anti-Anginal Medications in Patients with Chronic Stable Angina Pectoris.

The primary objective of this study was to determine the effect of ranolazine SR at doses of 750 mg twice a day and 1000 mg twice a day compared to placebo on symptom-limited treadmill exercise over 12 week treatment period. Study patients had chronic stable angina and were receiving a stable dose of a single concomitant anti-anginal medication (diltiazem 180 mg once a day in a formulation intended for once-a-day dosing, atenolol 50 mg once a day, or amlodipine 5 mg once a day).

A 2-day rebound assessment for possible increase in anginal events, as measured by exercise treadmill test duration, was included following discontinuation of ranolazine SR at doses of 750 mg twice a day or 1000 mg twice a day compared to patients who were maintained on placebo during a 12 week treatment period.

Demographics

Table 11B Demography by Treatment: Safety Population

		Treatment			Total n = 823***	P-value
		Placebo n = 269	Ranolazine SR 750 mg n = 279	Ranolazine SR 1000 mg n = 275**		
Gender	Male n (%)	202 (75.1)	217 (77.8)	219 (79.6)	638 (77.5)	0.45
	Female n (%)	67 (24.9)	62 (22.2)	56 (20.4)	185 (22.5)	
Age (years)	Mean	63.7	64.3	63.9	64.0	0.73
	SD	8.9	9.3	9.3	9.2	
	Min	36	38	36	36	
	Max	84	92	86	92	
Age Category	<65 years n (%)	129 (48.0)	141 (50.5)	138 (50.2)	408 (49.6)	0.80
	≥65 years n (%)	140 (52.0)	138 (49.5)	137 (49.8)	415 (50.4)	
Race	Asian n (%)	1 (0.4)	3 (1.1)	1 (0.4)	5 (0.6)	0.26*
	Black n (%)	0	1 (0.4)	2 (0.7)	3 (0.4)	
	Caucasian n (%)	265 (98.5)	269 (96.4)	269 (97.8)	803 (97.6)	
	Hispanic n (%)	1 (0.4)	4 (1.4)	0	5 (0.6)	
	Other n (%)	2 (0.7)	2 (0.7)	3 (1.1)	7 (0.9)	
Weight (kg)	Mean	79.7	80.2	81.9	80.6	0.13
	SD	12.4	13.0	13.0	12.8	
	Min	41	50	50	41	
	Max	122	124	150	150	
Height (cm)	Mean	169.3	169.7	170.7	169.9	0.14
	SD	8.6	8.3	8.7	8.5	
	Min	150	149	149	149	
	Max	192	190	195	195	

Note: Data summarized in the above table are located in Table 1.5.0.1.
*The treatment comparison p-value for race is for Caucasian vs non-Caucasian.
** n=274 for the weight variable in the ranolazine SR 1000 mg group.
*** n=822 for the weight variable.

Most patients were male, around 64 years of age, and almost completely white. The groups were similar in these characteristics.

Table 11C Cardiovascular History by Treatment, N (%): Safety Population

Cardiovascular History			Placebo n = 269	Ranolazine SR 750 mg n = 279	Ranolazine SR 1000 mg n = 275	Total n = 823	P-value
Unstable Angina >Two Months Before Randomization			**54 (20.1)**	**58 (20.8)**	**65 (23.6)**	**177 (21.5)**	**0.54**
Congestive Heart Failure			**77 (28.6)**	**87 (31.2)**	**78 (28.4)**	**242 (29.4)**	**0.72**
Congestive Heart Failure	NYHA Class I		33 (12.3)	35 (12.5)	35 (12.7)	103 (12.5)	0.68
	NYHA Class II		44 (16.4)	52 (18.6)	43 (15.6)	139 (16.9)	
Prior Myocardial Infarction			**150 (55.8)**	**166 (59.5)**	**158 (57.5)**	**474 (57.6)**	**0.67**
Number of Prior Myocardial Infarctions		0	119 (44.2)	113 (40.5)	117 (42.5)	349 (42.4)	0.55
		1	121 (45.0)	129 (46.2)	128 (46.5)	378 (45.9)	
		2	22 (8.2)	26 (9.3)	27 (9.8)	75 (9.1)	
		3	3 (1.1)	7 (2.5)	3 (1.1)	13 (1.6)	
		>3	4 (1.5)	4 (1.4)	0	8 (1.0)	
Prior CABG >Two Months Before Randomization			**36 (13.4)**	**53 (19.0)**	**56 (20.4)**	**145 (17.6)**	**0.067**
Number of Prior CABGs		0	233 (86.6)	226 (81.0)	219 (79.6)	678 (82.4)	0.13
		1	21 (7.8)	39 (14.0)	43 (15.6)	103 (12.5)	
		2	7 (2.6)	11 (3.9)	10 (3.6)	28 (3.4)	
		>2	8 (3.0)	3 (1.1)	2 (0.7)	13 (1.6)	
		Unknown	0	0	1 (0.4)	1 (0.1)	
Prior PTCA >Two Months Before Randomization			**53 (19.7)**	**46 (16.5)**	**53 (19.3)**	**152 (18.5)**	**0.57**
Number of PTCA Procedures		0	216 (80.3)	233 (83.5)	222 (80.7)	671 (81.5)	0.69
		1	35 (13.0)	25 (9.0)	40 (14.5)	100 (12.2)	
		2	13 (4.8)	14 (5.0)	8 (2.9)	35 (4.3)	
		>2	5 (1.9)	7 (2.5)	5 (1.8)	17 (2.1)	
Intermittent Claudication			**19 (7.1)**	**23 (8.2)**	**20 (7.3)**	**62 (7.5)**	**0.86**
Arrhythmias	**Atrial**		**20 (7.4)**	**22 (7.9)**	**23 (8.4)**	**65 (7.9)**	**0.91**
	Ventricular		**19 (7.1)**	**25 (9.0)**	**27 (9.8)**	**71 (8.6)**	**0.48**
	Other		**2 (0.7)**	**5 (1.8)**	**4 (1.5)**	**11 (1.3)**	**0.64**
Atrial Arrhythmias	**Ectopy**		**8 (3.0)**	**9 (3.2)**	**11 (4.0)**	**28 (3.4)**	**0.76**
	Tachycardia		**2 (0.7)**	**1 (0.4)**	**4 (1.5)**	**7 (0.9)**	**0.37**
	Fibrillation or Flutter		**10 (3.7)**	**13 (4.7)**	**12 (4.4)**	**35 (4.3)**	**0.85**
Ventricular Arrhythmias	**Ectopy**		**16 (5.9)**	**23 (8.2)**	**25 (9.1)**	**64 (7.8)**	**0.35**
	Tachycardia		**3 (1.1)**	**2 (0.7)**	**1 (0.4)**	**6 (0.7)**	**0.54**
	Fibrillation or Flutter		**3 (1.1)**	**1 (0.4)**	**1 (0.4)**	**5 (0.6)**	**0.46**
Clinically Significant Valvular Disease			**19 (7.1)**	**23 (8.2)**	**12 (4.4)**	**54 (6.6)**	**0.17**
Clinically Significant Valvular Disease	Aortic Stenosis		2 (0.7)	4 (1.4)	0	6 (0.7)	0.13
	Aortic Insufficiency		6 (2.2)	7 (2.5)	5 (1.8)	18 (2.2)	0.88
	Aortic Insufficiency Repaired		1 (0.4)	0	1 (0.4)	2 (0.2)	0.55
	Mitral Insufficiency		12 (4.5)	17 (6.1)	9 (3.3)	38 (4.6)	0.27
	Mitral Insufficiency Repaired		0	2 (0.7)	1 (0.4)	3 (0.4)	0.78
	Other		2 (0.7)	6 (2.2)	3 (1.1)	11 (1.3)	0.41
	Other Repaired		0	0	1 (0.4)	1 (0.1)	0.66
Cardiac Arrest			**6 (2.2)**	**6 (2.2)**	**1 (0.4)**	**13 (1.6)**	**0.13**
Hypertension			**173 (64.3)**	**177 (63.4)**	**177 (64.4)**	**527 (64.0)**	**0.97**
Stroke			**11 (4.1)**	**15 (5.4)**	**15 (5.5)**	**41 (5.0)**	**0.73**
Pulmonary Embolism			**2 (0.7)**	**4 (1.4)**	**1 (0.4)**	**7 (0.9)**	**0.47**

Note: Data summarized in the above table are located in Table 1.6.0.

About one fifth of the population had unstable angina at least 2 months prior to study enrollment, about 30% had congestive heart failure (NYHA class I or II), and more than half had a prior MI. The groups were well balanced with rare exception.

Study completion

No. and (percent) of patients

	Placebo N=269	Ran 750 mg N=279	Ran 1000 mg N=275
Completed trial	243 (90.3)	250 (89.6)	238 (86.5)
Early withdrawal	26 (9.7)	29 (10.4)	37 (13.5)
For AE	16 (5.9)	22 (7.9)	25 (9.1)
Death	2 (0.7)	2 (0.7)	1 (0.4)
Elective withdrawal	4 (1.5)	1 (0.4)	5 (1.8)
Other^	7 (2.9)	6 (2.2)	7 (2.5)

^ includes non compliance, lost to follow up
table 12B, Table 1.4.1 study report

More patients failed to complete the study in the high dose ranolazine group (13.5%) compared to low dose ranolazine (10.4%) and placebo (9.7%). The main reason for discontinuation for all treatment groups was an adverse event. The high dose group had more discontinuations for adverse events (8.7%) compared to low dose (7.2%) and placebo (4.8%). The percent of reported deaths were similar across treatment groups.

Withdrawals by concomitant anti-anginal medication.

Percent of patients who withdrew early: placebo subtracted

	Ran 750 mg			Ran 1000 mg		
	Dilt N=74	Aten N=119	Amlo N=86	Dilt N=69	Aten N=117	Amlo N=89
Early withdrawal	3.3	5	-7.6	4.5	9.4	-4.4
For AE	6.5	5.1	-5.1	8.8	6.9	-4.0
Death	0	-0.8	1.2	-1.4	-0.8	1.1
Elective withdrawal	0	-1.7	-1.2	0	0.9	-0.1

There were more withdrawals for adverse events by patients taking diltiazem in all treatment groups including placebo (table 1.4.3).

N.B. Diltiazem (180-360 mg) in previous studies (CVT 3012, RAN0121, and RAN068) was shown to increase ranolazine average steady-state plasma concentrations of 1.5-2.4 fold.

Individual adverse events
Adverse events reported by at least 4 subjects in at least 1 of the ranolazine groups and more than the placebo group are shown below.

No. and (percent) of patients

Adverse event	Placebo N=269	Ran 750 mg N=279	% Pl subtracted	Ran 1000 mg N=275	% Pl subtracted
Any event	71 (26.4)	87 (31.2)	4.8	90 (32.7)	6.6
Constipation	2 (0.7)	18 (6.5)	5.8	20 (7.3)	6.6
Dizziness	5 (1.9)	10 (3.6)	1.7	19 (6.9)	5.0
Nausea	2 (0.7)	9 (3.2)	2.5	14 (5.1)	4.4
Asthenia	6 (2.2)	5 (1.8)	-0.4	13 (4.7)	2.5

Syncope	0	0	0	5 (1.8)	1.8
Abdominal pain	2 (0.7)	2 (0.7)	0	7 (2.5)	1.8
Sweating	0	3 (1.1)	1.1	4 (1.5)	1.5
Vomiting	1 (0.4)	2 (0.7)	0.3	4 (1.5)	1.1
Diabetes mellitus	0	5 (1.8)	1.8	2 (0.7)	0.7
Headache	4 (1.5)	7 (2.5)	1.0	6 (2.2)	0.7
Myocardial infarct	0	4 (1.4)	1.4	1 (0.4)	0.4
Dyspepsia	4 (1.5)	7 (2.5)	1.0	5 (1.8)	0.3
Dyspnea	4 (1.5)	5 (1.8)	0.3	1 (0.4)	-1.1

Table 3.0.1

Constipation was the most frequently reported adverse event for patients randomized to ranolazine with the 1000 mg dose group reporting more (6.6%) than the 750 mg dose (5.8%). Dizziness was the next most frequently reported event with the 1000 mg dose group reporting more (5.0%) than the 750 mg dose group (1.7%). Syncope was reported by 5 subjects, all from the 1000 mg dose group and 4 of these 5 subjects were taking concomitant diltiazem.

Serious safety

The table below shows the number and percent of patients how reported early withdrawal for an adverse event, a serious adverse event, and/or death.

No. and (percent) of patients

	Placebo N=269	Ran 750 mg N=279	Placebo subtracted (%)	Ran 1000 mg N=275	Placebo subtracted (%)
Death	3 (1.1)	2 (0.7)	-0.4	1 (0.4)	-0.7
Serious adverse event	15 (5.6)	20 (7.2)	1.6	19 (6.9)	1.3
Early withdrawal for AE	16 (5.9)	22 (7.9)	2.0	25 (9.1)	3.2

Table 3.0.0

There were 6 reported deaths with half occurring in the placebo group (3 placebo, 2 ranolazine 750 mg and 1 ranolazine 1000 mg).

There were more reported serious events in the ranolazine 1000 mg group (6.9%) and ranolazine 750 mg (7.2%), compared to placebo (5.6%). In addition, compared to placebo, there were more reported withdrawals for adverse event in the ranolazine 1000 mg group (9.1%) and the ranolazine 750 mg group (7.9%).

Deaths

There were 6 deaths and they are listed in the table below.

Patient ID	Treatment group/background med	Duration of treatment (days)	Cause of death
177/9027	Ranol 750 mg/amlodipine	33	Acute MI
704/7600	Ranol 750 mg/diltiazem	18	Sudden death
706/9575	Ranol 1000	13	Sudden death

	mg/amlodipine		
710/7631	Placebo diltiazem	18	Sudden death
717/8668	Placebo/atenolol	6	Acute coronary insufficiency
751/9386	Placebo/amlodipine	83	Cardiac arrest

Tables 3.2.0 and 3.2.1

There were 3 deaths reported in the placebo group, 2 in the ranolazine 750 mg group and 1 in the ranolazine 1000 mg group. The causes of deaths are not unusual for this type of patient population.

Serious adverse events
The numbers and percents of patients reporting a serious event are shown below by event.

Table 12G Incidence of Serious Adverse Events Occurring on or after Visit 2 by Body System and Preferred Term, N (%): Safety Population

COSTART Body System and Preferred Term	Treatment		
	Placebo (n=269)	Ranolazine SR 750 mg (n=279)	Ranolazine SR 1000 mg (n=275)
Patients with at least one SAE	**15 (5.6)**	**20 (7.2)**	**19 (6.9)**
Body as a whole	**2 (0.7)**	**2 (0.7)**	**3 (1.1)**
Asthenia	0	0	1 (0.4)
Carcinoma	0	1 (0.4)	0
Death	1 (0.4)	0	0
Headache	0	0	2 (0.7)
Sudden Death	1 (0.4)	1 (0.4)	1 (0.4)
Cardiovascular	**10 (3.7)**	**15 (5.4)**	**13 (4.7)**
Angina Pectoris	8 (3.0)	7 (2.5)	3 (1.1)
Bradycardia	0	0	1 (0.4)
Cerebral Ischemia	0	0	1 (0.4)
Cerebrovascular Accident	0	0	1 (0.4)
Coronary Artery Disorder	2 (0.7)	2 (0.7)	1 (0.4)
Heart Arrest	0	0	1 (0.4)
Hypotension	0	0	1 (0.4)
Myocardial Infarct	0	4 (1.4)	1 (0.4)
Myocardial Ischemia	0	2 (0.7)	0
Sinus Bradycardia	0	0	1 (0.4)
Syncope	0	0	3 (1.1)
Digestive	**0**	**1 (0.4)**	**2 (0.7)**
Cholecystitis	0	0	1 (0.4)
Colitis	0	1 (0.4)	0
Nausea	0	0	1 (0.4)
Metabolic and Nutritional	**0**	**1 (0.4)**	**0**
Dehydration	0	1 (0.4)	0
Musculoskeletal	**1 (0.4)**	**0**	**0**
Arthritis	1 (0.4)	0	0
Nervous	**0**	**1 (0.4)**	**3 (1.1)**
Dizziness	0	0	2 (0.7)
Meningitis	0	1 (0.4)	0
Vertigo	0	0	1 (0.4)
Respiratory	**2 (0.7)**	**0**	**1 (0.4)**
Bronchitis	1 (0.4)	0	0
Pneumonia	1 (0.4)	0	1 (0.4)
Special	**0**	**0**	**1 (0.4)**
Tinnitus	0	0	1 (0.4)

Note: Data presented in this table are located in Tables 3.0.0 and 3.0.4.
Multiple occurrences of the same event are counted once per patient using the maximum severity.

Cardiovascular events combined were reported by ranolazine subjects more often than placebo (3.7%) compared to the ranolazine groups (5.4% and 4.7% for 750 mg and 1000 mg, respectively).

Serious adverse events reported by 3 or more subjects in 1 or both of the ranolazine groups and reported by more ranolazine subjects than placebo subjects include myocardial infarct and syncope. On the other hand, angina pectoris was reported more often by placebo patients. No particular event, other than syncope (all in ranolazine 1000 mg), was convincingly reported more often in the ranolazine group compared to placebo.

The patients taking concomitant diltiazem with ranolazine had more serious adverse events compared to patients taking atenolol or amlodipine (table 3.0.6).

Withdrawals for adverse events

Table 12H Number of Patients with Adverse Events Leading to Discontinuation of Study Drug: Safety Population

	Treatment			
	Placebo	Ranolazine SR 750 mg	Ranolazine SR 1000 mg	Total
Number (%) of patients with adverse events leading to study drug discontinuation	16 (5.9)	22 (7.9)	25 (9.1)	63 (7.6)
Number of events leading to study drug discontinuation	17	41	47	105

Note: Data summarized above is presented in Table 3.0.0.

Adverse events leading to discontinuation reported for more than one subject included nausea, headache, asthenia, dyspnea, dyspepsia, palpitations, syncope, angina pectoris, dizziness, atrial fibrillation, myocardial infarction, constipation, myasthenia, abdominal pain, tinnitus, vomiting, coronary artery disorder, myocardial ischemia and sudden death.

The table below shows the adverse event leading to discontinuation in 3 or more ranolazine subjects and more in the ranolazine than the placebo subjects are shown below.

No. and (percent) who discontinued for adverse event

	Placebo N=269	Ran 750 mg N=279	Ran 1000 mg N=275	Total ranol N=554	% Placebo subtracted
Total discont	16 (5.9)	22 (7.9)	25 (9.1)	47 (8.5)	2.6
Nausea/N&V/vomiting	0	2 (0.7)	6 (2.2)	8 (2.9)	2.9
Dizziness	1 (0.4)	2 (0.7)	7 (2.5)	9 (1.6)	1.2
Constipation	0	2 (0.7)	2 (0.7)	4 (0.7)	0.7
Asthenia	0	1 (0.4)	3 (1.1)	4 (0.7)	0.7
Syncope	0	0	3 (1.1)	3 (0.5)	0.5
Headache	0	1 (0.4)	2 (0.7)	3 (0.5)	0.5
MI	0	2 (0.7)	1 (0.4)	3 (0.5)	0.5
Myocardial ischemia	1 (0.4)	2 (0.7)	1 (0.4)	3 (0.5)	0.1

Attachment 6 dated 3-18-03

Nausea (with the addition of nausea & vomiting and vomiting) was the leading adverse event resulting in discontinuation for the ranolazine group (2.9%), compared to placebo (0). Dizziness was the next most cited adverse event followed by constipation and asthenia. Syncope was reported only by the high dose group.

Patients were more likely to discontinue study early because of an adverse event if they were receiving diltiazem and ranolazine (table 3.0.6).

Syncope

There were patients reporting serious syncope/dizziness and they are listed in the table below.

Patient ID	Treatment group/background med	Days on drug at time of event	Comments
174/7012	Ranolazine 1000/diltiazem	3	Lab tests and ECG were reported as normal. Withdrawn from study
530/7169	Ranolazine 1000/diltiazem	9	Experienced dizziness on day 7 followed by syncope 2 days later
549/7219	Ranolazine 1000/diltiazem	5	Witnessed event with loss of consciousness and "jerking movements" and "snorting breathing" Pulse not palpable, systolic BP 88 mmHg. Remained on drug.
562/8071	Ranolazine 1000/atenolol	70	This 86 year old female was hospitalized for syncope reported as mild. Withdrawn from drug.
569/7065	Ranolazine 1000/diltiazem	17 and 33	Treatment interrupted
177/7406	Ranolazine 1000/diltiazem	18	Nausea and vomiting followed by syncope. Withdrawn from study

Appendix 14.7.2

There were 5 patients reporting syncope as an adverse event. Of the 5, 4 were receiving ranolazine 1000 mg plus diltiazem and 1 was receiving ranolazine 1000 mg plus atenolol.

Clinical Laboratory

Hematology

The mean changes from baseline at the last double blind visit are shown below by treatment group.

Table 12l ***Mean Change from Baseline Hematology Results at the Last Double-Blind Visit: Safety Population***

Parameter	Statistic	Treatment		
		Placebo	Ranolazine SR 750 mg	Ranolazine SR 1000 mg
Hemoglobin (g/dL)	N	213	236	221
	Mean	-0.11	-0.55	-0.56
	SE	0.06	0.06	0.05
	Range	-3.1, 2.1	-4.5, 2.2	-3.0, 1.8
Hematocrit (%)	N	211	229	218
	Mean	0.1	-1.0	-1.2
	SE	0.2	0.2	0.2
	Range	-10, 11	-11, 10	-9, 6
WBC ($x10^3$/uL)	N	213	236	221
	Mean	-0.190	-0.159	-0.265
	SE	0.102	-0.16	0.105
	Range	-7.28, 3.22	-5.45, 10.13	-5.11, 6.73
Neutrophils (%)	N	213	236	221
	Mean	0.21	1.73	1.67
	SE	0.47	1.7	0.44
	Range	-29.2, 19.0	-18.0, 27.2	-20.0, 22.0
Lymphocytes (%)	N	213	236	221
	Mean	0.07	-1.61	-1.39
	SE	0.40	0.41	0.39
	Range	-15.7, 19.5	-24.3, 19.4	-19.0, 15.5
Monocytes (%)	N	213	236	221
	Mean	-0.14	-0.05	-0.07
	SE	0.11	0.12	0.11
	Range	-6.3, 7.8	-7.2, 9.4	-6.0, 4.8
Eosinophils (%)	N	213	236	221
	Mean	-0.16	-0.04	-0.11
	SE	0.10	0.12	0.11
	Range	-6.5, 6.5	-6.0, 13.2	-9.3, 5.9
Basophils (%)	N	213	236	221
	Mean	0.01	-0.04	-0.10
	SE	0.04	0.04	0.04
	Range	-2.1, 2.7	-2.6, 2.2	-2.2, 2.0
Bands (%)	N	213	236	221
	Mean	0.00	0.00	0.00
	SE	0.00	0.0	0.0
	Range	-0.3, 0.0	0.0, 0.0	0.0, 0.0
RBC ($x10^6$/uL)	N	213	236	221
	Mean	-0.03	-0.25	-0.30
	SE	0.02	0.02	0.02
	Range	-1.1, 0.8	-2.3, 0.8	-1.2, 0.4
Platelets ($x10^3$/uL)	N	204	228	215
	Mean	5.8	11.8	7.1
	SE	3.2	2.6	2.5
	Range	-166, 273	-132, 135	-127, 154

Note: Baseline is the visit closest to Visit 1
Data presented in this table are located in Tables 3.3.0.1.1 to 3.3.0.1.11

There were decreases in hemoglobin, hematocrit, and RBCs in all three treatment groups but more so in the ranolazine groups.

Mean changes from baseline at endpoint and (SE)

Parameter	Means		
	Placebo	Ranol 750 mg	Ranol 1000 mg
Hemoglobin g/dl	-0.11 (0.06)	-0.55 (0.06)	-0.56 (0.05)
Hematocrit %	0.1 (0.2)	-1.0 (0.2)	-1.2 (0.2)
RBC (10^6/uL)	-0.03 (0.02)	-0.25 (0.02)	-0.3 (0.02)

Table 12I

Shift changes for the 3 hematology parameters are shown below.

CVT 3033

TABLE 3.3.0.2.1

Hematology Results
Hemoglobin (g/dL)
Shift Values by Treatment and Visit
Summary Statistics: Safety Population

Baseline	Last Double Blind Visit	Placebo n	Placebo (%)	Ran SR 750 mg n	Ran SR 750 mg (%)	Ran SR 1000 mg n	Ran SR 1000 mg (%)
Low	Low	7	(3.3)	7	(3.0)	9	(4.1)
	Normal	4	(1.9)	2	(0.8)	1	(0.5)
	High	0		0		0	
Normal	Low	3	(1.4)	9	(3.8)	6	(2.7)
	Normal	192	(90.1)	210	(89.0)	200	(90.5)
	High	2	(0.9)	0		1	(0.5)
High	Low	0		0		0	
	Normal	4	(1.9)	7	(3.0)	2	(0.9)
	High	1	(0.5)	1	(0.4)	2	(0.9)

Appears This Way
On Original

CVT 3033

TABLE 3.3.0.2.1

Hematology Results
Hemoglobin (g/dL)
Shift Values by Treatment and Visit
Summary Statistics: Safety Population

Baseline	Last Double Blind Visit	Placebo n	Placebo (%)	Ran SR 750 mg n	Ran SR 750 mg (%)	Ran SR 1000 mg n	Ran SR 1000 mg (%)
Low	Low	7	(3.3)	7	(3.0)	9	(4.1)
	Normal	4	(1.9)	2	(0.8)	1	(0.5)
	High	0		0		0	
Normal	Low	3	(1.4)	9	(3.8)	6	(2.7)
	Normal	192	(90.1)	210	(89.0)	200	(90.5)
	High	2	(0.9)	0		1	(0.5)
High	Low	0		0		0	
	Normal	4	(1.9)	7	(3.0)	2	(0.9)
	High	1	(0.5)	1	(0.4)	2	(0.9)

CVT 3033

TABLE 3.3.0.2.10

Hematology Results
RBC (x10^6/uL)
Shift Values by Treatment and Visit
Summary Statistics: Safety Population

Baseline	Last Double Blind Visit	Placebo n	Placebo (%)	Ran SR 750 mg n	Ran SR 750 mg (%)	Ran SR 1000 mg n	Ran SR 1000 mg (%)
Low	Low	7	(3.3)	7	(3.0)	5	(2.3)
	Normal	5	(2.3)	3	(1.3)	0	
	High	0		0		0	
Normal	Low	3	(1.4)	14	(5.9)	20	(9.0)
	Normal	198	(93.0)	211	(89.4)	196	(88.7)
	High	0		0		0	
High	Low	0		0		0	
	Normal	0		0		0	
	High	0		1	(0.4)	0	

There were more subjects in the ranolazine groups compared to placebo who were normal at baseline and became abnormally low at endpoint.

Clinical chemistry

The mean changes from baseline at the last double blind visit are shown below by treatment group.

Table 12K ***Mean Change from Baseline Clinical Chemistry at the Last Double-Blind Visit: Safety Population***

Parameter	Statistic	Treatment		
		Placebo	Ran SR 750mg	Ran SR 1000mg
Urea Nitrogen (mg/dL)	N	250	263	256
	Mean	-0.1	1.1	1.1
	SE	0.3	0.3	0.3
	Range	-14, 15	-18, 12	-16, 16
Glucose (mg/dL)	N	235	252	246
	Mean	0.9	2.7	0.6
	SE	1.9	2.4	1.9
	Range	-135, 162	-224, 216	-184, 135
AST (U/L)	N	238	256	246
	Mean	0.3	-1.4	-2.3
	SE	0.9	0.7	0.4
	Range	-93, 101	-38, 109	-35, 18
ALT (U/L)	N	238	256	246
	Mean	-0.6	-2.5	-4.0
	SE	1.0	0.7	0.7
	Range	-100, 122	-46, 88	-46, 35
Alk Phos (U/L)	N	247	262	254
	Mean	-0.1	-3.3	-6.0
	SE	0.7	0.8	0.9
	Range	-42, 50	-90, 43	-144, 30
LDH (U/L)	N	243	254	251
	Mean	2.8	1.9	-3.4
	SE	2.2	2.4	1.5
	Range	-102, 294	-72, 391	-87, 81
Sodium (mEq/L)	N	250	263	254
	Mean	0.0	-0.6	-0.7
	SE	0.2	0.2	0.2
	Range	-8, 11	-13, 6	-9, 9
Potassium (mEq/L)	N	246	258	252
	Mean	-0.06	0.03	-0.02
	SE	0.03	0.03	0.03
	Range	-1.2, 1.5	-1.6, 1.2	-1.0, 1.2
Bicarbonate (mEq/L)	N	237	253	245
	Mean	-0.10	-0.03	0.13
	SE	0.18	0.17	0.18
	Range	-9.5, 10.3	-8.1, 8.9	-10.3, 9.1
Chloride (mEq/L)	N	250	263	254
	Mean	0.0	-0.7	-0.6
	SE	0.2	0.2	0.2
	Range	-11, 8	-10, 7	-10, 7
Creatinine (mg/dL)	N	250	264	256
	Mean	0.02	0.09	0.06
	SE	0.01	0.01	0.01
	Range	-0.6, 0.7	-0.4, 1.3	-0.8, 0.5

Note: Baseline is the visit closest to Visit 1
Data presented in this table are located in Tables 3.3.2.1.1 to 3.3.2.1.22

Table 12K (continued): Mean Change from Baseline Clinical Chemistry at the Last Double Blind Visit: Safety Population

Parameter	Statistic	Treatment		
		Placebo	Ran SR 750mg	Ran SR 1000mg
Phosphorus (mg/dL)	N	246	258	254
	Mean	0.02	0.08	0.08
	SE	0.03	0.03	0.04
	Range	-1.7, 1.5	-2.0, 1.4	-2.5, 2.0
Calcium (mg/dL)	N	250	264	256
	Mean	0.03	-0.01	-0.02
	SE	0.03	0.03	0.03
	Range	-1.1, 1.2	-1.4, 1.4	-1.1, 1.2
Total Bilirubin (mg/dL)	N	235	255	246
	Mean	0.00	0.01	-0.01
	SE	0.01	0.01	0.01
	Range	-0.6, 0.8	-0.7, 1.3	-0.7, 0.5
GGT (U/L)	N	250	264	256
	Mean	-1.8	-10.8	-12.2
	SE	1.1	1.6	1.9
	Range	-111, 71	-291, 71	-329, 47
CPK (U/L)	N	238	255	246
	Mean	8.8	-5.6	-12.4
	SE	8.7	4.7	4.0
	Range	-1636, 486	-355, 802	-496, 327
Uric Acid (mg/dL)	N	250	264	256
	Mean	0.07	-0.32	-0.41
	SE	0.05	0.05	0.06
	Range	-2.4, 5.2	-4.6, 2.9	-3.7, 2.7
Triglycerides (mg/dL)	N	250	262	255
	Mean	2.9	17.1	7.8
	SE	5.8	5.8	4.7
	Range	-218, 987	-331, 448	-292, 271
Cholesterol (mg/dL)	N	250	263	255
	Mean	-4.0	13.7	10.5
	SE	1.7	2.0	2.0
	Range	-102, 82	-95, 169	-107, 169
VLDL (mg/dL)	N	250	262	255
	Mean	0.6	3.4	1.6
	SE	1.2	1.2	0.9
	Range	-44, 197	-66, 89	-58, 54
LDL (mg/dL)	N	242	243	242
	Mean	-3.6	8.2	3.6
	SE	1.6	1.8	1.7
	Range	-105, 60	-80, 162	-106, 89
HDL (mg/dL)	N	250	262	255
	Mean	-0.3	2.4	3.6
	SE	0.4	0.5	0.5
	Range	-43, 21	-41, 63	-26, 33

Note: Baseline is the visit closest to Visit 1
Data presented in this table are located in Tables 3.3.2.1.1 to 3.3.2.1.22

Nothing seems alarming.

Resting ECG

Standard supine 12-lead ECGs were obtained at Screening (Visit 1), at trough at Visits 2-6 (or early withdrawal), and peak at Visits 2, 3,and 5, and whenever clinically indicated. The ECG was to be inspected by the investigator to ensure patient safety. The QT interval was to be examined for evidence of prolongation. Any other new clinically significant ECG findings appearing during treatment with study medication was to be discussed with a study monitor to determine whether the patient should continue in the study.

Official reading of each ECG for analysis was measured on the supine rest electrocardiogram and performed by the ECG core laboratory. The patient was to be withdrawn from the study and monitored to ensure the QTc returned to baseline if, at any point during the study, the QTc interval widened to 130% of its duration at Visit 2 and was longer than 500 msec.

In the ECG safety population, key parameters from the centrally coded electrocardiogram (e.g., corrected QT interval, T wave amplitude, T wave notching) were to be analyzed using analysis of variance for continuous measures or Cochran-Mantel-Haenszel tests for categorical measures.

ECG Interval changes

Mean ECG changes from baseline at week 12 at peak (4 hrs $\pm$ 0.5 after dosing) drug concentrations are shown below.

Table 12S Statistical Analysis of ECG Variables at Peak at Week 12 by Treatment: Safety Population

Variable		Treatment	
		Ranolazine SR 750 mg vs Placebo	Ranolazine SR 1000 mg vs placebo
Heart Rate	Mean difference (b.p.m)	-1.5	-0.8
	SE of mean difference	0.8	0.8
	Confidence interval	-3.0, 0.1	-2.4, 0.8
	p-value	0.066	0.33
PR Interval	Mean difference (ms)	2.3	2.4
	SE of mean difference	1.5	1.5
	Confidence interval	-0.6, 5.3	-0.6, 5.4
	p-value	0.12	0.12
QRS Interval	Mean difference (ms)	2.2	2.0
	SE of mean difference	0.9	0.9
	Confidence interval	0.4, 3.9	0.2, 3.7
	p-value	0.014	0.030
T amplitude	Mean difference (ms)	-0.6	-0.8
	SE of mean difference	0.1	0.1
	Confidence interval	-0.8, -0.3	-1.0, -0.5
	p-value	<0.001	<0.001
QT Interval	Mean difference (ms)	11.2	11.7
	SE of mean difference	2.3	2.3
	Confidence interval	6.7, 15.7	7.1, 16.2
	p-value	<0.001	<0.001
QTc Interval (Bazett)	Mean difference (ms)	6.1	9.2
	SE of mean difference	1.3	1.4
	Confidence interval	3.5, 8.8	6.5, 11.9
	p-value	<0.001	<0.001
QT Dispersion	Mean difference (ms)	2.2	0.0
	SE of mean difference	1.3	1.3
	Confidence interval	-0.3, 4.7	-2.5, 2.6
	p-value	0.079	0.97

Note: Data summarized above are located in Tables 3.8.5.0, 3.8.6.0, 3.8.7.0, 3.8.8.0, 3.8.9.0, 3.8.13.0 and 3.8.14.0.

Heart rate was essentially unchanged by ranolazine. Mean changes in QT and QTc intervals were significantly longer ($p<0.001$) in the ranolazine 750 mg and ranolazine 1000mg groups compared to placebo.

T wave amplitude decreased significantly ($p<0.001$) from baseline in both ranolazine groups compared to placebo.

The table below shows the QT interval changes at weeks 2 and 12 comparing the ranolazine groups to placebo using ANCOVA model.

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TABLE 3.8.8.0
ECG Safety Analysis: QT Interval at Peak at Week 2 and 12
Comparison of Treatment Differences from ANCOVA Model 1
Statistical Analysis: ECG Safety Population

Assessment	Statistic	Ran SR 750 mg vs Placebo	Ran SR 1000 mg vs Placebo
Week 2	Mean Difference	7.5	8.6
	S.E. of Mean Difference	2.0	2.0
	95% Confidence Interval	(3.6,11.4)	(4.6,12.6)
	P-value	<0.001	<0.001
Week 12	Mean Difference	11.2	11.7
	S.E. of Mean Difference	2.3	2.3
	95% Confidence Interval	(6.7,15.7)	(7.1,16.2)
	P-value	<0.001	<0.001

Note: Model 1 for Week 2 includes effects for treatment (p=<0.001), baseline covariate (p=<0.001), pooled site(p= 0.083) and background therapy (p=<0.001) using TYPE III sum of squares
Note: Model 1 for Week 12 includes effects for treatment (p=<0.001), baseline covariate (p=<0.001), pooled site(p= 0.034), and background therapy (p=<0.001) using TYPE III sum of squares
Note: P values obtained from ANCOVA model adjusted for stated effects
Note: Mean difference and SE of mean difference are Least Squares mean estimates from ANCOVA model
Note: Baseline covariate is the QT Interval at peak obtained from Visit 2

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Mean differences of ranolazine versus placebo for QT interval at peak were 7.5 msec at week 2 and 11.2 msec at week 12 for ranolazine 750 mg and 8.6 msec for ranolazine 1000 mg at week 2 and 11.7 msec at week 12. Both doses at both time points were statistically significantly different from placebo (p<0.001).

The upper limits of the 95% confidence interval for change at peak at week 12 were 15.7 msec for the 750 mg dose and 16.2 msec for the 1000 mg dose.

The table below shows the number and percent of patients with selected QT changes from baseline, by treatment group.

No. and (percent) of patient with selected QT changes

QT changes from baseline msec	Placebo N=257		Ranolazine 750 mg N=271		Ranolazine 1000 mg N=255	
	Week 2	Week 12	Week 2	Week 12	Week 2	Week 12
0-<30	123 (48)	102 (42)	125 (46)	121 (48)	134 (53)	112 (47)
30-<60	9 (4)	12 (5)	29 (11)	33 (13)	26 (10)	34 (14)
≥60	4 (2)	5 (2)	12 (4)	13 (5)	9 (4)	12 (5)

Attachment 3 dated 3-18-03

The percents of patients with prolonged QT intervals at Weeks 2 and 12 are at least twice as high in the ranolazine groups compared to placebo. There is little difference between the ranolazine groups.

Trough changes

Mean ECG changes from baseline at week 12 at trough drug concentrations are shown below.

Table 12Q Statistical Analysis of ECG Variables at Trough at Week Treatment: Safety Population

Variable		Treatment	
		Ranolazine SR 750 mg vs Placebo	Ranolazine SR 1000 mg vs placebo
Heart Rate	Mean difference (b.p.m)	-1.1	-0.5
	SE of mean difference	0.8	0.8
	Confidence interval	-2.6, 0.4	-2.0, 1.1
	p-value	0.14	0.56
PR Interval	Mean difference (ms)	0.9	0.6
	SE of mean difference	1.4	1.4
	Confidence interval	-1.8, 3.7	-2.2, 3.4
	p-value	0.51	0.66
QRS Interval	Mean difference (ms)	0.8	1.3
	SE of mean difference	0.9	0.9
	Confidence interval	-0.9, 2.5	-0.5, 3.0
	p-value	0.36	0.16
T amplitude	Mean difference (ms)	-0.4	-0.6
	SE of mean difference	0.1	0.1
	Confidence interval	-0.7, -0.2	-0.8, -0.4
	p-value	<0.001	<0.001
QT interval	Mean difference (ms)	8.5	10.0
	SE of mean difference	2.0	2.1
	Confidence interval	4.5, 12.5	5.9, 14.1
	p-value	<0.001	<0.001
QTc Interval (Bazett)	Mean difference (ms)	4.5	7.7
	SE of mean difference	1.1	1.2
	Confidence interval	2.3, 6.7	5.4, 10.0
	p-value	<0.001	<0.001
QT Dispersion	Mean difference (ms)	0.5	-0.5
	SE of mean difference	1.2	1.2
	Confidence interval	-1.9, 2.8	-2.9, 1.9
	p-value	0.70	0.70

Note: Data summarized above are located in Tables 3.7.6.0, 3.7.7.0, 3.7.8.0, 3.7.9.0, 3.7.10.0, 3.7.14.0 and 3.7.15.0.

As with peak effects, the mean changes at week 12 for QT and QTc intervals at trough were statistically significantly greater compared to placebo (8.5 msec and 4.5 msec for ranolazine 750 mg, respectively, and 10.0 msec and 7.7 msec for ranolazine 1000mg, respectively). There was little effect on heart rate, but the effect on T wave amplitude was significantly different from placebo for both treatment groups.

The table below shows the number and percent of patients with selected QTc changes from baseline, by treatment group, at weeks 2, 6 and 12.

No. and (percent) of patient with selected QTc changes

	Placebo		Ranolazine 750 mg		Ranolazine 1000 mg	
QT changes from baseline msec	Week 6	Week 12	Week 6	Week 12	Week 6	Week 12
<0	141 (56)	134 (54)	102 (38)	112 (44)	89 (35)	78 (33)
0-<30	110 (43)	112 (45)	156 (59)	134 (52)	154 (61)	152 (63)
30-<60	1 (0)	0	4 (2)	8 (3)	4 (2)	6 (3)

Table 3.7.10.6.1

The incidence rates for QTc changes less than 0 msec at weeks 6 and 12 were higher for placebo than for the 2 ranolazine groups. For changes greater than 0 msec, incidence rates greater than 0 msec at both weeks were higher for the ranolazine groups than placebo groups.

T wave morphology

Changes in T wave morphology by drug group are shown below.

CVT 3033 TABLE 3.8.0 Page 2 of 3

ECG Characteristics at Peak Levels of Ranolazine SR
By Treatment and Week
Summary Statistics: ECG Safety Population

	Stati	Placebo		Ran SR 750 mg		Ran SR 1000 mg	
	stic	2	12	2	12	2	12
T Wave Morphology							
Positive	N (%)	237(92.2)	224(91.8)	228(84.1)	221(87.7)	237(92.9)	207(87.0)
Negative	N (%)	6(2.3)	5(2.0)	18(6.6)	13(5.2)	4(1.6)	5(2.1)
Flat	N (%)	3(1.2)	5(2.0)	4(1.5)	5(2.0)	0	5(2.1)
Biphasic (+/-)	N (%)	6(2.3)	4(1.6)	4(1.5)	4(1.6)	6(2.4)	6(2.5)
Biphasic (-/+)	N (%)	3(1.2)	5(2.0)	4(1.5)	4(1.6)	2(0.8)	7(2.9)
Notched	N (%)	1(0.4)	0	11(4.1)	3(1.2)	5(2.0)	8(3.4)
Major T Wave							
Yes	N (%)	42(16.3)	37(15.2)	43(15.9)	39(15.5)	31(12.2)	28(11.8)
No	N (%)	215(83.7)	207(84.8)	228(84.1)	213(84.5)	224(87.8)	210(88.2)
Minor T Wave							
Yes	N (%)	67(26.1)	76(31.1)	89(32.8)	80(31.7)	68(26.7)	68(28.6)
No	N (%)	190(73.9)	168(68.9)	182(67.2)	172(68.3)	187(73.3)	170(71.4)
Left Ventricular Hypertrophy	N (%)	32(12.5)	24(9.8)	19(7.0)	21(8.3)	29(11.4)	27(11.3)

Note: Data summarised in the above table are listed in data listings 9.2.3.1, 9.2.3.2 and 9.3
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The numbers of patients with notched T waves were greater in the ranolazine groups.

No of patients with notched T waves

	Placebo		Ranolazine 750 mg		Ranolazine 1000 mg	
	peak	trough	peak	trough	peak	trough
Week 2	1	1	11^	7	5#	8
Week 6	-	0	-	4	-	6
Week 12	0	1	3	2	8	4

^2 patients also had notched T waves at baseline/screening
1 patient also had notched T waves at baseline/screening

Subject 218/7250 (ranolazine 1000 mg) was withdrawn on day 12 because of an increase of >25% QTc, asthenia, nausea, and dizziness. Events started on day 1 of study drug dosing.

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Memo to File:

Addendum to Efficacy review for ranolazine:

Subsequent to the filing of the efficacy review of ranolazine, the sponsor submitted responses to additional questions posed in the review. In the opinion of the medical reviewer, these responses do not alter the reviewer conclusions.

The following additional information was sent by the sponsor:

1. **CVT 3033: the sponsor was asked to supply the Interim Analysis Procedure:**
An Interim Analysis Procedure was received by the medical reviewer. The purpose of the Interim Assessment was to re-evaluate sample size using the standard deviation of the change from baseline in ETT duration from the first half of the study population without unblinding the study with respect to treatment assignment. According to this procedure, the sponsor will remain blinded to any treatment-specific outcome and associated information.
The medical reviewer found this document to be satisfactory.

2. **The sponsor was asked to explain why the first period analysis in RAN 1514 did not show statistical significance for peak or trough**. In a fax received 8/28/03, the sponsor responded that the first-period-only analysis has low power relative to the primary analysis. In addition, RAN 1514 showed high variability of the between-patient comparisons (evident in the width of the confidence intervals for the treatment differences). By contrast, the power of the primary analysis using all of the corssover periods and within-patient comparisons allows for detection of the statistically significant treatment effects at peak in that analysis. The sponsor also claimed that the first-period-only analysis can be useful for a crossover study in which there is evidence of a carryover effect; according to the sponsor, they have no evidence of a carryover effect in this or any other ranolazine study.

The sponsor also reviewed Table 1 (controlled clinical trials) from the Integrated Summary of Efficacy. The sponsor offered the following comments/corrections to the reviewer's table (received by the reviewer on 8/29/03): 1. RAN 054 contained 144, not 137, randomized; 2. RAN 072 was a single-dose study and therefore, the ranolazine IR single doses (not bid) were 10, 60, 120 and 240 mg; 3. Parallel group studies CVT 3033, RAN 1513 and RAN 2240 were multiple dose; 4. RAN 020 included, as primary endpoints, angina frequency, nitroglycerin consumption, time to exercise-induced angina, total treadmill time, HR/BP/RPP/ workload at end of exercise; 5. RAN 054 included, as primary endpoints, angina frequency, nitroglycerin consumption, total exercise time plus time to exercise-induced angina at peak and trough. 6. RAN 1490 included, as primary endpoint, exercise duration at peak and trough.

The medical reviewer concurs with points #1-3 and notes that RAN 020 did not contain a primary endpoint that was explicitly prespecified in the protocol. According to the sponsor, RAN 054 contained multiple endpoints (as can be seen above). However, from the Statistical Report of RAN 054, the primary efficacy variable of interest was peak total exercise time.
Please note (as the sponsor also noted) that studies RAN 054, RAN 020, RAN 1490 and RAN 015 did not contribute to evaluation of efficacy.

Shari Targum, MD
Medical Reviewer

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Shari Targum
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