

# CLINICAL REVIEW

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

### II. Summary of Clinical Findings

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#### 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

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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<sup>1</sup>/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-1.3.2.1 vol 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).

<sup>1</sup> From fax dated 6-27-03

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#### % 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.<sup>2</sup> 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.<sup>3</sup> This pattern has been associated with a poor prognosis.<sup>4</sup>

#### 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)<sup>5</sup>. The effect on QTc is shown below.

<sup>2</sup> Roden DM, Spooner PM. Inherited long QT syndromes: a paradigm for understanding arrhythmogenesis. *J Cardiovasc Electrophysiol.* 1999; 10: 1664-1683.

<sup>3</sup> Schwartz PI, Moss AJ, Vincent GM, and et al. Diagnostic criteria for the long QT syndrome: an update. *Circulation.* 1993; 88: 78-784.

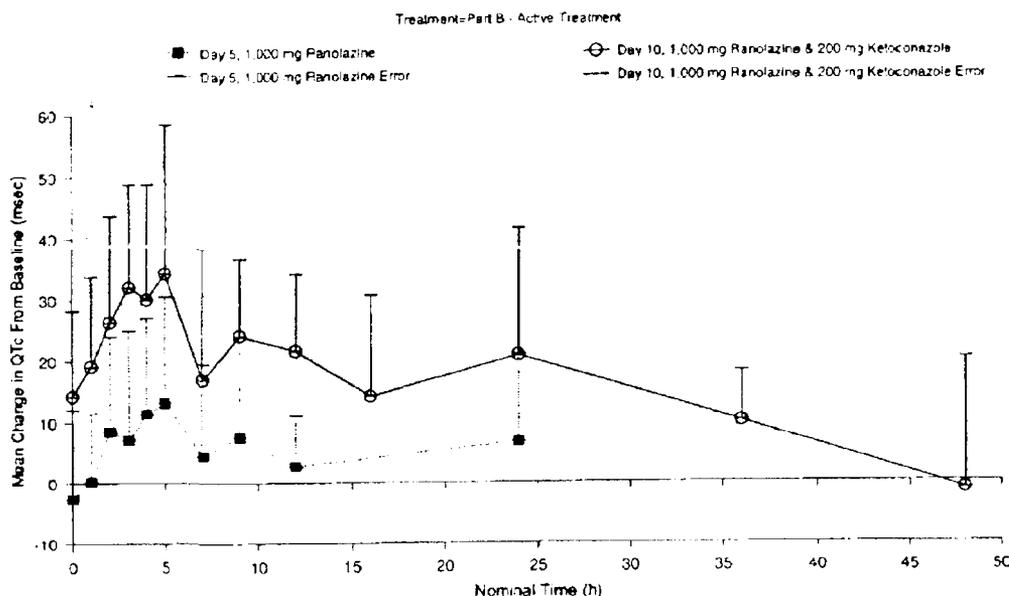
<sup>4</sup> Malfatto G, Beria B, Sala S, et al. Quantitative analysis of T wave abnormalities and their prognostic implications in the idiopathic long QT syndrome. *J Am Coll Cardiol.* 1994; 23: 296-301.

<sup>5</sup> Study CVT 301-10

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**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)<sup>6</sup>. Ranolazine 1,000 mg bid at steady-state caused a less than two-fold increase simvastatin exposure dosed at 80 mg qd<sup>7</sup>.

#### Hepatic impairment:

Subjects with moderate hepatic impairment had increases in AUC and C<sub>max</sub>. 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 C<sub>max</sub>.

#### Adverse events:

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

<sup>6</sup> Studies CVT 3012, RANO121, and RANO6S  
<sup>7</sup> Study CVT 3017

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#### 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.

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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.

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#### 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.

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#### 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

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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.<sup>8</sup>

## **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 25°C/60%RH and no degradation products were observed. Based on test data, eighteen months (18) 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 I<sub>kr</sub>. 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.

<sup>8</sup> 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.

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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 from 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.

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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.

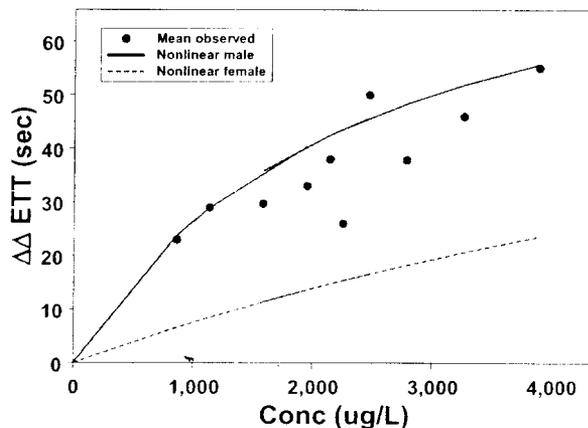
The potent 3A4 inhibitors ketoconazole, diltiazem and verapamil, when co-administered, impact the PK of ranolazine in a clinically significant manner. These in vivo results are in agreement with the in vitro findings indicating that a substantial fraction of ranolazine is metabolized by CYP 3A4.

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  $\Delta\Delta\text{ETT}$  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.



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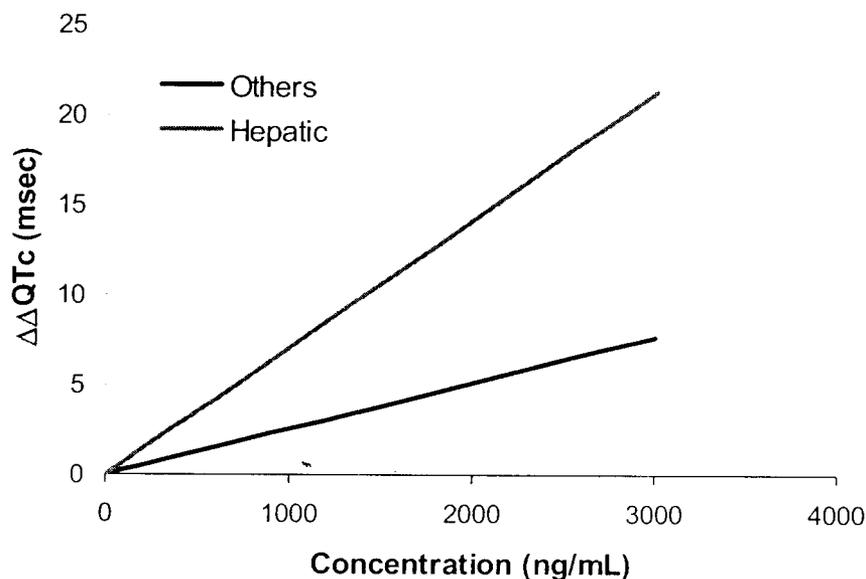
The following table shows the model predicted effectiveness in males and females.

**Table 1. Reviewer's model predicted peak and trough mean  $\Delta\Delta ETT$  (seconds)**

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

Concentration – QTc prolongation relationship: The QTc prolonging effect of ranolazine 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 significant 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  $\Delta\Delta QTc$  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.)



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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

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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] [REDACTED]<sup>9</sup> The total amount of consulting payments made to [REDACTED] [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

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<sup>9</sup> The role of National Coordinator 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 National Coordinator did not serve in a supervisory capacity to the clinical investigators, who were solely responsible for study management at their sites.

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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)<sup>10</sup>. 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 C<sub>max</sub> 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.

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<sup>10</sup> Study CVT 301-10

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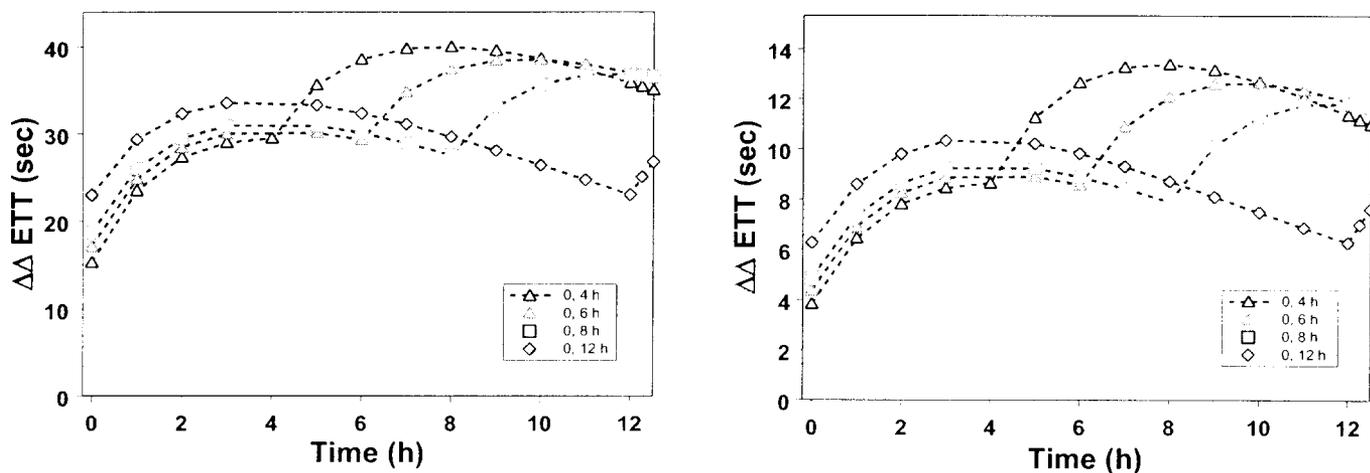
### VIII. Dosing, Regimen, and Administration Issues

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

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42 % of the effect in males. The statistical significance of the effect of ranolazine 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  $\geq 65$  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  $\geq 65$  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.

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#### **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 I<sub>Kr</sub>, 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.

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**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

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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)

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	Interaction	crossover, 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 $\mu$ Ci 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 $\pm$ 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