

Integrated Summary of Efficacy:
NDA 21-526
Drug name: ranolazine
Sponsor: CV Therapeutics

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Studies CVT 3033 and CVT 3031 were reviewed jointly by the medical and statistical reviewers.

Integrated Summary of Efficacy:

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Statement of Conclusions:

1. The pivotal studies, CVT 3031(first period) and CVT 3033, show a treatment effect at peak. One study (CVT 3033) shows a marginal effect at trough. Because of issues of interpretability concerning the sponsor's crossover analysis in CVT 3031, a statistically significant effect at trough cannot be concluded based on the first period data.
2. Ranolazine appears to exhibit an anti-anginal effect, as measured by exercise testing, at the time of peak levels (4 hours after dosing).
3. A statistically significant treatment effect at trough, for the SR formulation, can be seen after 2 weeks of treatment in one study (CVT 3033).
4. Since only one study in the submission demonstrates a significant treatment effect at the time of trough ranolazine concentrations, there is insufficient evidence to conclude that ranolazine SR, when given bid, is effective throughout the inter-dosing interval.
5. Therefore, the concern remains that the duration of effect, and consequent dosing schedule, is uncertain.
6. There appears to be no greater treatment effect with increase in dose from 750 to 1000 mg bid.
7. In the proposed labeling submitted by the sponsor, the proposed indication is for "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." Neither pivotal trial specifically studied this group or predefined "inadequate or not tolerated."
8. There are insufficient data, whether in the pivotal trials or Integrated Summary of Efficacy, to show efficacy of the primary endpoint in certain subgroups, including those with low blood pressure or reactive airway disease, mentioned in the labeling.
9. In the gender subgroup analysis, the treatment effect at peak, in females, showed a trend that was unfavorable for ranolazine.
10. The study population was about 98% Caucasian. Other race groups were not well studied. There are insufficient data to demonstrate efficacy of ranolazine in non-Caucasian subgroups.
11. The data are insufficient to demonstrate whether ranolazine has a beneficial effect in symptomatic patients on maximal anti-anginal therapy.
12. There are no studies in this submission demonstrating superiority of ranolazine over another anti-anginal medication.

Background:

Clinical trials of ranolazine were first initiated by Syntex in 1985 using immediate release (IR) an intravenous (iv) formulations. A sustained release (SR) formulation was later developed by the sponsor. In 1996, CV Therapeutics acquired the license for ranolazine. Studies sponsored by CVT are identified with the code CVT in the study number. Three efficacy studies (CVT 3033, CVT 3031 and RAN 2240) used the SR formulation and the rest used the IR formulation of ranolazine.

The current proposed indication is "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."

Note: Ranolazine and RS 43285 are used interchangeably in the individual study reviews.

General Approach to Review of the Efficacy of the Drug

The reviewer analyzed both individual trial results and the Integrated Summary of Efficacy. The data, protocols, study reports and case report forms were supplied by the sponsor in a combination of paper and electronic formats. This NDA contained five efficacy trials which, according to the sponsor, demonstrated the efficacy of ranolazine and were included in the ISE analysis (see Table 1, studies marked with an asterisk). Of these five efficacy trials, two (CVT 3031 and CVT 3033) were considered to be Phase III studies.

Table 1. Controlled clinical trials (as listed in the submission: Item 8, Volume 1, pages 6-7)

Study number	Design	Treatment groups	Background Rx	Randomized	Exercise method	Primary endpoint
CVT-3031*	Multiple dose Crossover	Placebo, Ran SR 500, 1000, 1500 mg bid	Sublingual ntg prn	191	Treadmill	ETT duration at trough
CVT-3033*	Parallel group	Placebo, Ran SR 750, 1000 mg bid	Amlodipine, diltiazem, or atenolol; sublingual ntg prn.	823	Treadmill	ETT duration at trough
RAN 072*	Single-dose crossover	Placebo, Ran IR 10, 60, 120, 240 mg bid	Beta-blocker or calcium channel-blocker; short-acting nitrates	106	Bicycle	Exercise duration at peak (2.5-3 hours post-dose) ¹
RAN 080*	Multiple dose crossover	Ran IR 400 mg tid	Nitrates, calcium channel-blocker except verapamil	158	Either bicycle or treadmill	Time to angina at peak (1 hour post-dose)
RAN 1514*	Multiple dose crossover	Placebo, Ran IR 267 mg tid, 400 mg bid, 400 mg tid.	Beta-blockers and calcium channel-blockers; sublingual ntg prn	318	Treadmill	Time to angina at trough
RAN 015	Multiple dose Crossover	Placebo, Ran IR 120 and 180 mg tid.	Sublingual ntg prn	12	Treadmill	Total exercise time; workload/HR/RPP end of exercise.
RAN 020	Multiple dose crossover	Placebo, Ran IR 60 and 120 mg tid	Sublingual ntg prn	36	Treadmill	Not specified. ETT done at peak/trough
RAN 054	Multiple dose Crossover	Placebo, Ran IR 120 and 240 mg tid	Sublingual ntg prn	137	Treadmill	Total exercise time at peak (1 hour post-dose)
RAN 1490	Ascending dose	Placebo, Ran IR 60 mg tid	Sublingual ntg prn	12 (48-72 planned)	Treadmill	Exercise duration
RAN 2240	Parallel group	Ran SR 1000 mg bid	Sublingual ntg prn (background medications)	11	N/A	Time to revascularization (PTCA or CABG)
RAN 1513	Parallel group	Placebo, Ran IR 30, 60, 120 mg tid	Sublingual ntg prn	319	Treadmill	Exercise duration at peak (1 hour post-dose)

*Studies Demonstrating Efficacy of Ranolazine included in the ISE Analysis.

The five key trials, especially the two pivotal studies, were reviewed in greater detail, since they form the basis for efficacy conclusions. These five studies used exercise performance measurements (exercise duration or time to angina) as primary efficacy parameters. Of these key studies, CVT 3033, CVT 3031 and RAN 1514 utilized sites in the USA.

Table 2. Summary of Studies Demonstrating Efficacy of Ranolazine included in the sponsor's ISE

Study	Patients Randomized	Patients Included in Efficacy analyses	Ranolazine		Placebo
			< 240 mg	≥ 240 mg	
Phase 3 Studies					
CVT 3031 (SR)	191	175	0	191	179
CVT 3033 (SR)	823	791	0	554	269
Other Controlled Studies Demonstrating Efficacy					
RAN 072 (IR)	106	104	79	27	106
RAN 080 (IR)	158	153	0	155	154

¹ This parameter was not prespecified in the protocol but mentioned in the study report as the primary efficacy variable.

RAN 1514 (IR)	318	312	0	315	310
Studies Supporting Dosing Rationale					
CVT 3033 (SR)	823	791	0	554	269
CVT 3031	191	175	0	191	179
RAN 072	106	104	79	27	106
RAN 080	158	153	0	155	154
RAN 1514	318	312	0	315	310
Studies Supporting Long-term efficacy and withdrawal effects					
CVT 3033 (SR)	823	791	0	554	269
Studies Supporting Mechanism of Action					
CVT 3021 (SR)*	85	NA	0	49	34
RAN 003 (iv)	10	NA	10	0	9
RAN 004 (iv)	10	NA	6	0	3
RAN 011 (iv)	17	NA	17	0	0
RAN 014 (iv)	15	NA	15	0	0
RAN 070 (if)	20	NA	10	0	10

* This study was a pharmacokinetic/safety study and was analyzed by other reviewers.

In addition to the 11 studies listed in Table 2, thirteen other controlled studies did not support efficacy or contribute to the dose-response of ranolazine. These studies are summarized below:

Table 3. Studies that did not support efficacy

Study	Number planned/enrolled	Study Design	Treatment	Primary endpoint
RAN 2240	275/11	Parallel group	Placebo or Ran SR 1000 mg bid	Time to revascularization
RAN 007	12/12	Double-blind, Single dose crossover	Placebo or 10, 20 and 30 mg Ran IR	Not specified (ETT done 90 minutes after dose)
RAN 010	24/25	Double-blind, Parallel group	Placebo or 10, 30 and 50 mg Ran IR tid	Not specified (ETT done 60 minutes after dose, after 1 week of treatment)
RAN 012	15/16	Single-blind, ascending dose	Ran IR 30 mg tid x 2 weeks, 60 mg tid x 2weeks	nitrate consumption and exercise tolerance (under objectives)
RAN 015	24/12	Double-blind multiple dose crossover	Ran IR 120 mg, 180 mg or placebo tid (2 week treatment periods)	1. Total exercise time; 2. Heart rate, BP, and rate-pressure product at end of exercise; 3. Workload at termination of treadmill
RAN 017	24/19	Double-blind single-dose crossover	Ran IR 120 mg or 240 mg or placebo	ST depression during exercise and recovery (bicycle testing at 2 and 6 hours)
RAN 020	24-30/36	Double-blind multiple-dose crossover	Ran IR 60 mg, 120 mg or placebo tid	Not specified. Exercise tolerance, angina frequency, nitroglycerin use
RAN 054	120/144	Double-blind multiple-dose crossover	Ran IR 120 mg, 240 mg or placebo tid (4 week treatment periods)	peak (1 hour) total exercise time
RAN 064*	12/14	Double-blind Multiple-dose crossover	Ran IR 240 mg, 320 mg or placebo tid	Safety/tolerability
RAN 1490	48-72/12	Double-blind dose-ranging dose-scheduling	Ran IR 60 mg or placebo tid	Duration of treadmill exercise to maximal tolerated angina or other limiting symptomatology.
RAN 1513	284/319	Double-blind multiple-dose parallel-group	Ran IR 30, 60, 120 mg or placebo tid	Exercise duration at peak.

RAN 003B	10-12/11	Single-blind, single-dose	2 mg/ml saline, followed 30 minutes later by Ranolazine iv 200 mcg/kg	Time to pacing-induced angina and pharmacokinetic features, hemodynamic and cardiac metabolic effect
RAN 1789	90/95	Double-blind, parallel-group	Ranolazine 700 mcg/kg over 10 minutes via peripheral iv line	Time to development of ST deviation 0.1 mV on any surface or intracoronary ECG

*Not considered in this review because this was considered a safety study. Please see the safety review for detailed safety discussion.

Mechanism of Action:

According to the sponsor, the anti-anginal and anti-ischemic effects of ranolazine are believed to result from partial inhibition of fatty acid uptake and oxidation (pFOX inhibition). The shift away from fatty acid oxidation in favor of carbohydrate oxidation is felt by the sponsor to result in a more oxygen-efficient production of ATP, increasing cardiac efficiency and preventing the ischemia-induced increase in lactic acid and cellular acidosis.

RAN 011: was a 17 patient open-label, nonrandomized study of intravenous (iv) ranolazine in males with either CAD or atypical chest pain and normal coronary arteries. Patients were taken to the cardiac catheterization laboratory and central hemodynamic and metabolic measurements were taken at rest and during pacing (during a control period followed by ranolazine administration). A reduced free fatty acid uptake (during rest, pacing and recovery phases) was noted in ranolazine-treated patients; however, differences are also seen between patients with CAD and those with normal coronaries. Myocardial lactate production was only seen in 3 patients during control measurements. (Please see the Individual study review for further details).

RAN 70: was a 20 patient (19 male) single-blind study of iv ranolazine and placebo control in patients with angina and CAD. Central hemodynamic and metabolic measurements were taken at rest and during pacing during control followed by ranolazine administration. The only statistically significant finding was a median increase, during pacing, in free fatty acid uptake of 4.4 $\mu\text{mol}/\text{min}$ in the placebo group and decrease of 8.5 $\mu\text{mol}/\text{min}$ in the ranolazine group ($p=0.05$). Basal results for free fatty acid uptake were not significantly different between the two treatment groups. (Please see the Individual study review for further details).

Reviewer:

1. Of these two “mechanism of action” studies, neither was performed as a double-blind study.
2. Even if ranolazine were shown to decrease free fatty uptake in a placebo-controlled double-blind study, it is not clear whether this is the primary mechanism of drug effect.

Central hemodynamic effects:

RAN 003, RAN 004, RAN 006A, RAN 011 and RAN 014 were small studies, performed in the cardiac catheterization laboratory, using intravenous ranolazine and measuring drug effects on central right and left-sided pressures. These studies used doses of up to 200 $\mu\text{g}/\text{kg}$ (RAN 003, RAN 004, RAN 006A, RAN 014) or 140 $\mu\text{g}/\text{kg}$ bolus with 1.2 $\mu\text{g}/\text{kg}/\text{min}$ infusion (RAN 011). Measured and calculated parameters included: pulmonary artery pressures, LVEDP, cardiac output (thermodilution method), coronary sinus blood flow, coronary vascular resistance, as well as indices of inotropic state and relaxation. RAN 006A, RAN 011, and RAN 014 were open-label; RAN 004 was double-blind, and RAN 003 was initially open-label and changed to single-blind. The reviewer was unable to find any consistent ranolazine effects or patterns across these studies.

Detailed Review of Angina Trials:

Since the only indication in this submission is angina, this section will concentrate on efficacy-related issues for this claim. Two studies in the submission, RAN 2302 and RAN 2320, conducted in patients with intermittent claudication, were not used in support of efficacy in angina pectoris.

Efficacy in pivotal trials:

This submission contained two pivotal trials, CVT 3033 and CVT 3031, that evaluated the ranolazine SR formulation in patients with stable exertional angina. For both of these studies, the primary endpoint was the change from baseline, compared to placebo, in treadmill exercise test duration at the time of trough ranolazine concentrations (defined as 12 hours after the last drug dose). These two study designs are briefly summarized below:

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.

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 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, aspirin, and stable doses of antihypertensives were allowed in the study.

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.

Datasets analyzed: In study CVT 3033 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, was the primary analysis population.

In study CVT 3031 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. Other populations were also analyzed and presented in the submission (see Individual study reviews).

Patient Disposition: Patient disposition for the two pivotal trials is presented below.

Table 4. Patient Disposition: CVT 3033

N (%)	Placebo	Ran 750	Ran 1000
#Randomized	269	279	275
#Completed*	243 (90)	250 (90)	238 (87)
Early w/d	26 (10)	29 (10)	37 (14)
Unacceptable AE	13 (5)	20 (7)	24 (9)
Noncompliance	2 (0.7)	2 (0.7)	0
Elective withdrawals	4 (2)	1 (0.4)	5 (2)
Lost to follow-up	0	0	1 (0.4)
Death	2 (0.7)	2 (0.7)	1 (0.4)
Other	5 (2)	4 (1)	6 (2)

Source: sponsor: Table 1.4.1. * Completed = patient completed both double-blind and rebound phases.

The majority of early withdrawals in CVT 3033 occurred within the first 6 weeks after randomization. There were no withdrawals during the rebound assessment phase.

In Study 3031, A total of 191 patients were randomized into 4 treatment sequences (ABCD, BDAC, CADB and CDBA where A=500 mg bid, B=1000 mg bid, C=1500 mg bid and D=placebo). There were 45-50 patients randomized to each treatment sequence; the numbers of patients receiving each treatment (ie, placebo, ranolazine SR 500 mg bid, 1000 mg bid or 1500 mg bid) were 179-187. A total of 175 patients (92%) were included in the near/all completer population, 185 patients (97%) 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).

Baseline Characteristics:

In Study 3033 (ITT population), the mean age was 64 years, with half of the patients 65 years and older. About 75-80% were male, and 96-99% Caucasian. Mean vital signs and exercise test durations were similar across treatment groups (with lower heart rates in the group taking concomitant beta blocker). The treatment groups were also balanced with respect to stratified background medication, other concomitant medication, baseline weekly angina frequency, and weekly nitroglycerin consumption. Fewer patients on placebo had a history of prior CABG compared with those on ranolazine (see Individual Study Report, 3033); however, this difference was not statistically significant (p=0.06). About 55-60% had a prior MI and about 29-32% were classified as either Class I or II CHF. About 64% had a history of hypertension, 21-25% of patients were diabetic (most did not take insulin) and 5-10% had asthma/COPD.

In Study 3031, (all treated patients) baseline characteristics, except for gender (p=0.05, higher percentage males in the ABCD and BDAC sequences), appeared to be balanced among treatment sequences. Statistically significant differences were seen with regard to diabetics on insulin (p=0.02), history of unstable angina (p=0.037) and prior stroke (p=0.03); however the numerical differences between these groups were small.

Mean age was about 64 years and about half of the patients were 65 years and older. The safety population was about 90% Caucasian and 4-8% Black. About half had a prior MI, about 13-20% had a history of CHF, and 28% had a prior CABG. About 60-70% had a history of hypertension. No gross imbalances were seen with respect to concomitant medications. The most frequently used medications included antiplatelet agents (about 80%), ACE inhibitors (about 25-27%), nitrates (about 54%), HMG CoA reductase inhibitors (about 50%) and sulfonamides (about 10%).

Efficacy Results:

The primary efficacy endpoint for both pivotal studies was the change from baseline to endpoint in ETT duration at trough (12 hours post-dosing).

CVT 3033: efficacy variables:

The primary endpoint for Study 3033 is presented below:

Table 5. CVT 3033: Primary Efficacy analysis: Change from baseline in ETT (sec) at trough Week 12 (ITT LOCF)—comparison of treatment differences from ANCOVA Model 1*

	Ran SR 750 mg bid vs. placebo	Ran SR 1000 mg bid vs. placebo
LS Mean difference (SE)	23.7 (10.9)	24 (11)
95% CI	(2.3, 45.1)	(2.4, 45.7)
p-value	0.03	0.029

Source: Table 2.0.0. Study 3033

*Model 1: effects for treatment, baseline covariate, pooled site and background therapy using type III sum of squares. Baseline covariate is the average of visits 1 and 2 data.

When the primary endpoint was analyzed via the efficacy evaluable population, results were statistically significant only for the Ran SR 1000 mg bid group.

The primary efficacy endpoint was also analyzed by stratified medication, pooled/individual site, and other subgroups. Please see Subgroup Section and the Individual study review for further details.

Secondary efficacy variables, related to exercise testing, are presented below. The treatment effect in any variable does not increase when the dose is increased from 750 to 1000 mg bid. Treatment effects are greater at peak times compared to trough.

Table 6. CVT 3033: Exercise Efficacy Variables (primary and secondary): Change from baseline at Week 12 (ITT LOCF) at peak and trough

	Ranolazine SR 750 mg bid				Ranolazine SR 1000 mg bid			
	N	Trough	N	Peak	N	Trough	N	Peak
Exercise duration (sec)								
LS Mean (SE)	272	115.4 (8)	270	99.4 (7.8)	261	115.8 (8.2)	255	91.5 (8.1)
Mean difference vs. placebo (SE)		23.7 (10.9)		34 (10.7)		24 (11)		26.1 (10.8)
p-value		0.03		0.001		0.029		0.016
Time to Onset of Angina (sec)								
LS Mean (SE)	272	144 (8.9)	270	126.9 (9.1)	261	140.3 (9.1)	255	126.8 (9.4)
Mean difference vs. placebo (SE)		29.71 (12.07)		38.02 (12.38)		26.01 (12.2)		37.88 (12.56)
p-value		0.014		0.002		0.033		0.003
Time to 1 mm ST depression (sec)								
LS Mean (SE)	260	145.1 (9)	248	100 (8.7)	244	146.2 (9.3)	236	93.8 (8.9)
Mean difference vs. placebo (SE)		19.9 (12.2)		40.8 (11.8)		21.1 (12.4)		34.5 (11.9)
p-value		NS		<0.001		NS		0.004
Maximum ST depression (mm)								
LS Mean (SE)	266	0.37 (0.05)	254	0.10 (0.05)	251	0.21 (0.05)	240	0.03 (0.05)
Mean difference vs. placebo (SE)		0.18 (0.07)		0.10 (0.07)		0.02 (0.07)		0.03 (0.07)
p-value		0.006		NS		NS		NS
Primary Reason for Stopping ETT, n (%)								
Angina	254	178 (70.1)	249	143 (57.4)	239	168 (70.3)	237	136 (57.4)
p-value (vs. not angina)		NS		0.011		NS		0.011

CVT 3033: Angina/nitroglycerin consumption: Weekly anginal episodes and nitroglycerin consumption, as reported by patients in a weekly diary, were secondary efficacy variables in Study CVT 3033. Results (below) showed a significant improvement in patient-reported weekly anginal episodes and nitroglycerin consumption.

Table 7. CVT 3033: Weekly angina episodes and nitroglycerin consumption (ITT)

	Ranolazine SR				Placebo	
	750 mg bid		1000 mg bid		N	
Angina episodes/wk	N		N		N	
Mean (SE) baseline	272	4.4 (0.3)	261	4.4 (0.3)	258	4.6 (0.4)
Mean (SE) during double-blind	272	2.47 (0.23)	261	2.13 (0.24)	258	3.31 (0.3)
p-value vs. placebo		0.006		<0.001		

	Ranolazine SR				Placebo	
	750 mg bid		1000 mg bid			
Nitroglycerin use/wk	N		N		N	
Mean (SE) baseline	258	4 (0.5)	244	3.7 (0.5)	247	4.1 (0.4)
Mean (SE) during double-blind	262	2.11 (0.27)	244	1.76 (0.28)	252	3.14 (0.38)
p-value vs. placebo		0.016		<0.001		

Ranolazine vs. placebo calculated from ANOVA using ranked scores data adjusted for treatment, baseline covariate, pooled site and background. Also see Individual study review.

Efficacy Analysis: CVT 3031:

The individual study review of CVT. 3031 highlighted issues in study design (lack of interim washout periods, lack of baseline measurements for each period, etc) as well as the presence of treatment-by-period interaction and possible carryover effect. Because of these issues, analysis of the first period was taken as the double-blind portion not subject to bias. Results are presented below:

Table 8. 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

Source: CVT 3031. Table 2.3.2. ANCOVA model includes effects for baseline ETT duration, treatment, pooled site.

These results do not support a statistically significant effect at trough; however, there appears to be a treatment effect at peak (with marginally significant results at the lowest and highest doses). In this study, there does not appear to be further improvement in the primary efficacy variable above the ranolazine SR dose of 1000 mg bid.

Ranolazine IR studies demonstrating efficacy at peak:

The following three ranolazine IR crossover studies were cited by the sponsor to support efficacy at peak. Potentially confounding issues include: use of more than one testing method in the same study; lack of interim washout period/ variable interim period, and significant sequence effects. Significant sequence effects were seen in several efficacy variables in RAN 72 and RAN 1514.

Of the three studies, only RAN 80 also included a “first period” analysis that showed a statistically significant treatment effect, supporting efficacy at peak. The first period analysis of RAN 1514 did not support a significant treatment effect (at peak or trough).

It should also be noted that the definition of peak time differed across studies.

RAN 72: This was a single-dose crossover study of ranolazine IR 10, 60, 120 or 240 mg and placebo in CAD patients who were symptomatic despite medical therapy and admitted for coronary angiography. Background medication included either beta blocker or diltiazem. Each patient would receive a dose of ranolazine on one study day and placebo on the other study day. Bicycle exercise testing was performed at peak only, at a median interval of 5-7 days (range 1-17 days) between study days. The primary efficacy variable was not explicitly prespecified in the protocol, but the main exercise-related test variable was exercise duration at peak (2.5-3 hours post-dosing).

Results: Significant improvements compared to placebo are only seen in the 240 mg group (combined and on beta blocker). The percentage increase in exercise duration, time to 1 mm ST depression and time to angina were all consistent in that statistically significant improvements,

compared to placebo, were seen at the 240 mg dose and in the group receiving beta blocker (but not calcium channel blocker) as background therapy. Sequence effects were seen with respect to “time to angina” and ST depression and treatment-by-period interactions cannot be excluded.

Table 9. RAN 072: Exercise duration (sec) at peak

	N	Adjusted difference (R minus P)* (SE)	p-value
Beta blocker group:			
Ran 10 mg	14	7.21 (16.24)	NS
Ran 60 mg	15	21.28 (15.73)	NS
Ran 120 mg	17	5.11 (14.98)	NS
Ran 240 mg	15	39.42 (16.02)	0.02
Calcium channel blocker group			
Ran 10 mg	10	11.9 (19.22)	NS
Ran 60 mg	11	6.2 (18.4)	NS
Ran 120 mg	12	-8.82 (17.79)	NS
Ran 240 mg	10	33.8 (19.22)	0.08
Combined			
Ran 10 mg	24	9.56 (12.58)	NS
Ran 60 mg	26	13.74 (12.1)	NS
Ran 120 mg	29	-1.86 (11.63)	NS
Ran 240 mg	25	36.6 (12.51)	0.004

Source: RAN072 Table 5. *Ranolazine minus placebo. Differences were adjusted to account for imbalance of patients in each group on each sequence.

RAN 80: This was a double-blind, crossover study of ranolazine IR 400 mg tid, atenolol 100 mg qd (double dummy) and placebo tid in stable angina patients responding to medical therapy. Each double-blind treatment was administered for one week. No interim washout period was planned between treatments. Exercise testing (either bicycle or treadmill, depending on the site) was done 1 hour post-dose. The primary efficacy variable was the time to onset of angina at peak (1 hour post-dose).

Results: Significant treatment effects were seen for both ranolazine and atenolol (without superiority) in the primary efficacy variable; in addition, a significant treatment effect was seen in the first period analysis. Similar results were seen in the evaluable population (please see the Individual Study review for further details). Overall analyses of the time to onset of angina showed significant treatment by investigator interaction, suggesting heterogeneity across centers. In the “all patients” analysis of time to onset of angina, there was also a significant treatment by method interaction (p=0.01).

Table 10. Study RAN 080: Time to Onset of Angina: First Period Analysis

	Baseline	Ranolazine	Atenolol	Placebo
N	158	53	51	51
Mean time to angina (SEM) (sec)		62.5 (11.9)	59.6 (12.2)	23.2 (12.2)
		Ranolazine vs. placebo	Atenolol vs. placebo	Ranolazine vs. atenolol
Mean difference		39.3	36.4	2.9
95% CI		6.7, 72.1	3.4, 69.4	-29.8, 35.6
p-value		0.02	0.03	NS

Source: RAN 080, Table 12. Means are adjusted. Statistics calculated from ANOVA.

RAN 1514: This was a double-blind, Latin square crossover study of placebo and ranolazine IR: 267 mg tid, 400 mg bid, and 400 mg tid for one week treatment periods with no interim washout period between treatments. The double-blind treatment phase lasted a total of 5 weeks, with one of the treatments repeated during a fifth period. Exercise testing was performed at trough (8 or 12 hours post-dosing) or peak (1 hour post-dosing). The primary efficacy variable was time to onset of angina at trough.

Results: No statistically significant treatment effects were demonstrated for the primary endpoint, or for other trough exercise variables (exercise duration, time to 1 mm ST depression). For peak results (secondary efficacy variables), analysis of time to angina, exercise duration and time to 1 mm ST depression showed statistically significant differences vs. placebo. Significant period effects ($p < 0.01$) were seen with regard to duration of exercise and time to 1 mm ST depression. A first-period analysis showed no statistically significant treatment effects for either peak or trough exercise variables. No treatment-by-period analysis was submitted, and a treatment-by-period interaction therefore cannot be excluded.

Table 11. RAN 1514: Peak exercise treatment change from baseline to endpoint pairwise treatment comparisons: First period per-protocol analyses (n=304)

		Ran 400 mg bid vs. DB placebo	Ran 267 mg tid vs. DB placebo	Ran 400 mg tid vs. DB placebo
Time to Onset of Angina (min)	Mean difference (SEM)	0.78 (0.43)	0.59 (0.43)	0.43 (0.42)
	95% CI	-0.07, 1.63	-0.25, 1.43	-0.40, 1.27
Duration of exercise (min)	Mean difference (SEM)	0.39 (0.3)	0.29 (0.3)	0.13 (0.29)
	95% CI	-.20, 0.98	-0.29, 0.88	-0.45, 0.71
Time to 1 mm ST depression (min)	Mean difference (SEM)	0.40 (0.38)	0.94 (0.38)	0.48 (0.38)
	95% CI	-.35, 1.15	0.19, 1.68	-.26, 1.22

Statistics were estimated by the sponsor from ANOVA. The overall test was not significant.

Ranolazine IR studies that did not demonstrate efficacy:

Most of these studies (see table 3) either used Ran IR ≤ 240 mg, or were stopped/discontinued.

Reviewer:

1. Three ranolazine studies, CVT 3033, CVT 3031 (first period) and RAN 80 (first period) support efficacy at peak, where peak is defined as 4 hours post-dose (am) in studies CVT 3033 and 3031, and 1 hour post-dose in RAN 80.
2. Study CVT 3033 supports efficacy at trough, where trough is defined as 12 hours after the p.m. dose.
3. The statistically significant (patient-reported) decreases in angina episodes and nitroglycerin use also support efficacy, but were only demonstrated in CVT 3033.

Dose-response/Drug concentration-response Relationship:

According to the sponsor, the IR formulation used the dihydrochloride salt of ranolazine, in contrast to the SR formulation, in which ranolazine base is the active ingredient. The conversion factor for ranolazine dihydrochloride salt to ranolazine base is 0.854.

Ranolazine dihydrochloride and free base equivalent plasma concentrations (ng/ml) at Trough and Peak doses for the three ranolazine IR efficacy studies (RAN 072, RAN 080 and RAN 1514) are presented below:

Table 12. Ranolazine Dihydrochloride and Free Base Equivalent Plasma Concentrations (ng/mL at Trough and Peak doses for the three ranolazine IR studies

Ranolazine IR dose	Ranolazine dihydrochloride mean (SD)			Ranolazine free base mean (SD)**			
	N	Trough	Peak	N	Trough	N	peak
<i>RAN 072*</i>							
10 mg		NA	20 (46)		NA	20 (39)	
60 mg		NA	18 (249)		NA	18 (213)	
120 mg		NA	23 (589)		NA	23 (503)	

240 mg		NA	21	1,030 (556)		NA	21	880 (475)
<i>RAN 080</i>								
400 mg tid		NA	143	2,039 (1201)		NA	143	1,741 (1026)
<i>RAN 1514</i>								
267 mg tid	292	371 (394)	298	1,576 (965)	292	317 (336)	298	1,346 (824)
400 mg bid	302	275 (338)	304	2,204 (1,281)	302	235 (289)	304	1,882 (1094)
400 mg tid	311	602 (585)	308	2,492 (1403)	311	514 (500)	308	2,128 (1198)

Source: ISE * Single dose study. **Conversion: 1 mg ranolazine dihydrochloride = 0.854 mg ranolazine free base. Ranolazine free base is the active ingredient in the ranolazine SR formulation.

Using the preceding table, coupled with the sponsor's claim of efficacy at peak of the ranolazine doses in RAN 072, RAN 080 and RAN 1514, the sponsor concludes that concentrations of ≥ 880 ng/ml, corresponding to the ranolazine IR dose of 240 mg (from RAN 072), are effective.

Table 13. CVT 3033: Ranolazine Plasma Concentrations (ng/ml) at Week 12 at Trough and Peak during the Double-blind phase: safety population

	Ranolazine SR 750 mg	Ranolazine SR 1000 mg
Trough Mean (SE)	1577.6 (71)	2164.7 (89.2)
Peak Mean (SE)	2031.1 (78.8)	2607.1 (90)

Source: Table 11P, Table 3.5.0, 3.6.0.

Table 14. CVT 3033: Trough and Peak mean (SD) exercise duration at baseline and Change from baseline at Week 12 (ITT LOCF)

	Ran SR 750 mg bid				Ran SR 1000 mg bid				Placebo			
	Trough		Peak		Trough		Peak		Trough		Peak	
	N	Value	N	Value	N	Value	N	Value	N	Value	N	Value
Baseline mean (SE), sec	272	416.4 (6.2)	270	464.8 (8.1)	261	414.7 (6.3)	255	470.4 (7.9)	258	418.3 (6.3)	256	466.5 (8.2)
Mean difference (SE), sec		23.7 (10.9)		34 (10.7)		24 (11)		26.1 (10.8)		--		--
p-value		0.03		0.001		0.029		0.016		--		--

In the above table, the sponsor has made the point that baseline mean exercise duration was about 50 seconds longer at peak than at trough. According to the sponsor, these differences may have occurred, at least in part, because levels of background anti-anginal medications were lower at trough and higher at peak. The sponsor also claims that the difference in baseline exercise duration between peak and trough may explain why changes from baseline are smaller at peak than trough.

Table 15. CVT 3031: Ranolazine SR concentration measurements—Safety population (N=191)

Parameter	Placebo (N=179)	Ran SR 500 mg (N=181)	Ran SR 1000 mg (N=180)	Ran St 1500 mg (N=187)
	N=175	N=173	N=175	N=170
Trough plasma concentration (ng/ml) mean (SE)	16 (11.3)	848.9 (55)	1959.2 (107.5)	3241 (150.9)
	N=173	N=169	N=174	N=166
Peak plasma concentration (ng/ml) mean (SE)	35.2 (19.5)	1122.6 (55.9)	2476 (115.1)	3930.5 (161.3)

Source: Panel 11E, Table 1.14.0, (CVT 3031)

In study CVT 3031, the sponsor has noted that ranolazine levels at trough for ranolazine SR 500 mg are close to 880 ng/ml. If one accepted the sponsor's claim of efficacy at a serum concentration of 880 ng/ml, then, following this line of argument, it would mean that ranolazine SR 500 should be an effective dose.

Onset of effect:

According to the sponsor, the anti-anginal effect of ranolazine occurs with the first dose and is maintained for the duration of treatment with ranolazine.

In CVT 3033, statistically significant treatment effects at trough were noted as early as Week 2 (see Individual study review) for both ranolazine doses.

A statistically significant increase in exercise duration was seen at *peak* (2.5-3 hours post-dose) with a single dose of ranolazine IR 240 mg (Study RAN 072). However, sequence effects were seen with other exercise measurements in RAN 072.

Two other studies did not demonstrate significant treatment effects with ranolazine IR 240 mg (see Table 3: RAN 017, RAN 054); however, it might be argued that these other studies suffered from either small numbers or administrative problems.

Study RAN 080 showed a significant treatment effect at *peak* (1 hour post-dose) time to angina) after one week dosing with ranolazine IR 400 mg tid (see Individual study review).

However, RAN 1514 (n=72 to 72 per ranolazine treatment group and n=84 for placebo) showed no statistically significant treatment effect at peak (1 hour post-dosing) in the first-period analysis (after one week of dosing) using doses (ranolazine IR 400 mg bid, 267 mg bid, or 400 mg tid) larger than 240 mg.

Reviewer:

1. A statistically significant treatment effect at trough is demonstrated as early as Week 2 in a single study (CVT 3033).
2. Results of RAN 1514 (first period) is inconsistent with the sponsor's claim of significant treatment effect at peak after a single dose.

Maintenance of anti-anginal effect/Testing for Rebound effects:

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 would undergo an ETT at trough.

As noted in the CVT 3033 individual study review, large differences in the change from baseline in 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 or nitroglycerin consumption.

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.

Table 16. CVT 3033: Mean Difference in Change from Baseline in ETT duration at Trough at the End of the Rebound Assessment Phase (ITT)

	Ran 750/placebo vs. Placebo/placebo	Ran 1000/placebo vs. Placebo/placebo	Ran 750/placebo vs. Ran 750/Ran 750	Ran 1000/Placebo vs. Ran 1000/Ran 1000
Mean Difference (SE)	4.7 (14.7)	-1.5 (15.1)	-21.8 (17.1)	-33.9 (17.5)
95% CI	-24.2, 33.5	-31, 28.1	-55.3, 11.7	-68.2, 0.5
p-value	NS	NS	NS	0.053

Source: ISE, CVT 3033

Effects on heart rate and systolic blood pressure:

From the sponsor's analyses, there appear to be small decreases in heart rate and SBP compared to placebo. These decreases appear to be largely consistent across studies. Decreases in heart rate and SBP were also seen in Study CVT 3031, with statistically significant decreases in standing pre-exercise heart rate (both trough and peak) in the ranolazine SR 1500 mg bid group (LSM difference from placebo of -2.8 and -2.6 bpm, $p < 0.001$ and $p = 0.001$, respectively). Also in CVT 3031, the standing pre-exercise SBP was significantly decreased vs. placebo (LSM difference from placebo = -2.3 mm Hg, $p = 0.039$).

Table 17. CVT 3033: HR and SBP data (All patients with ETT data at Week 12 (N=737))

	LSM Difference from placebo p-values < 0.05			
	750 mg bid		1000 mg bid	
	Trough	Peak	Trough	Peak
Standing pre-exercise HR (bpm)	-1.5 NS	-1.4 NS	-1.5 NS	-1.3 NS
Standing pre-exercise SBP (mm Hg)	-1.8 NS	-1.6 NS	-2.8 NS	-2.8 NS

Source: ISE. Differences from placebo are from ANCOVA model with effects for baseline, pooled site, background therapy and treatment.

Table 18. Heart rate and BP data in Studies RAN 072, RAN 080 and RAN 1514.

	LSM Difference from placebo p-values ≤ 0.05				
	240 mg (RAN 072)*	267 mg tid (RAN 1514)	400 mg bid (RAN 1514)	400 mg tid (RAN 1514)	400 mg tid (RAN 080)*
	Peak	Peak	Peak	Peak	Peak
Standing pre-exercise HR (bpm)	-2.2 NS	-0.3 NS	-0.6 NS	-0.2 NS	1.5 NS
Standing pre-exercise SBP (mm Hg)	-0.1 NS	-1.4 NS	-0.6 NS	-2.7 NS	-0.5 NS

* All patients analysis. In study RAN 1514, a per-protocol complete squares analysis was performed (HR/BP analysis was not performed on all patients).

Interaction with Background Therapy:

Study CVT 3033: Study CVT stratified patients to background therapy of amlodipine, atenolol and diltiazem. The primary efficacy endpoint by background therapy is shown below. There appears to be an interaction with diltiazem with greater differences vs. placebo in the diltiazem group, especially at the higher doses and at peak (where the treatment effect at peak, on ranolazine SR 750 mg bid, is two-fold higher in the diltiazem group, compared to other subgroups).

Table 19. CVT 3033. Change from baseline in Exercise duration at Trough and Peak at Week 12 (ITT LOCF) by stratified background therapy

	Treatment and Background Therapy					
	Ranolazine 750 mg bid vs. placebo			Ranolazine 1000 mg bid vs. placebo		
	Diltiazem 180 mg qd	Atenolol 50 mg qd	Amlodipine 5 mg qd	Diltiazem 180 mg qd	Atenolol 50 mg qd	Amlodipine 5 mg qd
Trough (sec)						
LSM difference (SE) vs. placebo	20.6 (21.5)	23.2 (16.5)	27.4 (19.7)	42.9 (22.1)	7.5 (16.7)	32.3 (19.7)
95% CI	-21.7, 62.9	-9.2, 55.6	-11.2, 66.1	-0.6, 86.4	-25.2, 40.2	-6.4, 70.9
p-value	NS	NS	NS	0.053	NS	NS
Peak (sec)						
LSM difference (SE) vs. placebo	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
p-value	0.008	NS	NS	0.002	NS	NS

According to the sponsor, the treatment by background therapy was not statistically significant.

In study RAN 72, a single-dose crossover study, increased serum concentrations at peak (2.5-3 hours post-dosing) for ranolazine are seen in diltiazem-treated patients compared to patients on beta-blocker. Statistically significant treatment effects are seen in the overall group and the group on beta-blocker (effects that are not consistent with CVT 3033).

Efficacy in Subgroups:

Efficacy by Geographic Region

Please see CVT 3033 (individual study review). According to the sponsor, there was no significant difference by pooled site (based on geographic region) for the effect of ranolazine SR on exercise parameters. However, heterogeneity by pooled sites was noted by the reviewers. Exclusion of one outlier site (710) resulted in a statistically “non-significant” treatment effect.

Efficacy by Gender, Race, Age

Gender:

Subgroup analyses by gender are presented below. Sample size imbalances are noted between genders and other imbalances between the subgroups cannot be excluded. Results appear consistently significant for males and not significant for females. Note the trends in opposite directions at the time of peak ranolazine concentrations. The sponsor found no statistically significant differences in the response to ranolazine between male and female patients for any of the peak/trough ETT variables.

Table 20. 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)	
	Female (N=59)	Male (N=211)	Female (N=47)	Male (N=208)
peak				
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				
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

Race: Because 98% of patients in CVT 3033 were Caucasian, a subgroup analysis by race was not done. There are insufficient numbers of non-Caucasians in this submission to allow reasonable interpretation of efficacy.

Age:

In study CVT 3033, no consistently significant treatment effects are seen at trough when analyzed by the age subgroup and no definitive patterns at peak or trough can be concluded.

Table 21. Change from baseline ETT duration (sec) at trough and peak by Age (ITT LOCF)

trough	Ran SR 750 (N=272)		Ran SR 1000 (N=261)	
	< 65 (N=140)	≥ 65 (N=132)	< 65 (N=134)	≥ 65 (N=127)
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.

Efficacy in “Intolerant” Populations:

The sponsor has presented efficacy data in groups of patients who may be intolerant to currently available anti-anginal medication. Included were those patients with low BP, low heart rate/prolonged PR interval and co-morbid conditions including reactive airway disease, CHF or diabetes.

Low heart rate, low BP and/or prolonged PR interval: The sponsor selected a threshold of standing SBP ≤ 100 mm Hg or standing HR ≤ 60 bpm as a lower limit to define a *post-hoc* subgroup of patients with low blood pressure and/or low heart rate. Prolonged PR interval was defined as PR ≥ 200 msec.

Analysis of this subgroup using data from CVT 3033 is presented in the following table:

Table 22. CVT 3033. Exercise Performance by Subgroup: Patients with baseline SBP ≤ 100 mm Hg, HR ≤ 60 bpm, or PR interval ≥ 200 msec (ITT)

	Placebo		Ran 750 mg bid		Ran 1000 mg bid	
	Yes	No	Yes	No	Yes	No
Change from baseline ETT duration at Trough (sec)						
N	79	179	88	184	82	179
LSM (SE)	90.8 (14.5)	92.2 (9.8)	125 (13.8)	110.8 (9.6)	125.6 (14.1)	111.2 (9.8)
Treatment difference vs. placebo (SE)	--	--	34.2 (19.5)	18.6 (13.2)	34.8 (19.9)	19 (13.3)
p-value	--	--	0.080	NS	0.080	NS
Change from baseline in Time to onset of Angina at Trough (sec)						
N	79	179	88	184	82	179
LSM (SE)	116.6 (16.1)	113.3 (10.8)	152.7 (15.4)	139.8 (10.7)	149.6 (15.7)	135.9 (10.9)
Treatment difference vs. placebo (SE)	--	--	36.1 (21.6)	26.5 (14.7)	33 (22)	22.6 (14.7)
p-value	--	--	0.095	0.072	NS	NS

Change from baseline in Time to 1 mm ST depression at Trough (sec)						
N	76	171	84	176	79	165
LSM (SE)	128.3 (16.2)	123.6 (10.9)	137.6 (15.6)	148.6 (10.8)	148.6 (15.8)	145 (11.2)
Treatment difference vs. placebo (SE)	--	--	9.4 (21.9)	24.9 (14.9)	20.3 (22.2)	21.4 (15.1)
p-value	--	--	NS	0.094	NS	NS
Change from baseline in ETT duration at Peak (sec)						
N	79	177	88	182	81	174
LSM (SE)	43.9 (14.1)	74.8 (9.6)	95.7 (13.5)	101.2 (9.4)	84.2 (13.8)	94.9 (9.7)
Treatment difference vs. placebo (SE)	--	--	51.8 (19)	26.3 (13)	40.3 (19.4)	20.1 (13.1)
p-value	--	--	0.007	0.043	0.038	NS
Change from baseline in time to onset of Angina at Peak (sec)						
N	79	177	88	182	81	174
LSM (SE)	73.1 (16.4)	95.9 (11.1)	119.7 (15.7)	130.4 (11)	116.7 (16.1)	131.7 (11.3)
Treatment difference vs. placebo (SE)	--	--	46.6 (22.1)	34.6 (15.1)	43.5 (22.5)	35.8 (15.2)
p-value	--	--	0.035	0.022	0.054	0.019
Change from baseline in time to 1 mm ST depression at Peak (sec)						
N	70	164	77	171	76	160
LSM (SE)	31.5 (15.8)	71 (10.5)	112.2 (15.2)	94.3 (10.3)	87.1 (15.1)	96.9 (10.7)
Treatment difference vs. placebo (SE)	--	--	80.7 (21.4)	23.4 (14.2)	55.6 (21.4)	25.9 (14.4)
p-value	--	--	0.0002	.10	0.01	0.073

Source: Table 36, ISE. Includes patients in the ITT population with baseline SBP \leq 100 mm Hg (N=26), HR \leq 60 bpm (N=163) or PR \geq 200 msec (N=102). According to the sponsor, the patients in this table were already on stratified background medication when these baseline measurements were done. Treatment by subgroup interactions, according to the sponsor, were not statistically significant for above peak or trough variables.

Reviewer:

1. Only 26 patients (total) in this subgroup analysis were noted to have a baseline SBP \leq 100 mm Hg. Most patients in this pooled subgroup analysis were noted to have baseline bradycardia or PR interval prolongation.
2. Since CVT 3033 stratified patients to background therapy of atenolol, diltiazem or amlodipine, it is not clear from this table what number (or percent) of patients with bradycardia were already on diltiazem or atenolol, medications associated with bradycardia.² Diltiazem is also associated with AV block. The three stratified medications are indicated for both angina and hypertension. Drug effects related to concomitant medications (and imbalances across groups due to concomitant medications) cannot be excluded.
3. Effects related to diltiazem or interactions with diltiazem (especially at peak) on the above exercise performance parameters cannot be excluded.
4. Significant treatment effects are not seen with respect to trough parameters. One might then conclude that ranolazine does not show a significant benefit at trough in this subgroup. However, study 3033 was also not “powered” to show a treatment difference in this subgroup. The lack of statistically significant subgroups at trough may be consistent with a modest overall treatment effect at trough, where subgroup analyses “wipe out” any significant p-values.

The sponsor presented subgroup analyses for patients with low SBP, slow HR and prolonged PR interval (as defined above) in CVT 3031, and in pooled studies RAN 72, 80 and 1514. From RAN 72, RAN 80 and

² Bradycardia has been reported in placebo-controlled angina and hypertension trials in patients receiving diltiazem up to 360 mg daily (Source: Cardizem CD labeling, Physician’s Desk Reference).

RAN 1514, pooling included patients with baseline SBP \leq 100 mm Hg (N=9), HR \leq 60 bpm (N=56) or patients with PR \geq 200 msec (N= 40).

Reviewer:

1. Because of the difficulty in interpreting the primary efficacy results of Study 3031, subgroup analyses related to Study 3031 will not be further interpreted.
2. A small number of patients relative to the submitted database (only 9 in the pooled IR studies) were noted to have baseline SBP \leq 100 mm Hg.
3. It is not clear whether RAN 72, 80 and 1514 are appropriate for pooling given the different concomitant medications, exercise testing methods, length of treatment and primary efficacy variables.
4. RAN 80 included patients on diltiazem and atenolol. Drug effects (bradycardia, first degree AV block) related to concomitant medications cannot be excluded.

Co-Existing Medical Conditions:

Reactive Airway Disease: Studies CVT 3033 included 58 patients (total) and CVT 3031 included 13 patients with reactive airway disease.

Analysis of results by the subgroup with and without reactive airway disease are presented below:

Table 23. CVT 3033: Selected Exercise Performance parameters by Presence of Reactive Airway Disease

	Placebo		Ran 750 mg bid		Ran 1000 mg bid	
	Yes	No	Yes	No	Yes	No
Change from baseline in ETT duration at Trough (sec)						
N	14	244	26	246	17	244
LSM (SE)	14.7 (33.7)	96.2 (8.4)	101 (24.9)	117 (8.3)	90.6 (30.7)	117.5 (8.4)
Treatment difference vs. placebo (SE)	--	--	86.3 (41.6)	20.8 (11.3)	75.9 (45.3)	21.3 (11.3)
p-value	--	--	0.038	0.066	0.094	0.060
Change from baseline in time to onset of Angina at Trough (sec)						
N	14	244	26	246	17	244
LSM (SE)	30.6 (37.3)	119.2 (9.4)	149.9 (27.5)	143.5 (9.2)	87.7 (34)	144 (9.3)
Treatment difference vs. placebo (SE)	--	--	119.3 (46)	24.3 (12.5)	57.1 (50.1)	24.8 (12.5)
p-value	--	--	0.0097	0.053	NS	0.048
Change from baseline in time to 1 mm ST depression at Trough (sec)						
N	14	233	25	235	16	228
LSM (SE)	83.5 (37.1)	127.6 (9.5)	152.1 (28)	144.3 (9.4)	135.2 (34.8)	146.9 (9.6)
Treatment difference vs. placebo (SE)	--	--	68.6 (46.1)	16.7 (12.7)	51.7 (50.6)	19.3 (12.8)
p-value	--	--	NS	NS	NS	NS
Change from baseline in ETT duration at Peak (sec)						
N	14	242	26	244	17	238
LSM (SE)	27.3 (32.9)	67.6 (8.3)	90.5 (24.3)	100.4 (8.2)	60.7 (30)	93.7 (8.4)
Treatment difference vs. placebo (SE)	--	--	63.2 (40.7)	32.8 (11.1)	33.4 (44.3)	26.1 (11.2)
p-value	--	--	NS	0.003	NS	0.02

Includes patients in the ITT populations with baseline reactive airway disease. According to the sponsor, the diagnosis of reactive airway disease was made by a review of the patient's medical history by CVT clinicians. Patients were included in this subgroup (under "yes") if a diagnosis of asthma, COPD or chronic bronchitis was recorded. This analysis was performed after the code was broken; according to the sponsor, the patient history was considered without attention paid to treatment group.

Exercise performance parameters (change in ETT duration, time to onset of angina, time to 1 mm ST depression) at Peak showed treatment differences vs. placebo that trended in a direction favorable for ranolazine (p=NS for subgroups with reactive airway disease); the subgroup without reactive airway disease included a greater sample size and showed statistically significant improvements vs. placebo. For purposes of brevity, only the change in ETT duration at peak is shown in the above table.

Reviewer:

1. The sample size of patients with baseline reactive airway disease is small and numerically imbalanced relative to the subgroup without reactive airway disease. Other imbalances across subgroups (for example, related to concomitant therapy or other conditions) cannot be excluded.
2. The standard errors are also larger in the subgroup with baseline reactive airway disease.
3. It does not seem reasonable that ranolazine is effective at trough (with significant treatment effects vs. placebo) and not effective at peak.

There are insufficient data to permit definitive conclusions regarding effectiveness in this subgroup.

Congestive Heart Failure:

In CVT 3033, 242 patients with NYHA Class I or II CHF and 581 non-CHF patients were randomized. At trough, there was minimal improvement vs. placebo in patients treated with ranolazine SR 750 mg bid for the 3 measured exercise parameters (ETT duration, time to onset of angina, time to 1 mm ST depression). For patients treated with ranolazine SR 1000 mg bid, there were improvements, compared to placebo, in the measured exercise parameters at trough (p=NS for all). Subgroup analyses at peak are presented below:

Table 24. CVT 3033: Exercise Performance parameters at Peak by CHF

	Placebo		Ran 750 mg bid		Ran 1000 mg bid	
	Yes	No	Yes	No	Yes	No
Change from baseline in ETT duration at Peak (sec)						
N	74	182	86	184	76	179
LSM (SE)	56.5 (15.8)	68.4 (9.6)	79.9 (14.9)	107.8 (9.4)	99.5 (15.9)	87.2 (9.6)
Treatment difference vs. placebo (SE)	--	--	23.4 (19.4)	39.4 (12.8)	43 (20)	18.9 (12.9)
p-value	--	--	NS	0.002	0.032	NS
Change from baseline in time to onset of Angina at Peak (sec)						
N	74	182	86	184	76	179
LSM (SE)	87.7 (18.3)	88.9 (11.1)	109.2 (17.3)	134.6 (10.9)	131.2 (18.5)	124.2 (11.1)
Treatment difference vs. placebo (SE)	--	--	21.5 (22.5)	45.7 (14.9)	43.5 (23.2)	35.3 (15)
p-value	--	--	NS	0.002	0.061	0.02
Change from baseline in time to 1 mm ST depression at Peak (sec)						
N	66	168	75	173	65	171
LSM (SE)	51 (17.7)	62.6 (10.6)	101.5 (16.9)	99.5 (10.3)	101.3 (18.1)	91 (10.4)
Treatment difference vs. placebo (SE)	--	--	50.5 (21.9)	36.8 (14.1)	50.3 (22.6)	28.4 (14.1)
p-value	--	--	0.021	0.009	0.027	0.045

According to the sponsor, treatment by subgroup interaction p = NS

Reviewer: At peak, treatment differences vs. placebo trend in favor of ranolazine with statistically significant results in the Ran SR 1000 mg bid group.

Because of the numerical imbalances between subgroups (CHF vs. non-CHF), lack of appropriate power and post-hoc nature of these subgroup analyses, this reviewer is wary of forming definitive conclusions based on these data. Also, imbalances between subgroup due to factors other than CHF cannot be excluded.

Diabetes:

In CVT 3033, 189 diabetic and 634 non-diabetic patients were randomized. At trough, the change from baseline in exercise performance parameters (ETT duration, time to onset of angina, time to 1 mm ST depression) in diabetic patients showed an improvement with ranolazine compared to placebo that was statistically significant only with respect to the time to onset of angina in the Ran SR 750 mg bid group ($p=0.044$). Treatment by diabetes interaction p -values, according to the sponsor, were not significant for any measured exercise performance parameter.

At peak, results of exercise performance in diabetics also showed improvement in ranolazine-treated groups vs. placebo with statistically significant results obtained for the time to onset of angina at peak (Ran SR 1000 mg bid group), and time to 1 mm ST depression (both ranolazine groups); there was a trend toward treatment by subgroup interaction ($p=0.09$) in the time to 1 mm ST depression at peak. (please see individual study review for further details).

Anti-Anginal efficacy of Ranolazine in Patients Taking Maximal Therapy:

The sponsor has noted patients taking ranolazine against a background of atenolol 50 mg qd (CVT 3033) and claims that the maximum effect of atenolol on exercise tolerance is achieved 3 hours after a steady-state dose of 50 mg qd.

Reviewer: It is not clear from labeling that the maximum effect of atenolol is achieved with 50 mg once daily³.

1. The two pivotal trials, CVT 3033 or CVT 3031, as well as RAN 72, RAN 80 or RAN 1514 did not specifically study patients on maximal anginal therapy, whether by maximal dosing or via maximal concomitant medications (including long-acting nitrate, calcium channel blocker, and beta-blocker).
2. According to the sponsor, a small number of patients in the database were on 3 concomitant anti-anginal medications. No specific analyses on these patients were performed.
3. It is not known, from the available data, whether ranolazine provides a benefit to patients on maximal anti-anginal therapy.

The sponsor has defined “adequacy of background anti-anginal dose” by using criteria of clinical response to the anti-anginal drug, projected plasma concentration of the background anti-anginal drug, and labeled dosage strength of the anti-anginal drug. According to the sponsor, efficacy of ranolazine in patients with low BP, low heart rate and/or prolonged PR interval is evidence of ranolazine effectiveness in patients receiving adequate doses of other anti-anginal medication.

Reviewer: Ranolazine treatment effects are statistically significant at peak but not at trough in a post-hoc pooled subgroup of patients with low BP, low heart rate and /or prolonged PR interval. These results, however, may merely reflect a more robust result at peak and a marginal result at trough.

The sponsor also used a pharmacokinetic/pharmacodynamic rationale to evaluate adequacy of dosing of background anti-anginal medication. With diltiazem pharmacokinetic modeling, the sponsor has predicted plasma diltiazem levels of about 105-115 ng/ml at about 2.5-3 hours after steady-state dosing with diltiazem IR 60 mg tid. The plasma diltiazem level at trough (24 hours after dosing) with steady-state diltiazem CD 360 mg qd was predicted at 128 ng/ml. Since plasma diltiazem concentrations are generally dose-proportional, therefore, trough plasma diltiazem levels at steady state dosing with diltiazem CD 300 mg qd were predicted to be about 5/6 of that predicted with 360 mg qd, or about 107 ng/ml, or similar to the levels expected with diltiazem IR 60 mg tid at 2.5-3 hours post-dose (the time of exercise testing in RAN 072).

³ From current TENORMIN labeling: Under Dosing and Administration in Angina, “The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within one week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect. Twenty-four hour control with once daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once a day oral doses of 200 mg.” (Source: electronic Physician’s Desk Reference).

The sponsor has also stated that “any dose of an anti-anginal drug greater than the labeled starting daily dose for chronic angina is considered to be an adequate dose of that background anti-anginal therapy in this ISE.”

Reviewer: This definition of “adequate dosing” is generated by the sponsor. This reviewer does not necessarily agree with the sponsor’s definition. In addition, the design of the major studies in this submission did not allow for up-titration to maximally tolerated doses; thus, it cannot be known whether patients were given therapeutic doses of background anti-anginal medication.

Since CVT 3033 utilized stratified background medication, the table of the primary endpoint by background stratified medication (from the Individual study review) is presented in the section on Stratified medication (table 19). Results show trends in a direction favorable to ranolazine (less so for patients on high doses with concomitant atenolol) with wide confidence intervals. Statistically significant treatment effects are only seen at the time of peak ranolazine in patients receiving concomitant diltiazem therapy.

Individual Study Reviews:

Phase 3 Studies:

CVT 3033:

Title: 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
(Protocol date: March 26, 1999)

Primary Objective: Effect of ranolazine SR 750 mg bid and 1000 mg bid, compared to placebo, on symptom-limited treadmill exercise duration at trough ranolazine concentrations (12 hours postdose) after 12 weeks of treatment in patients with chronic stable angina receiving a stable dose of a single concomitant antianginal medication.

Secondary Objectives:

1. Effect of ranolazine, during exercise treadmill testing (ETT) (at trough: 12 hours post dose), on time to onset of angina, time to 1 mm ST depression, maximum ST depression, and reason for stopping exercise;
2. Effect of ranolazine, during ETT (at peak: 4 hours post-dose) on exercise duration, time to onset of angina, time to 1 mm ST depression, maximum ST depression, reason for stopping exercise;
3. Effect of ranolazine on angina frequency, severity and duration, as well as nitroglycerin consumption;
4. Determine if there are any rebound increases in angina, as measured by exercise duration, following discontinuation of ranolazine SR compared to patients maintained on ranolazine SR.

Study Summary:

This was a multicenter, double-blind, randomized, stratified, placebo-controlled, parallel study. The study was comprised of three phases: a single-blind placebo qualifying phase lasting approximately 1-2 weeks, a double-blind treatment phase lasting 12 weeks, and a rebound assessment phase lasting 2 days. A safety follow-up visit was scheduled 2 weeks after study completion. The allowed concomitant anti-anginal medications were: diltiazem 180 mg PO QD in a once-daily formulation, atenolol 50 mg PO QD, or amlodipine 5 mg PO QD. Sublingual nitroglycerin was permitted only as treatment for anginal attacks.

Patients were treated with one of the 3 allowed anti-anginal medications at the specified dose for a minimum of 5 days prior to Visit 1. Those meeting study inclusion/exclusion criteria entered the single-

blind placebo qualifying phase. Single-blind qualifying visits consisted of physical examinations, laboratory tests, and ECGs, with one trough exercise treadmill test (ETT) at Visit 1, and two (trough and peak) ETT at Visit 2.

Qualifying patients at Visit 2 were stratified according to background antianginal therapy and randomized to either ranolazine SR 750 mg BID, ranolazine SR 1000 mg BID or placebo (BID) for the 12 week double-blind treatment phase. At each of 3 double-blind visits (Visits 3, 4, and 5, corresponding to Weeks 2, 6 and 12 of double-blind), patients underwent trough ETT (12 hours after the previous dose taken the evening before). At Visits 3 and 5 (Weeks 2 and 12), patients remained in the clinic and underwent peak ETT 4 hours after the in-clinic dose. Plasma levels for trough and peak ranolazine levels were drawn with the corresponding ETT. At the end of the 12 week double-blind treatment phase, patients entered a 2-day Rebound Assessment Phase where they received, in a double-blind manner, either the same treatment as during the 12 week double-blind phase or placebo. After 2 days, patients returned to the clinic (Visit 6) for a final trough ETT. Two weeks after completing the study, patients returned for a safety follow-up Visit (Visit 7) comprising a history (concomitant medication, adverse events) and physical examination.

Table 1. CVT 3033: Schedule of events

Visit	1	2	3	4	5	6	7
Procedure	Screening	Screen/Qualifying	Double-blind		Double-blind/early withdrawal	Rebound Assessment	Safety follow-up
Time		1-2 weeks	2 weeks	6 weeks	12 weeks	2 days	2 weeks later
History	X						
Physical exam	X				X		X
Body weight	X				X		
Inclusion/exclusion criteria	X	X					
Vital signs	X	X	X	X	X	X	
Angina/ntg use diary review		X	X	X	X	X	
Lab tests*	X				X		
Trough levels			X	X	X	X	
Peak levels			X				
Trough ECG and ETT	X	X	X	X	X	X	
Peak ECG and ETT		X	X		X		
Adverse events		X	X	X	X	X	X
Concomitant meds	X	X	X	X	X	X	X

* TSH and T4 were only done at screening. Serum HCG in females was planned at Visits 1,3, 4, and 5.

Table 2. CVT 3033: inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria (similar to CVT 3031)
<ol style="list-style-type: none"> ≥ 21 years old; at least 3 month history of stable effort angina relieved by rest/sublingual nitroglycerin; diagnosis of coronary disease via at least one: ≥ 60 % stenosis of ≥ 1 major coronary artery on angiogram, past MI documented by enzymes/ECG changes, exercise/pharmacologic stress/echo study; minimum of 5 days treatment prior to Visit 1 with either diltiazem 180 mg QD, atenolol 50 mg QD or amlodipine 5 mg QD; willing to discontinue other antianginals 5 days prior 	<ol style="list-style-type: none"> ECG/other factors interfering with ECG interpretation or associated with false + ETT; NYHA Class III-IV CHF; Significant valvular/congenital heart disease; MI/unstable angina/CABG or PCI within past 2 months; 2nd/3rd degree AVB, uncontrolled arrhythmias or life-threatening ventricular arrhythmias unassociated with MI; QTc > 500 msec at Visit 1; Requiring medications known to prolong QTc or

<p>to Visit 1 and throughout study;</p> <p>6. stable tobacco habits throughout study;</p> <p>7. if female of childbearing potential, then not pregnant/breastfeeding, using contraceptives and not intending to become pregnant;</p> <p>8. sign approved consent form;</p>	<p>inducing/inhibiting cytochrome P450 3A4;</p> <p>8. Unwilling to refrain from grapefruit (juice) consumption;</p> <p>9. Requiring digoxin;</p> <p>10. Active acute myocarditis/pericarditis;</p> <p>11. Hypertrophic cardiomyopathy;</p> <p>12. Uncontrolled hypertension or SBP < 100 mm Hg;</p> <p>13. Chronic illness likely to alter f/u evaluation;</p> <p>14. Significant laboratory abnormality;</p> <p>15. Participation in another study w/investigational agent within 1 month of this study;</p>
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Qualifying for Double-Blind Phase:

1. Symptom-limited exercise duration during trough ETT at Visits 1 and 2 was 3-9 minutes (incl.) of exercise on a modified Bruce protocol.
2. Exercise duration for the two trough ETT at Visits 1 and 2 did not differ by more than 20% of the longer of the two times and did not differ by more than 60 seconds.
3. The primary reason for stopping the two trough ETT at Visits 1 and 2 must be moderately severe angina.
4. Definite ECG signs of ischemia during the ETT at both Visits 1 and 2 (ie, one additional mm of horizontal or downsloping ST depression beyond baseline and at least 1mm below the isoelectric line) were present in at least one standard ECG leading during ETT with a modified Bruce protocol.
5. At Visit 1, the 1 mm ST depression must be verified by the ECG Core laboratory prior to the patient being allowed to continue on to Visit 2.
6. For the Visit 2 ETT, the Investigator should determine if the patient has met study entry criteria and enter this information on the CRF. Patients will enter the double-blind portion based on this determination. The ETT will be sent to the ECG Core laboratory.⁴

Concomitant medications:

Besides the stratified background antianginal medication and sublingual nitroglycerin (as needed), aspirin and stable doses of antihypertensive medications (diuretic or ACE inhibitor) were allowed. Ophthalmic beta blockers were allowed if their use was constant throughout study. Diltiazem, atenolol or amlodipine were allowed only if used as the single concomitant antianginal medication.

Efficacy Evaluations:

1. Exercise treadmill tests: (ETT). A modified Bruce protocol was used. Testing was planned under uniform conditions, optimally by the same technician and supervising physician each time⁵. Trough ETTs were done between 7 am and 12 noon, prior to scheduled morning dose of study medication. If patients did not take their medication 12 hours (\pm ½ hour) prior to the trough ETT, then the ETT was rescheduled within 3 days. ETT at the time of peak plasma concentrations were planned at 4 hours (\pm ½ hour) after the in-clinic dose of study medication. The following efficacy variables were recorded: time to onset of angina, symptom-limited exercise duration, primary reason for stopping exercise. In addition, BP/HR were recorded at rest (supine/standing), during the last minute of each stage, at end of exercise, and during recovery (every minute for the first 5 minutes and then q5 minutes until values return to baseline). Standard supine and standing 12-lead ECG recordings were taken at rest.
 1. Efficacy variables recorded by the Investigator during each ETT: time to onset of angina, symptom-limited exercise duration, primary reason for stopping exercise.
 2. ECG variables measured by the Core Laboratory included: time to 1 mm ST depression, maximum ST depression during exercise. The ST depression recorded was to be the average of at least 3 consecutive ST segments.
 3. According to the protocol the ECG lead that best reflected exercise-induced ischemia during Visit 1 was identified and used throughout the study to monitor the patient.

⁴ According to the sponsor, the ECG Core Lab was blinded to treatment.

⁵ According to the protocol, patients were not to be pushed, coached or encouraged to tolerate symptoms during ETT which are more severe than symptoms which would typically cause them to stop exercise.

4. At Visits 1 and 2, patients stopping exercise for any reason other than moderately severe angina failed to qualify for study entry and were considered screening failures. During double-blind and rebound assessment visits, reasons for stopping ETT could include: unacceptable angina, shortness of breath or fatigue, excessive BP rise, fall in BP during exercise, feeling of faintness, musculoskeletal pain/discomfort, completion of the modified Bruce protocol.
2. Angina and Nitroglycerin use diary: Patients were to maintain a diary of angina attacks and nitroglycerin use for review at each visit.

Pharmacokinetic Evaluations: Plasma concentrations were collected immediately before 12-lead ECG and ETT during Visits 3-6. Trough sampling was planned 12 hours (\pm ½ hour) after the last dose of study medication. The peak sample was drawn 4 hours (\pm ½ hour) after the in-clinic dose.

Safety Evaluation: physical examination, vital sign measurements, ECG data, laboratory tests, adverse events and concomitant medications. Official ECG reading was performed by the ECG Core Laboratory.

Analysis populations:

1. The Intent-to-Treat (ITT) population, all randomized patients who have taken at least one dose of study medication and have at least one ETT performed during double-blind, was the population for the primary efficacy analysis.
2. The efficacy-evaluable (EFF) population, all randomized patients with 67-125% compliance during double-blind and rebound assessment phases, with Visit 5 ETT within the stated window and have not violated key protocol criteria, inclusion/exclusion criteria, or have not taken prohibited medications (defined prior to database lock).
3. The general safety population (GSP), all randomized patients who have taken at least one dose of double-blind study medication.
4. The ECG safety population (ECG-SP), all randomized patients who have taken at least one dose of double-blind study medication and have at least one ECG performed during double-blind or rebound assessment phases.

Timepoints:

Baseline was defined as the average from the two ETT during single-blind placebo or, if only one ETT was done, then the single measurement from this phase.

Endpoint was defined as the last post-randomization visit carried forward (LOCF).

Primary Efficacy Variable: Change from baseline in ETT duration at 12 hours post-dose (trough ranolazine concentration) using LOCF.

Secondary Efficacy Variables:

1. Time to onset of angina and change from baseline during trough ETT;
2. Time to 1 mm ST-depression and change from baseline during trough ETT;
3. Change from baseline in maximum ST depression during trough ETT;
4. Primary reason for stopping trough ETT;
5. Change from baseline in exercise duration during peak ETT (4 hours post-dose);
6. Time to onset of angina and change from baseline during peak ETT;
7. Time to 1 mm ST depression and change from baseline during peak ETT;
8. Change from baseline in maximum ST depression during peak ETT;
9. Primary reason for stopping ETT at peak;
10. Exercise duration during ETT comparing patients who were discontinued 48 hours previously from ranolazine after 12 weeks of treatment to placebo-treated patients;
11. Self-reported frequency, severity and duration of anginal episodes during 12 weeks of double-blind treatment;
12. Self-reported nitroglycerin consumption during 12 weeks of double-blind treatment.

Statistics:

Unless otherwise indicated, all statistical tests were to be two-sided. An alpha of 0.05 determined statistical significance.

The primary efficacy parameter, change from baseline in ETT duration at trough ranolazine levels, was prespecified for the ITT population at endpoint using analysis of variance (ANOVA). Terms for treatment, pooled site, and baseline ETT duration would be included. Treatment by site interaction would be tested and included if significant. Type III sums of squares would be used to produce the test statistics.

The assumption of normality would be investigated; if this assumption did not hold, then the primary efficacy parameter was to be analyzed non-parametrically, with baseline ETT duration and primary efficacy parameter ranked across all sites and background therapies. Residuals were to be computed from fitting an ANOVA model with ranked primary efficacy parameter as the response variable, and with effects for pooled site, background therapy and ranked baseline ETT duration.

In addition, the primary efficacy parameter would be analyzed for the ITT and EFF populations to explore possible interaction of treatment with pooled site, background therapy, or baseline ETT separately. If a statistically significant (level of 0.05) interaction was found, the treatment effect would be described for the different levels of the factor. The primary efficacy parameter (ITT) would also be analyzed using Generalized Estimating Equations (GEE) incorporating change from baseline in ETT duration at 2nd, 6th, and 12th week visits.

For the primary efficacy parameter, the multiple comparisons issue was to be addressed by a two-stage step-down procedure.

Interim Assessment: An interim assessment was planned when one-half of the planned completed study patients (N=231) were followed for 12 weeks. Randomized patients who took at least one dose double-blind medication and performed at least one ETT during double-blind were included in this assessment. The purpose of this interim look at the data was to recalculate the standard deviation of change from baseline in ETT duration at trough. Based on these results, the sponsor planned to increase the sample size by no more than 186 additional evaluable patients. (please see Protocol Amendment 2, below).

Reviewer's note: According to the sponsor, the interim assessment was performed, without unblinding, by the Contract Research Organization carrying out the study and the sponsor had no direct involvement.⁶

Sample Size Calculation: The sample size was based on the change from baseline in ETT duration at trough plasma ranolazine levels. Assuming a normal distribution and standard deviation of 80 seconds, a sample size of 462 evaluable patients was projected, with 90% power, to detect a minimum difference of 30 seconds between ranolazine (750 mg, 1000 mg) and placebo. Adjusting for a 20% potential dropout rate increased the sample size to 577 randomized patients to provide 462 completed, evaluable patients. The sample size could be reevaluated based on the interim assessment of the standard deviation.

Amendments to the Protocol:

1. (August 13, 1999): Ensured that no more than 50% of randomized patients will be on one of the three antianginal medication strata; changed qualifying ECG lead (Visit 2) to any lead with 1 mm ST depressions; for ECG analysis, the ECG Core laboratory will identify one lead, best reflecting ischemia, to be used throughout the study for maximum ST depression and time to 1 mm ST depression.
- 1A. (January 27, 2002): Added 2D-echocardiographic parameters from Italian centers.
2. (January 3, 2001): Clarified steps/logistics of adjusting sample size, specified a maximum enrollment, incorporated a non-parametric analysis as potential primary efficacy analysis if the assumption of normality was not satisfied; included background therapy as covariate in the analyses of primary and secondary efficacy variables.

⁶ According to the Study Report (Section 9.7.3, paragraph 2), the procedure followed an Interim Procedure Document, dated January 2, 2001, and listed in Appendix 16.1.13; a copy of this document has been requested by the reviewer.

Amendments to the Statistical Analysis Plan (SAP): The Statistical Analysis Plan was issued on May 24, 2001. Four amendments (7/31/01, 9/26/02, 10/12/01 and, following unblinding, 2/27/02) were submitted. These amendments do not impact the primary analysis.

Results:

Patient disposition:

This study was performed at 118 sites in 15 countries.

A total of 823 patients were randomized (269 to placebo, 279 to ranolazine 750 mg QD, and 275 to ranolazine 1000 mg QD). The highest percentage of randomized patients came from the Czech Republic (24.4 %), followed by Russia (23.8 %), with 6.9% of patients from the U.S. (Source: sponsor, Table 1.1.1).

Of those randomized, 90% of those treated with placebo and ranolazine 750 mg QD, and 87% of those treated with ranolazine 1000 mg QD, completed the trial (including double-blind and rebound phases). Background therapy (diltiazem, atenolol, or amlodipine) was well balanced between the three treatment arms; about 117-119 were on atenolol, 81-89 on amlodipine, and 69-74 on diltiazem per treatment arm.⁷ Percentages of dropouts are shown below. In the safety population, increased percentages of dropouts due to unacceptable AE are seen in ranolazine patients given diltiazem as background therapy; this difference was not seen in the ITT analysis.

A majority of the withdrawals occurred by Week 6 (the second visit after randomization), regardless of background therapy.

Table 3. CVT 3033. Patient populations

	Placebo	Ran 750	Ran 1000	Total
All randomized patients	269	279	275	823
Safety population	269	279	275	823
ECG Safety population	262	273	269	804
ITT	258	272	261	791
Efficacy-evaluable	176	184	177	537
Efficacy rebound	174	181	171	526

Reviewer: Patients were most commonly excluded from the ITT population for not performing an ETT after the start of study medication, with the largest number of exclusions in the ranolazine 1000 group (14 patients) and the smallest in the ranolazine 750 group (7 patients). Also note that the efficacy-evaluable population is about 65% of the safety population. The most common reason for exclusion was ST depression < 0.9 mm at either visit 1 or 2 (135 patients). The second most common reason was < 67% or > 125% compliance during entire study period. Thirty-five patients were excluded from the efficacy-evaluable analysis due to early withdrawal and lack of Visit 5 trough ETT data. Please note that patients may have been excluded because of more than one factor.

Echocardiogram Sub-Study Note: According to the sponsor, only one patient (on placebo) was enrolled and withdrew prior to study completion. Therefore, no echocardiographic analyses were performed.

Table 4. CVT 3033. Patient Disposition (All Randomized patients).

N (%)	Placebo	Ran 750	Ran 1000
#Randomized	269	279	275
#Completed*	243 (90)	250 (90)	238 (87)
Early w/d	26 (10)	29 (10)	37 (14)
Unacceptable AE	13 (5)	20 (7)	24 (9)
Noncompliance	2 (0.7)	2 (0.7)	0

⁷ According to the sponsor, nearly all patients in CVT 3033 took the protocol-specified dose of background therapy for the duration of the study (5 days prior to Visit 1 through Visit 6). In the ITT population, there were 10 protocol violations related to background therapy. Of these, six took an incorrect dose of background medication (4 related to atenolol doses; in addition, one patient took amlodipine 10 mg qd and 1 patient took diltiazem 120 mg qd for the duration of the study).

Elective withdrawals	4 (2)	1 (0.4)	5 (2)
Lost to follow-up	0	0	1 (0.4)
Death	2 (0.7)	2 (0.7)	1 (0.4)
Other	5 (2)	4 (1)	6 (2)

Source: sponsor: Table 1.4.1. Percentages ≥ 1 are rounded off to the nearest integer.

* Completed = patient completed both double-blind and rebound phases.

Baseline characteristics: The study population (ITT) was about 97-98% Caucasian and majority (75-81%) male; mean age about 64 yrs (about half were 65 and older); weight, height were balanced between groups. The safety and efficacy-evaluable population yielded similar results.

Cardiac history (ITT): In terms of cardiac history, fewer patients in placebo (34 patients, or 13%) had a prior CABG performed > 2 months (before randomization) compared to ranolazine 750 mg (53 patients, 20%) and 1000 mg (52 patients, 20%) (p=0.06 for ITT population).

Otherwise, no obvious imbalances were seen between groups. In the ITT group, about 21-23% of patients experienced unstable angina > 2 months before randomization, and a majority (55-60%) had a prior MI. About 17-20% underwent a prior PTCA, 7-9% also had intermittent claudication, 4-6% had a history of prior stroke, and about 29-32% were classified as either Class I or II CHF (percentages of each were balanced between groups). About 7-8% had a history of atrial arrhythmias, 7-10% had a history of ventricular arrhythmias, and 0.4-2% had a prior cardiac arrest. About 4-8% had a history of clinically significant valvular disease. About 64% had a history of hypertension, 21-25% of patients were diabetic (most did not take insulin) and 5-10% had asthma/COPD. Results for the safety population were similar.

Baseline background medications (Visit 2 and continuing): Most common medications included: antiplatelet agents (excl. heparin), 78-95%; ACE inhibitors (37-44%), HMG CoA reductase inhibitors (40-54%), nitrates (81-90%). No gross imbalances were seen between treatment arms.

Background therapy prior to Visit 2 also appeared balanced between treatment arms. Most commonly prescribed anti-anginal agents included nitrates (about 50%) and beta blockers (about 40%).

Baseline vital signs/ETT: In general, peak values were lower than trough values. Heart rates and rate pressure products were consistently lower in the atenolol subgroup; end of exercise heart rates and rate pressure products were consistently higher in the amlodipine subgroup. Mean BP and HR appeared slightly, but consistently higher in the ranolazine SR 1000 mg bid group, with correspondingly higher RPP in that group. No gross imbalances were seen across treatment groups.

The baseline (average of visits 1 and 2) ETT duration at trough was 415-418 sec.

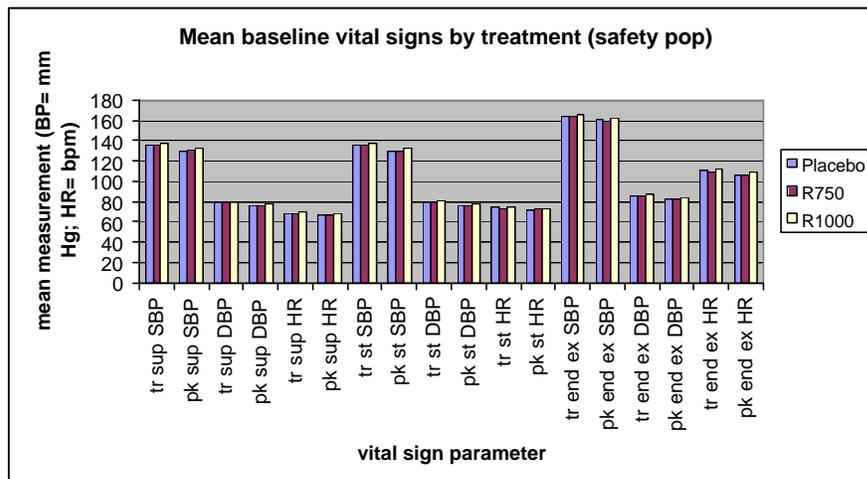


Figure 1. CVT 3033: Baseline vital signs by treatment (safety population)

Pk=peak; tr=trough, sup=supine; st=standing; end ex=end exercise

Number/discontinuations due to angina: A total of 4 patients (1 each from placebo and Ran 1000, and 2 from Ran 750) discontinued due to myocardial ischemia. There were no imbalances noted across groups.

Efficacy Results:

The primary efficacy analysis shows a significant improvement from baseline in the ranolazine groups vs. placebo. Results for the two ranolazine groups appear almost indistinguishable (see Table 4, Figure 3) and there does not appear to be further improvement with the higher dose.

Table 5. CVT 3033: Primary Efficacy analysis: Change from baseline in ETT (sec) *trough* Week 12 (ITT LOCF)—comparison of treatment differences from ANCOVA Model 1*

	Ran SR 750 mg vs. placebo	Ran SR 1000 mg vs. placebo
LS Mean difference (SE)	23.7 (10.9)	24 (11)
95% CI	(2.3, 45.1)	(2.4, 45.7)
p-value	0.03	0.029

Source: Table 2.0.0.*Model 1: effects for treatment, baseline covariate, pooled site and background therapy using type III sum of squares. Baseline covariate is the average of visits 1 and 2 data.

The change from baseline in ETT duration at Trough (ITT LOCF) was statistically significant (ANCOVA) for both ranolazine groups vs. placebo at Weeks 2, 6, and 12.

Table 6. CVT 3033: Change from baseline in ETT duration (sec) at Trough at Weeks 2, 6 and 12 (ITT)

	Ran SR 750 mg vs. placebo	Ran SR 1000 mg vs. placebo
Week 2 LSM difference (SE)	34.1 (8.8)	38.5 (8.9)
95% CI	16.8, 51.4	21, 55.9
p-value	<0.001	<0.001
Week 6 LSM difference (SE)	28.2 (10.6)	31.3 (10.8)
95% CI	7.4, 49	10.1, 52.5
p-value	0.008	0.004
Week 12 LSM difference (SE)	27.1 (11.3)	26.8 (11.5)
95% CI	4.9, 49.4	4.2, 49.3
p-value	0.017	0.020

Source: CVT 3033, Table 2.0.11. LSM difference, SE, p-values calculated from ANCOVA Model 1, including effects for treatment, baseline covariate, pooled site and background therapy using type III sum of squares. Baseline covariate was the average of Visits 1 and 2 data.

Results for the efficacy-evaluable population showed a smaller change from baseline for the 750 mg BID group, but trended in the same direction.

Table 7. CVT 3033: Change from baseline in ETT (sec) *trough* Week 12 (Efficacy evaluable population)—comparison of treatment differences from ANCOVA Model 1*

	Ran SR 750 mg vs. placebo	Ran SR 1000 mg vs. placebo
LS Mean difference (SE)	18.9 (13.3)	32.5 (13.4)
95% CI	(-7.3, 45.0)	(6.1, 58.9)
p-value	NS	0.016

Source: Table 2.0.1. See Table 4 for Model 1 adjustments. P-values obtained from ANCOVA model adjusted for stated effects.

Increases with dose are seen for the change from baseline ETT in the efficacy evaluable population. However, the treatment effect is smaller and not statistically significant in the 750 mg bid treatment arm.

Subgroup analyses:

Effect of background therapy:

Analysis by background therapy is shown in the next table:

Table 8. CVT 3033: Change from baseline ETT (sec) trough Week 12 (ITT LOCF) ANCOVA Model 2*

	Ran 750 mg vs. placebo			Ran 1000 mg vs. placebo		
	Diltiazem	Atenolol	Amlodipine	Diltiazem	Atenolol	Amlodipine
LS Mean difference (SEM)	20.6 (21.5)	23.2 (16.5)	27.4 (19.7)	42.9 (22.1)	7.5 (16.7)	32.3 (19.7)
95% CI	-21.7, 62.9	-9.2, 55.6	-11.2, 66.1	-0.6, 86.4	-25.2, 40.2	-6.4, 70.9
p-value	NS	NS	NS	0.053	NS	NS

Source: Table 2.0.3. *Model 2 includes effects for treatment, baseline covariate, pooled site, background therapy, and treatment by background therapy interaction using type III sum of squares. P-values obtained from ANCOVA model adjusted for stated effects.

The change from baseline (vs. placebo) is most pronounced in the high-dose group with diltiazem as background therapy, compared to background therapy with atenolol and amlodipine. The change from baseline in this diltiazem subgroup was not statistically significant in the efficacy-evaluable population.

Effect of Site/Pooled site:

The following table shows heterogeneity of the treatment effect over the pooled sites:

Table 9. Change from baseline ETT (sec) trough Week 12 (ITT LOCF) ANCOVA Model 3*

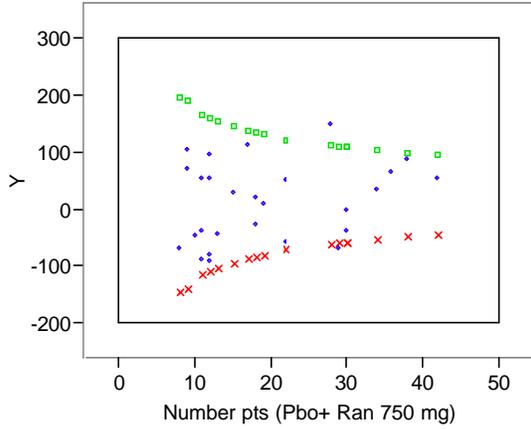
Ran SR 750 mg vs. placebo								
Pooled site	1	2	3	4	5	6	7	8
LS Mean difference (SEM)	69.1 (43.6)	12.2 (26.1)	12.4 (27)	67.2 (32.9)	-18.5 (21.3)	16.9 (33.9)	90.9 (40.6)	81.8 (46.5)
95% CI	-16.5, 154.7	-39.1, 63.4	-40.6, 65.4	2.5, 131.8	-60.4, 23.3	-49.7, 83.4	11.1, 170.6	-9.4, 173.1
p-value	NS	NS	NS	0.042	NS	NS	0.026	0.079
Ran SR 1000 mg vs. placebo								
Pooled site	1	2	3	4	5	6	7	8
LS Mean difference (SEM)	52.6 (44.2)	28.4 (25.9)	21.7 (28.1)	86.8 (33.4)	0.5 (21.1)	-20.3 (35.7)	26.7 (40.1)	50 (47.3)
95% CI	-34.1, 139.3	-22.5, 79.3	-33.5, 76.9	21.1, 152.5	-40.9, 41.9	-90.4, 49.9	-52, 105.4	-42.9, 142.9
p-value	NS	NS	NS	0.01	NS	NS	NS	NS

Source: Table 2.0.5. *Model 3 includes effects for treatment (p=0.003), baseline covariate (NS), pooled site (p=0.007), background therapy (NS) and treatment by pooled site interaction (NS) using type III sum of squares. P-values obtained from ANCOVA model adjusted for stated effects. Pooled site 4 =Russia; site 7 = Spain, New Zealand, UK, Australia, Greece, Ireland, Italy.

Funnel plot Analyses: To further explore the heterogeneity of the treatment effect by individual centers, the following funnel plot analyses were performed:

Funnel Plot 1.

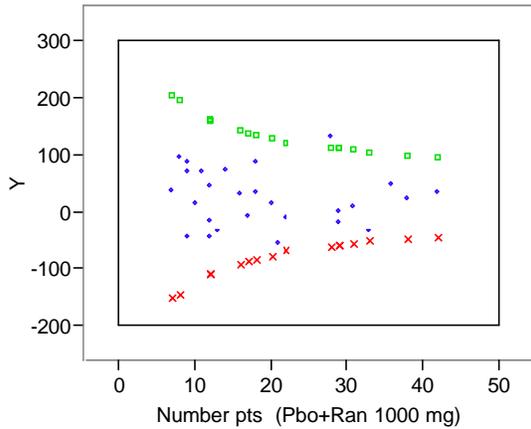
Ranolazine Study CVT 3033, ITT Population,
Change from Baseline to Week 12 in ETT Duration at Trough
Ran SR 750 mg minus Placebo (Centers with less than 10 patients are pooled into 8 pooled sites in which they fell in the original sponsor's analysis). The outlier above the 95% CI is Siberian center #710.



Y x Lower 95% CI, 750mg
■ Upper 95% CI, 750mg
◆ Ran 750 mg minus Placebo

Funnel Plot 2.

Ranolazine Study CVT 3033, ITT Population,
Change from Baseline to Week 12 in ETT Duration at Trough
Ran SR 1000 mg minus Placebo (Centers with less than 10 patients are pooled into 8 pooled sites in which they fell in the original sponsor's analysis). The outlier above the 95% CI is Siberian center #710.



Y x 1000 mg, Lower 95% CI
■ 1000mg, Upper 95% CI
◆ Ran 1000 mg minus Placebo

Of the 118 individual centers, 19 centers had 10 or more patients⁸. In this analysis, Siberian site #710 in Barnaul with 42 (5%) patients seemed to be a possible outlier with highly statistically significant (placebo adjusted) treatment effects: 152 seconds (p<0.001) for Ran 750 mg and 136 seconds (p=0.003) for Ran 1000 mg. All other 18 centers had non-significant treatment effects.

In a subsequent sensitivity analysis excluding Site #710, the following results were obtained:

Table 10. CVT 3033: Change from Baseline in ETT duration (sec) at Trough and Peak at Week 12 (ITT LOCF) Excluding Site 710

Statistic	Ran SR 750 mg vs. Placebo	Ran SR 1000 mg vs. Placebo
<i>Trough</i>		
LS Mean Difference (SEM)	16.5 (11.1)	17.6 (11.2)
95% Confidence Interval	(-5.3, 38.3)	(-4.4, 39.7)
p-value	NS	NS
<i>Peak</i>		
LS Mean Difference (SEM)	29.4 (10.9)	24.1 (11.1)
95% Confidence Interval	(8, 50.8)	(2.3, 45.9)
p-value	0.007	0.03

Treatment Differences were compared using ANCOVA Model 1, including effects for treatment, baseline covariate, pooled site and background therapy using Type III sum of squares. Baseline covariate for trough measurement was the average of visits 1 and 2 data; baseline covariate for peak measurement was visit 2 data.

Reviewer: The trough effect size, excluding site 710, is smaller and comparison vs. placebo is not statistically significant. While the peak effects in this analysis remain statistically significant, note that site 710 was excluded based on effects at trough, not peak. One implication of the data is that trough effects are not robust; hence, excluding an “outlier” site will take away statistical significance.

To support the robustness of the primary efficacy analysis, the sponsor performed an alternative analysis of exercise time with individual center and treatment-by-center interaction as random effects (Table 4, August 6, 2003 submission) that shows results similar to the primary efficacy results in Study CVT 3033. If the exercise time in this center is randomly high, then the sponsor’s analysis can support the robustness. However, if there is a systematic bias in Center #710, no statistical analysis can uncover it. The question remains whether there is a systematic or unquantifiable bias with this center.

Subgroups by gender, age, and presence of diabetes or heart failure:

Table 11: Change from baseline ETT (sec) *trough* Week 12 (ITT LOCF) ANCOVA Model 6*

	Ran SR 750 (N=272)		Ran SR 1000 (N=261)	
	Yes (N=87)	No (N=185)	Yes (N=76)	No (N=185)
CHF				
LS Mean Difference (SE) vs. placebo	2.1 (19.7)	34.7 (13)	26.9 (20.4)	22.2 (13)
95% CI	(-36.6, 40.8)	(9.2, 60.2)	(-13, 66.9)	(-3.3, 47.8)
p-value	NS	0.008	NS	0.087
Gender	<i>Female (N=59)</i>	<i>Male (N=213)</i>	<i>Female (N=51)</i>	<i>Male (N=210)</i>
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
Diabetes	<i>Yes (N=68)</i>	<i>No (N=204)</i>	<i>Yes (N=60)</i>	<i>No (N=201)</i>
LS Mean Difference (SE) vs. placebo	28.6 (22.8)	22.4 (12.5)	34.1 (23.5)	21.2 (12.5)
95% CI	(-16.1, 73.4)	(-2, 46.9)	(-12, 80.2)	(-3.4, 45.8)
p-value	NS	0.07	NS	0.09

⁸ In this analysis, centers with less than 10 patients were combined into 8 pooled sites. The pooling was performed in such a way that centers with less than 10 patients fell in the pooled sites used in the original analysis. Source: Sponsor's Table ETT-7 in the June 6, 2003, submission.

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

Source: Tables 2.0.13 -16. ANCOVA Model 6 includes effects for treatment, baseline covariate, pooled site, background therapy, subgroup, and treatment by subgroup interaction using type III sum of squares. P-values obtained from ANCOVA model adjusted for stated effects. Treatment by CHF, treatment by gender, treatment by diabetes and treatment by age interactions were not statistically significant.

Reviewer: The results of subgroup analyses by gender, race, age, show trends in the same direction (less so for females) with non-significant results for females, elderly and patients with CHF that are consistent across doses. It is entirely possible that ranolazine is less effective in females, the elderly, and patients with CHF. Given the wide confidence intervals and degree of confidence interval overlap between the various subgroups, the medical reviewer is wary of drawing definitive subgroup conclusions from the above analyses. It may be that the primary endpoint effect is modest, with statistically significant results rendered “nonsignificant” when the data are “sliced” in various ways. The change from baseline in ETT duration was smaller for females compared to males in all groups, including placebo.

Secondary endpoints:

ETT Duration at peak plasma concentration:

Table 12. CVT 3033: Change from baseline in ETT duration (sec) *peak* Week 12 ITT LOCF (ANCOVA Model 1)

	Ran SR 750 mg vs. placebo	Ran SR 1000 mg vs. placebo
LS Mean difference (SE)	34 (10.7)	26.1 (10.8)
95% CI	(13.1, 55)	(4.9, 47.4)
p-value	0.001	0.016

Source: Table 2.1.0. Model 1 includes effects for treatment, baseline covariate, pooled site and background therapy using type III sum of squares. P-values obtained from ANCOVA model adjusted for stated effects. Baseline covariate is the Visit 2 data.

The Week 12 change from baseline in ETT duration at peak, in the efficacy-evaluable population, showed mean differences of 28.5 sec (95% CI: 2.7, 54.2) for ranolazine SR 750 mg vs. placebo, and 14.8 sec (95% CI: -11.3, 40.9, p=NS) for ranolazine SR 1000 mg vs. placebo (source: Table 2.1.1).

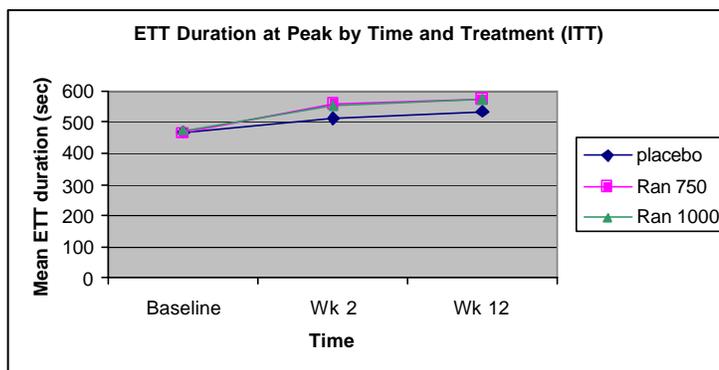
Change from baseline at Weeks 2 and 12 are presented below. For a given time point, the change from baseline at peak (vs. placebo) appeared larger in the 750 compared to the 1000 mg group.

Table 13. CVT 3033: Change from baseline in ETT duration at *peak* at Weeks 2 and 12 (ITT)

	R 750 vs. placebo		R1000 vs. placebo	
	Week 2	Week 12	Week 2	Week 12
LSM difference (SE)	51.2 (8.8)	34.2 (11.1)	41.7 (8.9)	24.3 (11.2)
95 % CI	34, 68.5	12.5, 55.9	24.2, 59.2	2.2, 46.3
p-value	<0.001	0.002	<0.001	0.03

Source: Table 2.1.5. LSM, SE and p-values calculated from ANCOVA model 1, including effects for treatment, baseline covariate, pooled site and background therapy using type III sum of squares. Baseline covariate was the Visit 2 data.

Figure 2. ETT duration at Peak by time and treatment (ITT). Source: Table 2.1.0.3. Baseline was the Visit 1 data. Means are unadjusted.



ETT duration at Peak: Subgroup analyses:

Background therapy:

There was a statistically significant difference between ranolazine and placebo for patients on diltiazem background therapy. P-values for ranolazine 750 and 1000 mg dose groups (on diltiazem) were 0.008 and 0.002, respectively.

Table 14. 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. LSM 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.

When the change from baseline at Weeks 2 and 12 were analyzed by stratified background therapy, significant differences vs. placebo were seen at week 2 for diltiazem ($p < 0.001$) and amlodipine (both doses of ranolazine) and a borderline significant result ($p = 0.054$) for atenolol only in the ranolazine 750 mg dose group; at Week 12, a statistically significant difference vs. placebo was seen at both doses only for the group on diltiazem.

Reviewer: The interaction with diltiazem appears to be consistent with findings seen in other studies, including pharmacokinetic studies.

Subgroup analysis: Interaction with Pooled Site: For the ranolazine 750 mg group, there were statistically significant differences vs. placebo for pooled sites 1, 7 and 8 ($p = 0.04, 0.02$ and 0.03 , respectively). For the ranolazine 1000 mg group, there were no statistically significant differences vs. placebo per pooled site.

Subgroups by gender, age, and presence of diabetes or heart failure:

Table 15. CVT 3033: Change from baseline ETT duration (sec) peak by CHF, Diabetes, Gender, Age (ITT LOCF)

	Ran SR 750 (N=272)		Ran SR 1000 (N=261)	
	Yes (N=86)	No (N=184)	Yes (N=76)	No (N=179)
LS Mean Difference (SE) vs. placebo	23.4 (19.4)	39.4 (12.8)	43 (20)	18.9 (12.9)
95% CI	-14.7, 61.4	14.3, 64.6	3.8, 82.2	-6.5, 44.2

p-value	NS	0.002	0.032	NS
Gender	<i>Female (N=59)</i>	<i>Male (N=211)</i>	<i>Female (N=47)</i>	<i>Male (N=208)</i>
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
Diabetes	<i>Yes (N=67)</i>	<i>No (N=203)</i>	<i>Yes (N=59)</i>	<i>No (N=196)</i>
LS Mean Difference (SE) vs. placebo	33.6 (22.3)	34.7 (12.2)	43.7 (23)	21.1 (12.3)
95% CI	-10.2, 77.4	10.8, 58.7	-1.5, 88.8	-3.1, 45.3
p-value	NS	0.005	0.058	0.087
Age (years)	<i>< 65 (N=139)</i>	<i>≥ 65 (N=131)</i>	<i>< 65 (N=133)</i>	<i>≥ 65 (N=122)</i>
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.

Reviewer: Subgroup analyses at the time of peak show trends in the opposite direction by gender. This finding, coupled with clinical pharmacology results, suggests a differential effect by gender. Trends favorable for ranolazine appear with respect to the elderly and CHF subgroups.

Time to Angina (trough and peak):

Results are presented below. At both trough and peak, the time to onset of angina showed statistically significant differences vs. placebo in favor of ranolazine. The effect size is larger for peak than trough. With the increase in dose from 750 to 1000 mg bid, the mean difference in the ITT population appears unchanged.

Table 16. CVT 3033: Change from baseline in Time to Onset of Angina (sec) at Trough Week 12 ITT LOCF (ANCOVA Model 1)

	Ran SR 750 mg vs. placebo	Ran SR 1000 mg vs. placebo
LS Mean difference (SE)	29.71 (12.07)	26.01 (12.2)
95% CI	(6, 53.4)	(2.1, 49.9)
p-value	0.014	0.033

Source: Table 2.4.0. Baseline covariate is the average of Visits 1 and 2 data. ANCOVA Model 1 includes effects for treatment, baseline covariate, pooled site and background therapy using type III sum of squares.

The same analysis for the efficacy-evaluable population showed mean differences of 27.8 (p=0.06) and 42.99 (p=0.004) for the ranolazine SR 750 mg and 1000 mg (vs. placebo), respectively.

Table 17. CVT 3033: Change from baseline in Time to Onset of angina (sec) at Peak Week 12 ITT LOCF (ANCOVA Model 1)

	Ran SR 750 mg vs. placebo	Ran SR 1000 mg vs. placebo
Mean difference (LSM) (SE)	38.02 (12.38)	37.88 (12.56)
95% CI	(13.7, 62.3)	(13.2, 62.5)
p-value	0.002	0.003

Source: Table 2.5.0. See Table 17 for ANCOVA Model 1.

The same analysis for the efficacy-evaluable population showed mean differences (vs. placebo) of 30.09 (p=0.47) and 29.18 sec (p=0.57) for the ranolazine SR 750 and 1000 mg groups, respectively.

A survival analysis of the time to onset of angina (trough and peak levels of ranolazine) using a log rank test did not support the primary analysis and was only significant between ranolazine 750 mg and placebo at peak.

Time to 1 mm ST depression (trough and peak):

For this analysis, greater effect sizes, with statistically significant results, are seen at the time of peak but not trough.

Table 18. CVT 3033: Change from baseline in Time to Onset 1 mm ST depression (sec) *trough* and *peak* Week 12 ITT LOCF (ANCOVA Model 1)

	Ran SR 750 mg vs. placebo	Ran SR 1000 mg vs. placebo
Trough		
Mean difference (LSM) (SE)	19.9 (12.2)	21.1 (12.4)
95% CI	(-4.1, 43.9)	(-3.3, 45.5)
p-value	NS	0.09
Peak		
Mean difference (LSM) (SE)	40.8 (11.8)	34.5 (11.9)
95% CI	(17.6, 63.9)	(11.1, 58)
p-value	<0.001	0.004

Source: Tables 2.8.0, 2.9.0

Change in maximum ST depression (trough and peak):

Statistically significant results are not consistently seen (only noted at trough for the 750 mg bid group) in the change from baseline in maximum ST depression.

Table 19. CVT 3033: Change from baseline Maximum ST-Depression (mm) *trough* Week 12 ITT LOCF (ANCOVA Model 1)

	Ran SR 750 mg vs. placebo	Ran SR 1000 mg vs. placebo
Mean difference (LSM) (SE)	0.18 (0.07)	0.02 (0.07)
95% CI	(0.05, 0.31)	(-0.11, 0.15)
p-value	0.006	NS

Source: Table 2.2.0. Model 1 includes effects for treatment, baseline covariate, pooled site and background therapy using Type III sum of squares. P-values obtained from ANCOVA model adjusted for stated effects. Baseline covariate is the average of Visits 1 and 2 data.

Consistent 95% CI and p-values were seen in the same analysis for the efficacy-evaluable population (although the mean difference was -0.01 for the ran SR 1000 mg vs placebo group).

Table 20. CVT 3033: Change from baseline in Maximum ST depression (mm) *peak* Week 12 ITT LOCF (ANCOVA Model 1)

	Ran SR 750 mg vs. placebo	Ran SR 1000 mg vs. placebo
Mean difference (LSM) (SE)	0.1 (0.07)	0.03 (0.07)
95% CI	(-0.03, 0.23)	(-0.10, 0.16)
p-value	NS	NS

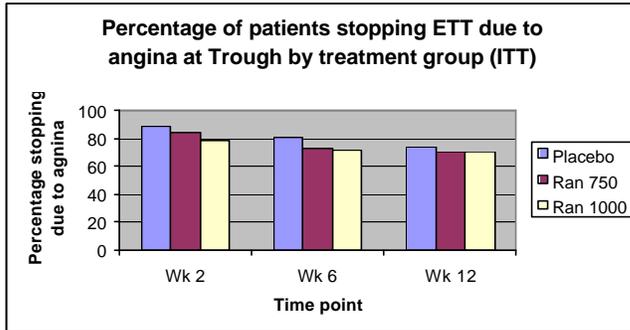
Source: Table 2.3.0. Please see preceding Table for further explanation of ANCOVA Model 1, p-values, baseline covariate.

The same analysis was consistent for the efficacy-evaluable population.

Reasons for Stopping ETT:

Percentage of patients stopping due to angina are presented below. For all 3 groups, including placebo, the percentage stopping due to angina decreased (and the percentage stopping due to overall fatigue increased) over time, especially (with regard to the ranolazine groups) from Weeks 2-6. The difference between Ran 750 and Ran 1000 at Week 12 was negligible.

Figure 3. Percentage of patients stopping ETT due to angina (trough, ITT)



Source: Table 2.12.0.

Pairwise comparisons (via CMH stratified for background therapy) at Weeks 2 and 6 were statistically significant for Ran 1000 vs. placebo; however, the same analysis was not statistically significant at 12 weeks. The same analysis was marginally significant ($p=0.059$) for Ran 750 only at the Week 6 timepoint. For the efficacy-evaluable population, statistically significant results, using the same CMH analysis, were only seen for the Ran 1000 vs. placebo group only at Week 2.

The percentage of patients stopping peak ETT due to angina also showed a decrease over time for all 3 groups, including placebo (with an increase in percentage, in all 3 groups) of patients stopping due to overall fatigue. The percentage stopping due to angina at Week 12 was the same for Ran 750 and 1000. Pairwise comparisons showed statistically significant differences for both dosage groups compared to placebo.

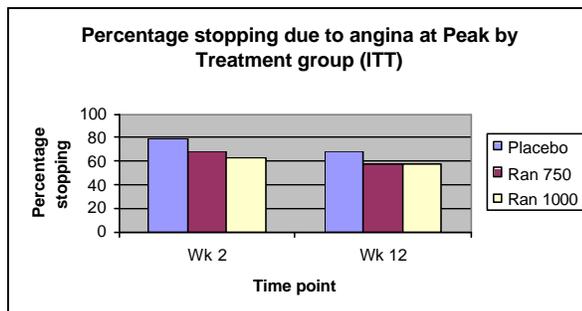


Figure 4. Percentage of patients stopping ETT due to angina at peak (ITT).

Source: Table 2.13.0. Pairwise comparisons of ranolazine 750 mg vs. placebo (via CMH stratified by background therapy) were statistically significant (p values of 0.006 and 0.011 at Weeks 2 and 12, respectively). Not surprisingly (judging from the graph), pairwise comparisons of ranolazine 1000mg vs. placebo (same analysis as above) were also statistically significant (p values of <0.001 and 0.011 at Weeks 2 and 12, respectively).

Other analyses:

Normalized frequency of angina during 12 Weeks by treatment (ITT): According to the sponsor, the normalized frequency of angina (i.e., total number of angina episodes during double-blind normalized by the number of weeks on double-blind) during the 12 week treatment period (ITT) showed a mean (SE) of 3.31 (0.3) events on placebo, 2.47 (0.23) on Ran 750 and 2.13 (0.24) events on Ran 1000. Using ranked scores data and non-parametric ANCOVA (model fitted with ranked data for treatment ($p<0.001$), baseline covariate ($p<0.001$), pooled site ($p=0.015$), and background therapy ($p=0.88$) using type III sum of squares), the sponsor calculated significant differences ($p=0.006$: Ran 750 vs. placebo; $p<0.001$: Ran 1000 vs. placebo) for the two active treatment groups vs. placebo. A similar evaluation of the efficacy-evaluable population was consistent.

Maximum and Average Duration of angina during 12 weeks by treatment (ITT, evaluable): The sponsor performed a similar analysis using ranked scores data and non-parametric ANCOVA. No statistically significant difference for ranolazine vs. placebo was demonstrated.

Maximum Severity of angina during 12 weeks by treatment (ITT): The percentage of moderate angina was slightly higher in the placebo group (50.4%) compared to Ran 750 (47.6%) and Ran 1000 (44.4%). However, the incidence of severe angina was similar in all 3 treatment groups (32%). Pairwise comparisons (van Elteren test stratified by background therapy) did not show any statistically significant differences.

Median Severity of angina during 12 weeks compared to baseline (ITT) (Source: Table 2.17.25): Based on patients with at least one episode of angina at baseline and double-blind, 14-15% of patients worsened (essentially no change across treatment groups); 66% on placebo, 57% on Ran 750 and 59% on Ran 1000 were unchanged; and 19% on placebo, 30% on Ran 750 and 26% on Ran 1000 were improved from baseline.

Nitroglycerin consumption: Analysis of normalized nitroglycerin consumption (number of uses of nitroglycerin during double-blind normalized by the number of weeks on double-blind) for the ITT population showed a mean (SE) of 3.14 on placebo, 2.11 (0.27) on Ran 750 and 1.76 (0.28) on Ran 1000. Statistics using ranked scored data and non-parametric ANCOVA (model fitted with ranked data for treatment (p=0.002), baseline covariate (p<0.001), pooled site (p=0.16) and background therapy (p=0.58) using type III sum of squares) showed statistically significant differences vs. placebo for Ran 750 (p=0.016) and 1000 (p <0.001) (Source: Tables 2.18.2, 2.18.2.1)

Rebound Effects:

The prespecified secondary efficacy parameter was the change from baseline in ETT duration at trough. This parameter is graphically depicted for both ITT and evaluable (eff) populations. For the ITT population, the change from baseline for Ran 1000/Placebo vs. Ran 1000 staying on therapy was borderline statistically significant (p=0.053,⁹ mean change -33.9 sec). For the evaluable population, the same parameter resulted in a mean change of -55.5 sec (p=0.007). The other comparisons did not show statistically significant effects.

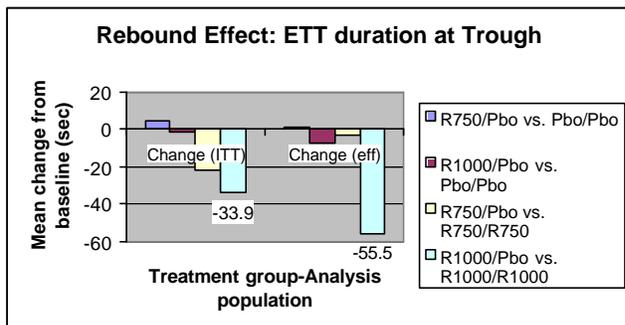


Figure 5. Rebound Assessment: ETT duration at trough.

Source: Table 2.19.0. Means are LSM estimates from ANCOVA model.

Reviewer: The results of withdrawal from therapy appear consistent with a treatment effect which appears attenuated after 48 hours of withdrawal from drug. Note that the R1000/placebo group (below) is similar to, and not worse than, placebo/placebo.

⁹ P-values obtained from ANCOVA model adjusted for effects for treatment sequence (p=0.11), baseline covariate (p=0.003), pooled site (p < 0.001) and background therapy (p=0.70) using Type III sum of squares.

Table 21. CVT 3033: Mean change in ETT duration at Trough at the end of the Rebound Assessment Phase (ITT)

	Placebo/placebo	R 750/placebo	R1000/placebo	R750/R750	R1000/R1000
N	243	128	118	120	118
LS Mean (SE)	98.6 (9.2)	103.3 (12.1)	97.2 (12.8)	125.1 (12.7)	131.1 (12.7)

Source: Table 2.19.0.1.

Also, there were no meaningful changes in frequency or severity of angina during the rebound assessment period. Nor were increases in nitroglycerin consumption seen (Source: Tables 2.19.7 (frequency), 2.19.8 (duration), 2.19.9 and 2.19.10 (maximum severity), 2.19.11 and 2.19.12 (median severity), 2.19.13 (nitroglycerin consumption)).

Table 22. CVT 3033: Change in Angina during the Rebound Assessment by Treatment (ITT)

N (%)	Placebo/placebo	R750/Placebo	R1000/placebo	R750/R750	R1000/R1000
Maximum severity of angina-- worsened	9 (11)	0	2 (6)	1 (4)	1 (3)
Maximum severity of angina—no change or improved	72 (89)	31 (100)	34 (94)	27(96)	30 (97)
Median severity of angina--worsened	16 (20)	6 (19)	7 (19)	4 (14)	8 (26)
Median severity of angina—no change or improved	65 (80)	26 (81)	29 (81)	24 (86)	23 (74)

Source: Tables 2.19.10, 2.19.12

Ranolazine Plasma Concentrations:

Table 23. CVT 3033: Ranolazine Plasma Concentrations (ng/ml) at Week 12 at Trough and Peak during the Double-blind phase: safety population

	Ranolazine SR 750 mg	Ranolazine SR 1000 mg	Ranolazine SR 1000 vs. 750 mg (mean difference)
Trough			
Mean (SE)	1577.6 (71)	2164.7 (89.2)	592.0 (110.1)
p-value			<0.001
Peak			
Mean (SE)	2031.1 (78.8)	2607.1 (90)	567 (118)
p-value			<0.001

Source: Table 11P, Table 3.5.0., 3.6.0. P-values obtained from ANOVA Model 7 including effects for treatment, pooled site and background therapy using type III sum of squares. Mean difference (SE) are LS mean estimates from ANOVA.

For the Rebound Assessment, plasma concentrations are shown below. Comparisons of R1000/1000 vs. R750/R750, R1000/placebo vs. R1000/R1000, and R750/placebo vs. R750/R750 were statistically significant (p <0.001). The comparison of R1000/placebo vs. R750/placebo was not statistically significant.

Table 24. CVT 3033: Ranolazine Plasma Concentrations (ng/ml) at Trough at Rebound: safety population

	R750/R750	SR750/Placebo	R1000/R1000	R1000/Placebo
N	119	124	118	117
LS Mean (SE)	1413.2 (76)	108.2 (72.9)	2080.1 (75.7)	128.3 (76.8)

Source: Table 3.5.1.1. LS mean and SE obtained from ANOVA Model 7 (see Table 18). Note: two placebo/placebo patients at Rebound had nonzero ranolazine plasma concentrations.

Safety: For a detailed safety discussion, please see the Safety Review.

Reviewer Comments:

1. This was an 823 patient, multicenter, randomized placebo-controlled parallel-group study including 12 weeks active treatment and a 2 week rebound assessment period. The study evaluated ranolazine SR in doses of 750 and 1000 mg po bid in a patient population with stable angina and symptom-limited ETT.
2. Patients were stratified to submaximal doses¹⁰ of background therapy of amlodipine, atenolol or diltiazem.
3. Analysis of the primary endpoint, ETT duration at trough, showed a statistically significant improvement in ranolazine groups compared to placebo. However, this effect was modest and differences were not consistently significant when the data were further examined by subgroup. In addition, when a single site outlier with highly significant results was excluded, the treatment differences were small and not statistically significant.
4. The prespecified primary analysis (ETT duration at trough, ITT) did not demonstrate a dose-response relationship at these dosages in this study.
5. Statistically significant changes from baseline to endpoint at *trough*, compared to placebo, were also seen with respect to time to onset of angina and time to onset of 1 mm ST depression.
6. Statistically significant effects at *peak* were seen with respect to: ETT duration, time to onset of angina, time to onset of 1 mm ST depression, and percentage of patients stopping ETT due to angina. The change in maximum ST depression did not show consistently significant results.
7. A statistically significant interaction with diltiazem was seen with respect to ETT duration at peak.
8. Results of the normalized frequency of angina during 12 weeks showed a significant decrease in mean events in ranolazine groups compared to placebo. Analyses of nitroglycerin consumption were also consistent with these findings.
9. Subgroup analyses (trough and peak) by gender showed differential effects. Results at peak, in the female subgroup, were favorable toward placebo.
10. A clinically significant 48 hour rebound effect was not seen when ranolazine, at these doses, was withdrawn.
11. Withdrawal of ranolazine after 12 weeks of treatment show a marginally statistically significant treatment effect (at trough) in the ranolazine 1000 bid group.

CVT 3031:

Title: 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. (Protocol date: September 3, 1997; amended October 29, 1997; April 8, 1998; August 25, 1998; December 28, 1998)

Primary objective: Determine effect of ranolazine SR monotherapy at doses of 500 mg bid, 1000 mg bid and 1500 mg bid, compared to placebo, on treadmill exercise duration at the time of trough ranolazine plasma levels (12 hours postdose).

Secondary objectives:

1. Determine effect of the three doses of ranolazine SR, compared to placebo, on time to onset of angina and time to 1 mm ST depression during exercise treadmill testing (ETT) at trough ;
2. Determine effect of the three doses of ranolazine SR, compared to placebo, on exercise duration, time to onset of angina, and time to 1 mm ST depression during ETT at the approximate time of peak ranolazine plasma levels (4 hours postdose; “peak”).

Patient population: An enrollment of 203 patients with chronic stable angina, responding to antianginal therapy, was planned in order to yield 152 evaluable patients.

¹⁰ Source: respective labeling of these medications.

Study summary: This was a double-blind, randomized, placebo-controlled, multiple-dose, 4-period crossover study. The study was composed of two phases: a single-blind placebo qualifying phase (2 screening visits) of about 1 week duration and a placebo-controlled double-blind phase lasting about 4 weeks, with a follow-up visit scheduled 2 weeks after completion of the double-blind phase.

Patients meeting inclusion/exclusion criteria entered the single-blind qualifying phase, where they underwent physical examination, laboratory testing, ECGs and ETTs. Those qualifying at Visit 2 entered the 4 week double-blind phase (Visits 3, 4, 5 and 6). Each week the patient received one of three active ranolazine treatments (500, 100 and 1500 mg bid) or placebo (given bid). Patients received one week treatment with each of the three dose regimens and placebo in random order. At each of the 4 double-blind visits, patients underwent trough ETT (12 hours after their previous drug dose from the evening before). Following the trough ETT, patients were given the final dose of that week’s double-blind treatment (in clinic) and then underwent peak ETT 4 hours after that in-clinic dose.

Blood samples for peak/trough plasma levels, vital signs, hemodynamic measurements, and ECGs were collected at each of the 4 double-blind visits. Laboratory tests were performed at the first screening visit and at the end of the double-blind phase. Where available, ACTH challenge testing was performed at the second screening visit and at the final double-blind visit.

Table 1. CVT 3031: Inclusion/exclusion criteria (single-blind phase)

Inclusion criteria	Exclusion criteria
<ol style="list-style-type: none"> 1. ≥ 21 years old 2. at least 3 month history of chronic stable effort angina, relieved by rest and/or sublingual nitroglycerin 3. coronary disease documented by any one or more of: angiographic evidence of $\geq 60\%$ stenosis of one or more major coronary arteries; history of MI documented by positive enzymes or ECG changes 4. improvement/control of angina/ischemia with at least one of the following: beta blockers, calcium channel blockers, long-acting nitrates 5. willingness to discontinue antianginal therapy 48 hours before Visit 1 and for the duration of the study 6. willingness to maintain stable tobacco usage habits throughout the study 7. signed an approved consent form. 8. female patients of childbearing potential who are not breastfeeding, who have a negative pregnancy test and have no intention to become pregnant during the study, and who use contraception. 	<ol style="list-style-type: none"> 1. ECG abnormality interfering with ETT interpretation or associated with false positive results 2. NYHA Class III-IV CHF 3. Clinically significant valvular or congenital heart disease 4. Unstable angina, MI, CABG, PCI within the past 2 months 5. 2nd /3rd degree AV block or uncontrolled cardiac arrhythmia or life-threatening ventricular arrhythmias unassociated with MI 6. QTc $> .50$ seconds at Visit 1 7. Requiring medications known to prolong QTc 8. Requiring medications which affect cytochrome P450 3A4 9. Unwillingness to refrain from grapefruit juice 10. Requiring digoxin 11. Acute myocarditis/pericarditis 12. Hypertrophic cardiomyopathy 13. Uncontrolled hypertension or SBP < 100 mm Hg 14. Chronic illness, clinically significant laboratory abnormality, participation in another study ≤ 1 month before this trial.

Qualifying criteria for double-blind:

See qualifying criteria for double-blind in CVT 3033 as these were the same in CVT 3031.

Concomitant antianginal medications:

Concomitant beta-blockers, calcium channel-blockers and long-acting nitrates were not allowed during the study. Aspirin was permitted during the study. Sublingual nitroglycerin was allowed for the treatment of acute anginal episodes, but was not to be used within 60 minutes of the ETT. Ophthalmic beta-blockers were allowed if their use was constant throughout the study.

Patients who elected not to enroll in the long-term, follow-up study (CV 3032) were allowed to resume their prior antianginal medications after completion of procedures at Visit 6 (Termination/Early Withdrawal).

Efficacy evaluations:

All patients were to have ETT under uniform conditions, optimally by the same personnel each time. Trough ETT were planned between 7:00 am and noon, $12 \pm \frac{1}{2}$ hour after their prior evening dose. Patients were to stop smoking at least 2 hours before testing.

Efficacy variables were: time to onset of angina, exercise duration, primary reason for stopping exercise; ECG variables from each ETT were: time to 1 mm ST depression, maximum ST depression during exercise.

Criteria for Patient Removal:

1. Serious adverse event
2. Grossly noncompliant
3. Continued participation would jeopardize patient health
4. QTc widens to 130% of baseline duration and longer than 500 msec;
5. Unsatisfactory therapeutic response/investigator judgment
6. Patient wishes to withdraw
7. Sponsor elects to end the study.

Patients who withdrew early from the study were to be replaced by another patient who was randomized to the same sequence as the patient who prematurely withdrew.

Safety evaluation: adverse event monitoring, vital signs, ECG, and routine laboratory tests. An ACTH stimulation test, with collection of cortisol levels was planned at Visits 2 and 6.

Statistics:

According to the sponsor, carryover effects on treadmill efficacy parameters were not expected in CVT 3031; this expectation was based on two previous crossover studies of IR ranolazine, which suggested that drug effect on treadmill efficacy was influenced primarily by plasma level at the time of ETT and no first-order carryover effects were seen.

Efficacy analyses were planned on:

1. Near/all Completers, all randomized patients with evaluable efficacy measurements at baseline and for at least 3 out of the 4 double-blind periods, irrespective of protocol violations. If this population included 75% or more of the randomized patients, then it will be the primary analysis population (otherwise the primary analysis population will be ITT, below (#2));
2. Intent to treat (ITT), consisting of all randomized patients with evaluable efficacy measurements at baseline and for at least one double-blind period, irrespective of protocol violations.
3. First-period population, consisting of all randomized patients with evaluable efficacy measurement at baseline and from the first double-blind treatment period, irrespective of protocol violations;
4. Per-protocol population, consisting of all randomized patients with evaluable efficacy measurement at baseline and with at least 3 out of 4 treatment periods completed in accordance with the protocol.

The baseline efficacy measurement was defined as the average from the two ETT performed during the single-blind placebo phase, or if only one ETT was done, the single measurement from this phase.

The primary efficacy variable was ETT duration at the time of trough ranolazine plasma levels (12 hours postdose).

Secondary efficacy variables:

1. Time to onset of angina during ETT at trough;
2. Time to 1 mm ST depression during ETT at trough;
3. Exercise duration during ETT at time of peak levels;
4. Time to onset of angina during ETT at the time of peak levels;
5. Time to 1 mm ST depression during ETT at the time of peak levels;
6. Maximum ST depression during exercise;
7. Primary reason for stopping test.

Efficacy analyses (as outlined in the protocol):

If 75% or more randomized patients complete at least three of four periods, then the primary efficacy analysis population will be the all/near completers, and the analysis will be a standard crossover ANCOVA with treatment, period and patient as factors. A secondary efficacy analysis based on ITT will be done. The first period population will be analyzed using ANCOVA with terms for treatment and baseline value. The per-protocol population will be analyzed using ANCOVA for crossover design.

Safety variables: history, physical examination, vital signs, AE, laboratory tests, concomitant medications.

Sample Size calculation:

The sample size estimate was based on ETT duration at trough plasma levels of ranolazine. Based on a previous study, a standard deviation of difference in exercise duration of 95 seconds was selected to use in the sample size calculation. A sample of 152 patients would be sufficient for declaring a statistically significant mean difference of 25 seconds between a result on active treatment vs placebo at the 5% level with a power greater than 90%.

Reviewer: No washout period was done between treatment periods during double-blind phase.

Protocol Amendments:

1. Amendment 1: Oct. 29, 1997: Sample size increased to 203 enrolled in order to discriminate a smaller change in exercise duration; number of antianginal medications required to show response decreased from two to one; blood draw amount corrected in informed consent; added analysis population to include near completers and ITT; defined baseline variable; added secondary efficacy variables: primary reason for stopping test and maximum ST depression during exercise; defined ANCOVA factors on the all/near-completers population (ITT planned as secondary analysis). Other secondary analyses: ANCOVA to investigate and rule out carryover effects and center by treatment interaction; GEE (including effects for baseline period, treatment and possibly other patient level covariates) to fit linear models to primary efficacy outcome.
2. Amendment 2: April 8, 1998: Defined serious adverse events per ICH guidelines; added information regarding ranolazine metabolism (cytochrome P450); clarified prohibited medications.
3. Amendment 3: August 25, 1998: Added prohibited medications (cytochrome P450 inducers); altered language to permit international sites; changed primary analysis population to all/near completers if this population included 75% or more of randomized patients; added that patients must discontinue antianginals for at least 48 hours prior to Visit 1.
4. Amendment 4: December 28, 1998: Added list of substances modifying CYP 3A4 activity (including grapefruit juice).

Interim Analyses: None performed in this study.

Results: Fifty-two sites recruited patients in the US (113 patients), Canada (15), Czech Republic (36) and Poland (27).

Patient Disposition: A total of 191 patients were randomized into 4 treatment sequences (ABCD, BDAC, CADB and CDBA where A = 500 mg bid, B = 1000 mg bid, C = 1500 mg bid and D = placebo).

A	B	C	D
B	D	A	C
C	A	D	B
D	C	B	A

There were 45-50 patients randomized to each treatment sequence; the numbers of patients receiving each treatment (i.e., placebo, ranolazine 500 mg bid, 1000 mg bid or 1500 mg bid) were 179-187. A total of 175 patients (92%) were included in the near/all completer population, 185 patients (97%) 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. Twenty-three patients (12%) discontinued the study before completing all

trough and peak assessments at all treatment periods. Fifteen (8%) patients discontinued prematurely due to AE (11 of these were in the highest dose ranolazine group). One hundred forty-six patients (76%) enrolled in a long-term follow-up study (CVT 3032). There was one death in the Ran SR 500 mg group.

Baseline characteristics:

Except for gender (p=0.05, higher percentage males in the ABCD and BDAC sequences), baseline characteristics appeared to be balanced among treatment sequences. Statistically significant differences were seen with regard to diabetics on insulin (p=0.02), history of unstable angina (p=0.037) and prior stroke (p=0.03); however the numerical differences between groups was small.

Mean age was about 64 years (39-85 range) and about half of the patients were 65 years and older. The safety population was about 90% Caucasian and 4-8% Black. Mean weight was about 83 kg and height about 171 cm. About half had a prior MI, about 13-20% had a history of CHF, and 28% had a prior CABG. About 60-70% had a history of hypertension.

Efficacy:

The sponsor’s analysis of the primary efficacy variable is presented below. According to the sponsor, a large effect size, statistically significant at all 3 doses, was seen. The results were consistent between ITT and all/near completers. An increase in mean difference was seen with increasing dose. The sponsor did not find statistically significant treatment by pooled site interaction, treatment-by-period interaction, or carryover effect¹¹. Results for the per-protocol population (both peak and trough) were consistent. A supportive GEE analysis showed that addition of gender, unstable angina and history of stroke as

Mean Difference Compared to Placebo in ETT Duration at Trough Levels of Study Drug (sec) All/Near Completers Population and ITT Population

Population	Statistic	Avg of (Ran SR			
		1500 mg and Ran SR 1000 mg)	Ran SR 1500 mg vs Placebo	Ran SR 1000 mg vs Placebo	Ran SR 500 mg vs Placebo
All/Near Completers ¹	Mean Difference	39.8	45.9	33.7	23.8
	S. E. of Mean Difference	6.9	8.0	8.0	7.9
	95% Confidence Interval	[26.3,53.3]	[30.2,61.7]	[18.1,49.2]	[8.2,39.4]
	P-value	< 0.001**	< 0.001**	< 0.001**	0.003**
ITT ²	Mean Difference	40.5	45.9	35.1	22.8
	S. E. of Mean Difference	7.8	8.5	8.8	8.4
	95% Confidence Interval	[25.1,55.8]	[29.2,62.6]	[17.9,52.3]	[6.3,39.4]
	P-value	< 0.001	< 0.001**	< 0.001**	0.007**

* 0.010 < p-value ≤ 0.050; ** p-value ≤ 0.010
¹A/NC Population analyzed using ANOVA for cross-over study design with effects for pooled site, patient within pooled site, period, and treatment.
²ITT Population analyzed using GEE with effects for baseline ETT duration, pooled site, period, and treatment.
 Note: Multiple comparisons adjusted for using closed testing and union intersection principles.
 Note: Ran SR = Ranolazine SR
 Data Source: Tables 2.1.2 and 2.2.2

Table 2. Primary Efficacy variable (analysis by sponsor).

variables into the GEE model did not alter results for treatment differences.

The sponsor’s results for peak values also showed statistically significant increases vs. placebo and increasing difference (vs. placebo) with increased dose.

¹¹ In the Statistical Methods section, the sponsor’s reference # 14 is a monograph by Stephen Senn, Crossover Trials in Clinical Research. In the introductory chapter, and in Sections 3.8 - 3.11, the author states that tests for carryover are virtually impossible to interpret: “I do not carry out tests for carryover and do not advise the reader to do so”. In Section 10.3, “Five Reasons for Believing that the Simple Carryover Model is not Useful”, and also in Section 1.8, Stephen Senn explains that including carryover in the model requires restrictive assumptions about the nature of the possible carryover. If slightly different forms of carryover hold, then the model is useless. Instead, the author recommends to carry out many studies with different designs to support the results of the crossover studies.

As with the trough results, the sponsor found no significant treatment by pooled site interaction, treatment-by-period interaction or carryover effect. The GEE analysis was consistent with the above ANOVA.

**Mean Difference Compared to Placebo in ETT Duration
at Peak Levels of Ranolazine (sec)
All/Near Completers Population and ITT Population**

Population	Statistic	Ran SR 1500 mg vs Placebo	Ran SR 1000 mg vs Placebo	Ran SR 500 mg vs Placebo
All/Near Completers ¹	Mean Difference	55.5	50.1	29.3
	S. E. of Mean Difference	7.3	7.2	7.2
	95% Confidence Interval	[41.2, 69.8]	[36.0, 64.2]	[15.2, 43.4]
	P-value	<0.001**	<0.001**	<0.001**
ITT ²	Mean Difference	55.6	51.5	28.7
	S. E. of Mean Difference	7.8	7.3	7.2
	95% Confidence Interval	[40.4, 70.8]	[37.3, 65.8]	[14.6, 42.9]
	P-value	<0.001**	<0.001**	<0.001**

* 0.010 < p-value ≤ 0.050; ** p-value ≤ 0.010.
¹ A/NC Population analyzed using ANOVA for cross-over study design with effects for pooled site, patient within pooled site, period, and treatment
² ITT Population analyzed using GEE with effects for baseline ETT duration, pooled site, period, and treatment.
 Note: Multiple comparisons adjusted for using closed testing and union intersection principles.
 Note: Ran SR = Ranolazine SR
 Data Source: Tables 2.1.2 and 2.2.2

Table 3. ETT duration at Peak (sponsor's analysis)

Reviewer's findings:

In study 3031, the sponsor's results for exercise duration were troubling to the reviewers and difficult to interpret:

1. There were very large differences in numerical increases of exercise time with ranolazine between periods. The first period was very different from the later periods. In the first period, each ranolazine dose had a small increase in exercise time as compared to placebo and there was no clear dose response. In the second and later periods, there was a very large increase in exercise time in favor of ranolazine.

Table 4. 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

As shown in Table 4, Ran 1500 mg had a very small effect of 4.5 seconds in the first period and a 9 - 15 fold increase in later periods. Likewise, ranolazine 1000 mg had a small effect of 12.7 seconds in the first period and 3 - 4 fold increase in later periods. A small effect of 34 seconds in the fourth period was observed probably because ranolazine 1000 mg immediately followed placebo in the sequence CADB. Ranolazine 500 mg also showed the tendency of a large increase in the third and fourth periods.

These observations seem to suggest the possible presence of treatment-by-period interactions that make it very difficult to interpret the results of the sponsor's crossover analysis pooling all periods.

The sponsor presented a non-significant p-value, $p=0.62$, for treatment-by-period interaction and stated that there was no treatment-by-period interactions. However, the study was planned to detect a treatment effect based on the crossover analysis pooling all the periods and assuming no treatment-by-period interactions. Thus, it can be expected that the sample size may not be sufficient to test treatment-by-period interactions. In the reviewer's view, the sponsor's non-significant p-values in the tests for these effects have no practical value.

- The study showed a large period effect as shown in Table 5 (this is also the sponsor's Table ET13A). In the April 30, 2003 submission, the sponsor stated that the strong period effect in the study represented a training effect or learning effect.¹² If we accept the sponsor's explanation, then Table 5 implies that the learning effects for ranolazine doses seemed to be numerically much larger than the learning effect for placebo. For placebo, learning effect was smaller and not significant ($p=0.50$). In contrast, for ranolazine doses, learning effect was much stronger (nominal p-value ranged from $p=0.027$ for Ran 1000 mg to $p<0.001$ for Ran 1500 mg). Does this mean that ranolazine promotes learning effect? If so, should the promotion of learning effect be counted as a clinical benefit of ranolazine?

Comparison	Statistics	Treatment			
		Placebo	Ran SR 500 mg	Ran SR 1000 mg	Ran SR 1500 mg
Exercise Duration at Trough (sec.), Period 4 minus Period 1	Mean Difference	36	70	54	97
	P-value	0.15	0.005	0.024	<0.001
Exercise Duration at Trough (sec.), Period 3 minus Period 1	Mean Difference	25	42	64	82
	P-value	0.32	0.046	0.004	<0.001
Exercise Duration at Trough (sec.), Period 2 minus Period 1	Mean Difference	12	4	29	45
	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.

- The numerical pattern in Table 5A seems to suggest possible differential carryover effects for the two higher ranolazine doses. Longer exercise duration was observed when following a ranolazine dose, compared with following placebo, though the sponsor argued that there was no carryover effect ($p=0.51$). However, the sponsor's further analysis adjusting for 1st order carryover effect (Table 2, August 06, 2003 submission) seems to show little impact of possible carryover effect, if any (see footnote 11).

Table 5A. 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)	--

First Period Population:

Because of the strong suggestion of treatment-by-period interaction, the first period data were analyzed to obtain unbiased estimates of ranolazine effects (Table 6). Of 184 patients in the first period population who underwent ETT at trough levels of study drug in Period 1, forty-five received placebo, 45 received ranolazine SR 500 mg, 49 received ranolazine SR 1000 mg, and 45 received ranolazine SR 1500 mg. The same numbers of patients underwent ETT at peak levels of study drug. For trough, the first period data at

¹² "Carryover effects can have a variety of forms. They can be learning effects or fatigue effects, having, respectively, a positive or negative effect on the response, or they can be of a psychological, rather than of a physical, form." (From: Ratkowsky DA et. al. Crossover Experiments. Marcel Dekker, Inc. 1993).

best show a small effect with ranolazine, if any, that was not statistically significant at trough. Even pooling three ranolazine doses versus placebo did not show a statistically significant effect (p=0.57). At peak, there appears to be a modest treatment effect that is statistically significant at Ran 1000 mg bid and marginally significant at the other two doses. There does not appear to be an increase in ETT duration at peak with Ran 1500 mg bid compared to Ran 1000 mg bid.

Table 6. 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

Source: Table 2.3.2. ANCOVA model includes effects for baseline ETT duration, treatment, pooled site.

Subgroup Analyses and Secondary Endpoints

Because of the difficulties in interpretability of the primary endpoint, analyses of subgroups, as well as secondary endpoints, are not presented in this review.

Serum Concentrations:

Serum ranolazine levels at peak and trough times are shown below:

Table 7. Ranolazine SR concentration measurements—Safety population (N=191)

Parameter	Placebo (N=179)	Ran SR 500 mg (N=181)	Ran SR 1000 mg (N=180)	Ran SR 1500 mg (N=187)
Trough plasma concentration (ng/ml) mean (SE)	N=175 16 (11.3) Range:0-1,650	N=173 848.9 (55) Range: 0-3,560	N=175 1959.2 (107.5) Range: 86- 8,090	N=170 3241 (150.9) Range: 0-11,000
Peak plasma concentration (ng/ml) mean (SE)	N=173 35.2 (19.5) Range: 0-2,130	N=169 1122.6 (55.9) Range: 0-3,800	N=174 2476 (115.1) Range: 228-8,650	N=166 3930.5 (161.3) Range: 543-14,300

Source: Panel 11E, Table 1.14.0, (CVT 3031)

Reviewer: Of note are serum levels (up to 1650 and 2130, trough and peak, respectively) for placebo-treated patients (where levels should be zero) and minimum ranges of zero in the Ran 500 mg-treated group (peak and trough) and Ran 1500 mg-treated group (at trough); these values—assuming that patients are compliant with medication-- do not make sense. The sponsor has suggested that serum levels for placebo likely represents sample mislabeling by the site. If one believes the concentrations of Ran 1000 mg (peak and trough) and Ran 1500 mg at peak, then the results show a wide variability in serum concentrations

Safety: Please see the Safety Review for further details.

Reviewer Comments/Conclusions:

Study 3031 was a four-period placebo-controlled crossover study. At the stage of designing the study, the sponsor probably did not expect any differential carryover effects, as they stipulated, based on earlier crossover studies for the IR formulation. So the study did not have any washout periods and did not have baseline ETT data prior to each treatment period. This design could lead to unknown serious risks

according to the statistical literature (e.g., ICH-E9). If the study data had been consistent with the expectation, then the crossover design would have been the most efficient design and this study could have been a powerful study. However, if not consistent, then the assumptions made to achieve efficiency become the burdens leading to the troublesome results that often cannot be interpreted.

The data of Study 3031 presented a number of major quandaries that make the results of the sponsor's crossover analyses difficult to interpret. One is the large period effects (Table 5). If the large period effects represented a learning effect as the sponsor asserted, then ranolazine seemed to result in a (at least numerically) much larger learning effect than placebo did (Table 5). Does this mean that ranolazine promotes learning effect? If so, should the promotion of learning effect be counted as a clinical benefit of ranolazine?

In addition, the data seemed to suggest possible treatment-by-period interaction, though the sponsor had performed many analyses to assert that there is no statistical evidence of the interactions. Despite the fact that the treatment-by-period interaction was not significant, the consistent troublesome numerical trend in Table 4 left the reviewers to suspect possible presence of treatment-by-period interactions. It is not clear whether these troublesome trends can ever be explained. Could these trends be attributed to learning effect alone? Or something else? The trial data implied that the treatment differences in favor of ranolazine in the 2nd-4th periods might not be entirely attributed to the therapeutic effect of the interest, because the first period data that are supposed to give the unbiased estimates of the effect at best yielded a small non-significant effect with any of the ranolazine doses.

Other Efficacy Studies:

RAN 072:

Title: An Investigation into the Anti-Anginal Efficacy and Dose Response Relationship of Ranolazine in Patients Taking Beta-Blockers or Calcium Antagonists (Protocol date: September 13, 1989)

Objectives (listed as "aims"):

1. Evaluate the antianginal effects of four different doses of ranolazine when taken in addition to beta blockers or calcium antagonists;
2. Investigate the relationship between dose and plasma level of ranolazine over a wide range of doses and expected plasma levels in patients with severe coronary artery disease.
3. Evaluate safety and tolerability of the addition of ranolazine to beta blockers or calcium antagonists.

Study Summary:

This was a double-blind crossover study of patients with CAD who remained symptomatic despite medical therapy with either a beta-blocker (atenolol or metoprolol) or a calcium antagonist (diltiazem) and who were admitted for diagnostic coronary angiography. Between 7 and 28 days prior to study entry, patients underwent history, physical examination and baseline exercise test. Patients were then instructed to continue beta-blocker or diltiazem; other cardiovascular medication, if not allowed, was discontinued.

Qualifying patients were randomized to receive a single oral dose of either placebo or ranolazine at one of four doses (10, 60, 120 or 240 mg) on two separate days a week apart. On each study day patients were to undergo exercise test after drug administration. It was planned to enroll 88 patients as 2 groups of 44 patients (group 1 = those on beta-blocker with short-acting nitrates/antiplatelet medication; group 2= diltiazem with short-acting nitrates/antiplatelet medication).

On Day 1, patients were inpatients at least 24 hours prior to coronary angiography; Day 2 was planned a minimum of one week later when the patient returned for results of their angiography. On Day 2 those who had received ranolazine would receive placebo, and vice versa.

Diltiazem administration was planned at 60 mg QID and metoprolol or atenolol dosing was planned at 100 mg QD unless sides effects/contraindications led to use of a lower dose.

Inclusion criteria:

1. Males or females, between 18-75 years, with chronic stable angina remaining symptomatic despite medical therapy;

2. Patients in sinus rhythm with at least 1 mm ST depression in one lead during prestudy stress test (absent digitalis use, LBBB or hypertrophy causing ST depression).

Reviewer's note: How "symptomatic" was not further defined. Dose of beta-blocker/calcium channel blocker (at which the patient was symptomatic) was not defined.

Exclusion criteria:

1. Termination of prestudy stress test for reasons other than angina (absent typical ECG changes);
2. Clinically significant arrhythmias or CHF;
3. Females of childbearing potential;
4. Use of investigational drug in the previous 28 days; previously entering this study; received group 1 or 2 medication for less than 7 days;
5. Current use of anticonvulsants or enzyme-inducing medication;
6. Alcohol or narcotic abuse;
7. Unwilling or unable to give informed consent.

Patient Withdrawal:

Patients who withdrew from the study were replaced, at the end of the study, by a patient on the same group medication at the same ranolazine dose in the same sequence.

Exercise test:

Exercise testing was planned at 2.5-3 hours (close to peak plasma ranolazine levels) post-drug administration. For each patient on the second day, all medication administration and exercise testing was planned at the same time points as the first study day (to within 30 minutes).

A bicycle exercise test was planned, starting with a load of 20 watts and increasing by 20 watts every minute until typical ST depression and angina occur. (MIBI tomospect scans were noted in the protocol to be documented in the CRF).

Blood samples for serum levels were to be drawn at peak (2.5-3 hours post drug administration) before and during peak exercise.

Efficacy measurements: During exercise testing: Heart rate, blood pressure (prior to exercise, at 50% of exercise, at maximum exercise, and at 2 minute intervals until return to within 10 mm Hg of baseline), exercise duration (if the patient discontinues for reasons other than safety, ST depression or angina, then the patient will be ineligible for analysis), ST depression 60 msec after the J point to the nearest 0.05 mV on computer averaged signals.

Statistics:

ANOVA was planned with effects of the additional medication, ranolazine dose, order of receiving ranolazine and placebo, and appropriate interactions (not specified in the protocol) included in the model. All tests were two-sided with a 5% level of statistical significance.

Amendments to the Protocol:

1. March 2, 1990: Study Day 2 could occur two days (instead of 7-14 days) after Study Day 1.
2. December 17, 1990: language added that optional scans should be quantified in the CRF; in addition, patients should be on cardiovascular medication for at least 7 days prior to study entry.
3. May 23, 1991: allowed 18 additional patients to be studied, to ensure that the 88 patients originally required were included from completed blocks.

Results:

Patient Disposition: A total of 106 patients entered the study. Of these patients, 62 were on beta blocker and 44 were on a calcium antagonist. No patients terminated early from the study.

Table 1. RAN 072: Patient disposition

	On beta blocker	On calcium channel blocker	Total
# receiving : Ran 10 mg	14	10	24
Ran 60 mg	15	11	26
Ran 120 mg	17	12	29
Ran 240 mg	16	11	27
Placebo/ranolazine	32	22	54
Ranolazine/placebo	30	22	52
# excluded from efficacy analysis	1 (pt #108/240 mg)	1 (pt #230/240 mg)	2

Source: Sponsor. * Pt #108 did not take his background beta blocker on study day 2. Pt #230 had unstable angina between eligibility ETT and the placebo period.

Baseline characteristics: This population was 100% Caucasian, majority male (about 60-80%) with a median age of 56-61 years (range 28-73 yrs). Mean pulse rates in the beta blocker group were 60-66 bpm and 66-78 bpm in the calcium channel blocker group; mean height, weight, rest systolic and diastolic blood pressures were similar between the two groups.

Concomitant medications: All of the patients on calcium channel blocker received diltiazem 60 mg TID. The patients on beta blocker received either atenolol (56 patients, 100 mg QD), metoprolol (5 patients, 200 mg QD) or propranolol (1 patient, 40 mg TID). Fifty-three percent of patients on beta-blocker and 59% of those on diltiazem also used aspirin. No imbalances were seen with regard to nitroglycerin use as a concomitant medication.

Efficacy: It should be noted that the median interval between study days was 5-7 days (range 1-17 days) for all doses of ranolazine whether on concomitant beta blocker or calcium channel blocker.

Exercise duration:

According to the sponsor, there were no significant sequence effects with regard to exercise duration. Exercise duration by dose (vs. placebo) is shown below.

Significant improvements compared to placebo are only seen in the 240 mg group (combined and on beta blocker). The percentage increase in exercise duration, time to 1 mm ST depression and time to angina were all consistent in that statistically significant improvements, compared to placebo, were seen at the 240 mg dose and in the group receiving beta blocker (but not calcium channel blocker) as background therapy. The time to angina analysis showed similar results whether patients who failed to reach angina on both study days were excluded or included. So too did the time to 1 mm ST depression show similar results whether patients who failed to reach 1 mm ST depression were included or excluded. However, a significant sequence effect (p=0.04) was seen in the analysis of time to angina. In this regard, the group randomized to placebo followed by ranolazine experienced a significant improvement with active drug (difference in exercise duration, Ranolazine minus Placebo, was 25.5 sec, p= 0.02) whereas the group receiving ranolazine followed by placebo performed better on placebo (Ranolazine minus Placebo was -4.46 sec, p=NS).

Reviewer comment : Patients experienced a longer time to angina on the second test (whether on ranolazine or placebo).

Table 2. RAN 072: Exercise duration (sec)

	N	Adjusted difference (R minus P)* (SE)	p-value
Beta blocker group:			
Ran 10 mg	14	7.21 (16.24)	NS
Ran 60 mg	15	21.28 (15.73)	NS
Ran 120 mg	17	5.11 (14.98)	NS
Ran 240 mg	15	39.42 (16.02)	0.02

Calcium channel blocker group				
Ran 10 mg	10		11.9 (19.22)	NS
Ran 60 mg	11		6.2 (18.4)	NS
Ran 120 mg	12		-8.82 (17.79)	NS
Ran 240 mg	10		33.8 (19.22)	0.08
Combined				
Ran 10 mg	24		9.56 (12.58)	NS
Ran 60 mg	26		13.74 (12.1)	NS
Ran 120 mg	29		-1.86 (11.63)	NS
Ran 240 mg	25		36.6 (12.51)	0.004

Source: RAN072 Table 5. *Ranolazine minus placebo. Differences were adjusted to account for imbalance of patients in each group on each sequence.

Table 3. RAN 072: Time to angina (sec) (all patients)

Ranolazine doses	N	Placebo	Ranolazine	Adjusted difference (R minus P)* (SE)	Statistical significance
10 mg	24	361.12	354.04	-5.84 (15.22)	NS
60 mg	26	377.81	387.5	8.42 (14.64)	NS
120 mg	29	354	357.55	-0.18 (14.06)	NS
240 mg	25	386.68	428.12	39.69 (15.13)	0.01

Source: RAN 072, Table 8. Sequence effect p=0.04. *Differences adjusted to account for imbalance in # patients in each group on each sequence.

Reviewer: Treatment effects by sequence were not submitted for exercise duration.

ST Depression and Exercise: There were no statistically significant differences in ST depression (ranolazine minus placebo) at rest, during exercise, and recovery for any single dose group/background therapy. A sequence effect was noted (p=0.01 for sequence, p=0.03 for group x sequence) where patients experienced more ST depression during the second sequence, whether on ranolazine or placebo.

Summed ST Depression: A trend in favor of ranolazine 240 mg (p=0.054) was seen with regard to summed ST depression. This trend was consistent in both beta blocker and diltiazem-treated groups.

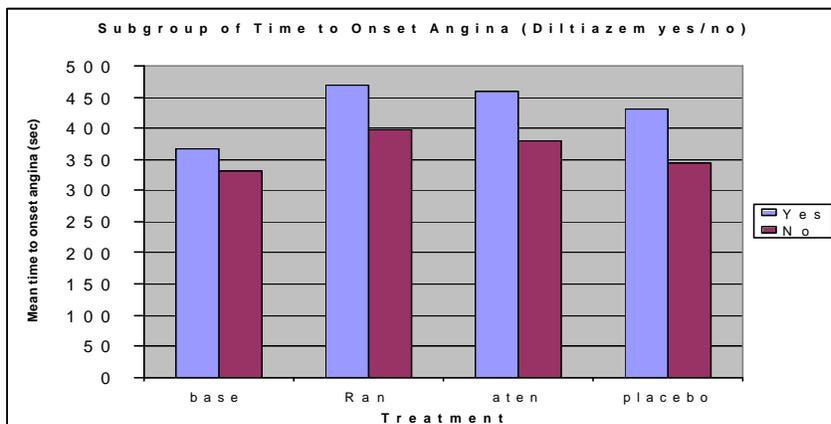
Heart rate:

At baseline, the mean HR for the group on beta blocker was about 59-68 bpm; the group on calcium channel blocker had a mean HR of about 69-84 bpm. At maximum exercise, the beta blocker group experienced mean HR in the 103-123 bpm range while the calcium channel blocker group experienced mean HR in the 124-143 bpm range. Similarly, the mean heart rate at recovery was 74-94 bpm for the beta blocker group and 94-115 bpm for the calcium channel blocker group. These results are consistent with expected effects of beta blockers (although patients do not appear maximally beta blocked).

In terms of ranolazine effects on heart rate, no gross pattern was seen at rest, during exercise or at recovery.

For each exercise category, four left bars represent beta blocker as background therapy. The legend represents ranolazine doses (10, 60, 120, 240 mg). During recovery, SBP was significantly reduced (p=0.01) in ranolazine + beta blocker (overall) vs. placebo.

Figure 1. Differences in SBP (vs. placebo) by dose, exercise, background therapy (ranolazine dose (mg) displayed in legend).

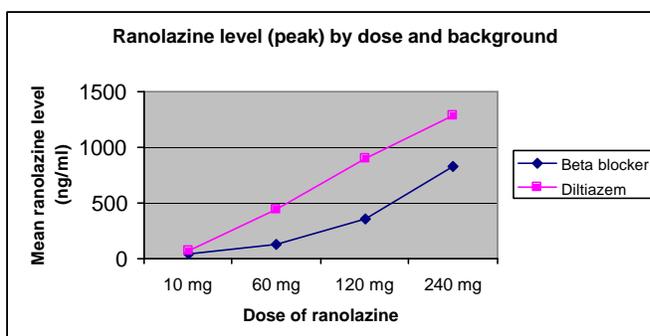


Blood Pressure Findings: Results for Systolic BP are graphically displayed. For diastolic BP, there was a statistically significant decrease in DBP at maximum exercise and recovery (calcium channel blocker group) in patients given placebo compared to ranolazine ($p=0.01$ and 0.03 , respectively). The difference in DBP was about 3 mm Hg.

Rate Pressure Product: In general, the RPP difference vs. placebo was larger in the group receiving calcium channel blockers (vs group on beta blockers); no striking pattern can be seen with regard to increasing dose. No statistically significant group, dose, sequence effects/interactions were cited by the sponsor.

Ranolazine assay: Increased serum levels are seen in the group taking diltiazem, as compared to the group on beta blocker.

Figure 2. Serum drug levels (peak) by dose and background



Safety: Please see the safety review for a detailed discussion of safety findings.

Reviewer Comments:

1. This was a single-dose placebo-controlled crossover study examining ranolazine IR doses up to 240 mg in patients with angina. Exercise testing was performed 2.5-3 hours post-dose.
2. A statistically significant improvement in exercise duration (at peak) was seen only in the ranolazine IR 240 mg group. Consistent with this finding were results for time to angina and time to 1 mm ST depression, also significant only in the ranolazine 240 mg group. A trend in favor of ranolazine was seen with respect to summed ST depression.
3. Statistically significant sequence effects were seen in the time to angina and ST depression measurements.
4. Higher peak serum ranolazine levels are noted in the diltiazem-treated patients.
5. No dose-related ranolazine effects are seen with regard to heart rate or resting/maximal blood pressure.

RAN 080:

Title: A Placebo-controlled Double-Blind Cross-over Comparison of the Efficacy of Ranolazine versus Atenolol in Patients with Chronic Stable Angina (Protocol date: November 12, 1991)

Objective: Compare the antianginal efficacy of ranolazine (IR) tid for one week with atenolol 100 mg once a daily for one week. Both drugs were to be compared with placebo.

Study Summary: This was a double-blind, randomized, placebo-controlled, double dummy, 3-way crossover study. Following a 7-10 day single-blind placebo (tid) period, eligible patients (via stress test)

were given one week of ranolazine 400 mg tid, atenolol 100 mg qd and placebo tid in random order. At the end of each week, a study day was scheduled (each study day 7-10 days apart) with exercise testing done 1 hour after drug administration at the same time of day at each clinic visit. Exercise testing was to be performed on a bicycle (2 sites) or a treadmill (the other study sites). No interim washout period was planned between treatment periods.

Table 1. RAN 080: Inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
<ol style="list-style-type: none"> 1. Informed consent; 2. Males or females, 18-75 years old; 3. Chronic stable angina responding to medical therapy (beta-blockers, calcium channel-blockers or long-acting nitrates)¹³ 4. Sinus rhythm with ECG signs of ischemia (≥ 0.1 mV ST depression in one lead during prestudy stress test) within 3-9 minutes after start of exercise; 5. Coronary artery disease confirmed by angiography or proven MI. 	<ol style="list-style-type: none"> 1. Termination of prestudy exercise test for reasons other than angina; 2. Clinically significant arrhythmias, or CHF; 3. Unstable angina or MI less than 1 month before placebo run-in; 4. Pregnant/breastfeeding/females of childbearing potential unless sterilized or taking adequate contraception; 5. Investigational drug in previous 28 days; taking part in another clinical study; previously entering this study; 6. Use of anticonvulsants/enzyme-inducing medication; 7. Alcohol/narcotic abuse; Hepatic/renal dysfunction; Unable to stop beta-blocker therapy; Sensitivity/allergy to beta-blocker; History of cerebral hemorrhage, thrombosis or aneurysm; Pulmonary hypertension; Surgically curable hypertension or malignant hypertension; COPD; Pacemaker.

Concomitant medication:

Allowed medications included long and short-acting nitrates and calcium antagonists except verapamil (and other cardiac depressant calcium antagonists). Prohibited medications were to be discontinued 24 hours prior to beginning placebo washout. Short-acting nitrates were not to be taken within 6 hours of the exercise test.

Exercise testing:

All exercise testing was planned 1 hour post-dose.

Bicycle:

Bicycle testing was performed with a starting load of 20 watts, increasing by 20 watts every minute until typical ST depression and angina occur.

Treadmill:

Treadmill testing was planned using a Bruce protocol¹⁴, beginning at 1.7 mph/0% grade, increasing to 1.7 mph/5% grade and 1.7 mph/10% grade at 3 minute stages.

Efficacy evaluations (during exercise testing):

1. Heart rate;
2. Blood pressure;
3. Rate-pressure product
4. Time to angina;

¹³ The protocol (p.3) specifically defined improvement with medical therapy as: 1. patients whose medical treatment was optimized using available exercise testing; 2. newly diagnosed patients with at least 30 sec improvement in time to angina on repeat exercise testing after a standard dose of beta-blocker or calcium antagonist; 3. secondary referral patients with at least 30 sec decrease in time to angina after withdrawal of one anti-anginal medication.

¹⁴ Reviewer: this is actually a modified Bruce protocol. A standard Bruce protocol would have involved a 10% grade (not 0%) at Stage 1.

5. Time to 0.1 mV ST depression;
6. Maximal ST depression (mV);
7. Exercise duration;
8. ST depression after 1 and 5 minutes of recovery;

Additional efficacy evaluation included nitroglycerin consumption and the number of anginal attacks (via diary).

A full ECG analysis of the whole stress test was done as a quality control.

Statistics:

The primary efficacy variable was time to angina (other variables: exercise duration, time to 1 mm ST depression, maximum ST depression, integrated ST depression). With a 90% power and significance level of 5%, 82 patients were felt needed to detect a 0.5 minute difference between any pair of treatments in the time to angina; this calculation was based on an estimated within patient SD of 0.983 (from study RAN 072).

Patients who fail to reach angina on all 3 study days will be excluded, while those who fail to reach angina on one or two study days may be substituted for time to angina, depending on how many patients this involves. A secondary analysis will be performed which substitutes exercise duration for all patients who fail to reach angina on any study day. If a large number of patients are protocol violators or noncompliant, this secondary analysis will be repeated, excluding those patients.

The number of angina attacks and nitroglycerin use will be listed and summarized but not formally analyzed.

The exercise protocols were designed to ensure that angina will occur at approximately the same time for a patient, regardless of the method of testing. Since some sites will use bicycle testing, center will be included in the analysis.

Data from those patients who fail to complete one or more phases of the study will still be included in the analysis.

The integrated ST depression will be calculated as the area under the ST depression/time curve. Rate pressure product will be calculated as heart rate x SBP.

Efficacy variables will be analyzed using ANOVA model, including treatment, period, center, subject within center and the treatment by center interaction. If the number of subjects within centers is small, the centers may be pooled.

All statistical tests were two-tailed, with a 5% level of significance. No adjustments for multiple comparisons were made.

Interim assessment: An interim assessment of safety was initially planned when data were available on approximately half of the total patients recruited. If assessment indicated unsatisfactory tolerability, then the study could be terminated or the ranolazine dose reduced to 320 mg tid for the remaining patients (see Protocol Amendment).

Protocol Amendments:

1. (March 26, 1992): Added double-blind placebo blister packs to that drugs, for patients who withdraw prior to active treatment phase, can be reused. Changed inclusion criterion for angiographic confirmation of CAD to include angiography prior to 12 months, or history of proven MI.
2. (May 14, 1992): Added bilirubin to testing. Interim safety assessment plan changed to occur instead when an excess of adverse events was noted on a blinded safety review. No statistical testing was planned during this interim assessment. If tolerability to ranolazine was unsatisfactory, then the study would be terminated or the dose reduced to 320 mg tid for the remaining patients.
3. (December 8, 1992): Allowed the use of long-acting nitrates.

Results:

Patient Disposition:

A total of 163 patients were enrolled, and 158 patients were randomized; 155 received ranolazine, 154 received atenolol and 154 received placebo. Of the 158 patients, 117 were considered to be evaluable for

the primary efficacy variable. Most common reasons for non-evaluability were: missing time to angina on all 3 active treatment studies, and failing to complete all 3 active treatment phases. A total of 152 patients completed all three study days. Four patients (2 on ranolazine, 2 on placebo) were terminated due to AE¹⁵; one patient (atenolol) was lost to follow-up, and one patient (ranolazine) was inappropriately enrolled. Of those randomized, 135 patients entered RAN081 follow-up study.

Baseline characteristics:

The study population was 89% male and 99% Caucasian, with mean age 59 yrs, weight 79 kg, BP 139/83 mm Hg, pulse 71 bpm. Ninety nine percent were on concomitant medications at any visit. Of 158 patients, 74% percent were taking aspirin; about 31% took concomitant nitroglycerin, 24% were on isosorbide dinitrate, 54% were on calcium channel blockers (27% were on diltiazem). Over 85% of patients experienced 4-10 day intervals between study visits. No imbalances between treatment groups was seen.

Efficacy:

Of note, 43 patients were tested with the bicycle method (3 sites); 74 patients were tested with the treadmill method.

Primary Efficacy Variable: Time to onset of angina is shown below. The mean difference between ranolazine and placebo was 51 sec with a 95% CI (34.2, 67.8) over zero and a p-value of < 0.001. A significant improvement in time to angina was also seen with atenolol. Similar results were seen with an analysis of evaluable patients (in the evaluable population, treatment by method interaction = NS and treatment by investigator interaction p=0.08).

Table 2. RAN 080: Time to Onset of Angina (all patients)

	Baseline (N=158)	Ranolazine (N=153)	Atenolol (N=153)	Placebo (N=152)
Mean time to onset angina (sec)* (SE)	342	409 (6)	398 (6)	358 (4)
Range (sec)	91-720	120-900	138-780	60-780

Source: Table 10. *Mean was adjusted for imbalance in number of patients receiving each treatment in each center. Treatment by investigator interaction p < 0.001; treatment by method interaction p=0.01

A **first period analysis** of the time to onset of angina also showed a significant improvement with ranolazine (mean difference 39 sec, 95% CI (7, 72), p=0.02) vs. placebo. A significant improvement vs. placebo was also seen with atenolol.

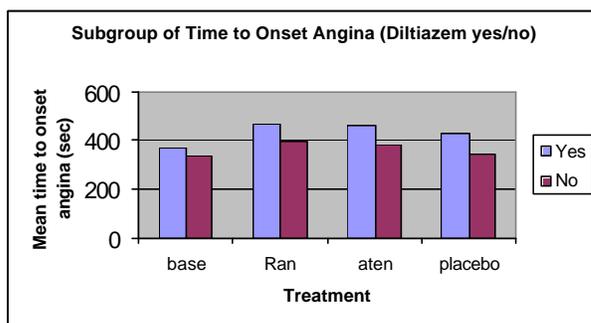


Figure 1. Time to onset angina by Diltiazem use

Please note that the number of patients taking diltiazem is 35-40 per treatment group, and the number not on diltiazem is 116-118 per treatment group. The means are not adjusted. There was no stratification for diltiazem use and no prespecified subgroup analysis.

¹⁵ The ranolazine AE were leukemia (patient #225) and chest pain (#105). The two placebo AE were chest pain (#130) and angina (#227).

Other variables:

Exercise duration:

The mean difference in exercise duration for ranolazine-placebo was 37.1 sec (95% CI 22.2, 52; $p < 0.001$). A significant improvement in exercise duration was also seen with atenolol. There were also significant treatment by investigator ($p < 0.001$) and treatment by method interactions ($p = 0.02$). Three sites (56 patients) used bicycle exercise tests; the other six sites (97 patients) used the treadmill. While the two groups are numerically unequal, it appears that treatment effects are not as obvious with bicycle testing. Even on placebo, duration of exercise is shorter.

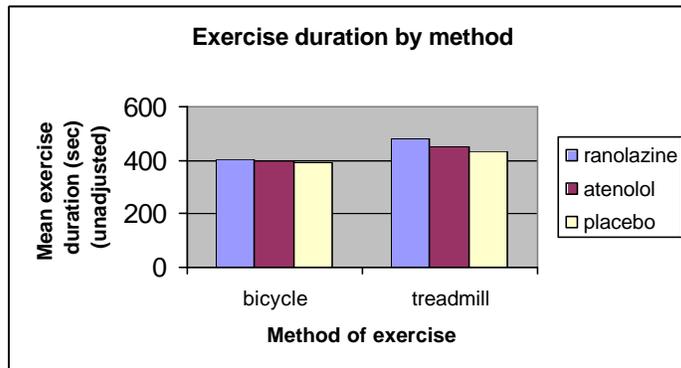


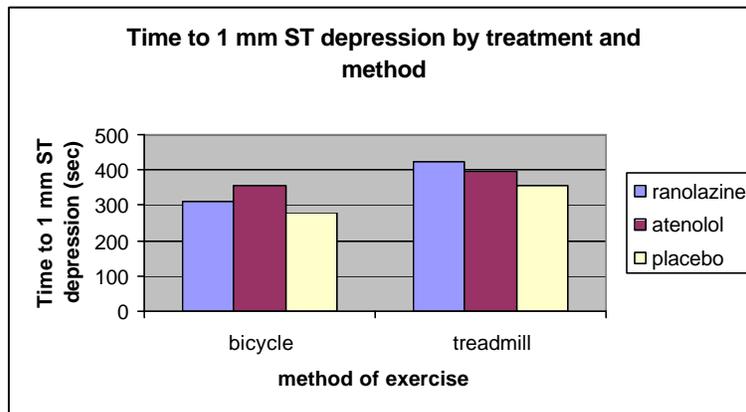
Figure 2. Exercise duration by method of testing.

Time to 1 mm ST depression

The mean difference in time to 1 mm ST depression for ranolazine vs. placebo was 52.6 sec (95% CI 34.8, 70.5; $p < 0.001$). Results for atenolol were favorable and statistically significant as well. There were significant treatment by investigator ($p < 0.001$) and treatment by method ($p = 0.002$) interactions. Results for the evaluable population were similar.

Figure 3. Time to 1 mm ST depression by method

Means are unadjusted. Time to ST depression is longer with the treadmill method for all groups, including placebo.



Ranolazine vs. atenolol:

For the primary endpoint, time to 1 mm ST depression, and exercise duration (evaluable patients) there were no significant differences between ranolazine and atenolol. For the parameter exercise duration (all

patients), there was a significant¹⁶ improvement with ranolazine vs. atenolol (mean difference = 21.1 sec, 95% CI = 6.2, 36.0, p-value =0.006). However, results were not consistent across centers (p <0.001). In one site (Dr. Cocco's center¹⁷), the difference between ranolazine IR and atenolol was 107 seconds in ranolazine's favor.¹⁸

There were also significant differences in heart rate (greater mean decrease in heart rate in the atenolol group) both at rest, onset of angina, and end-exercise. Significant differences were seen vs. atenolol with respect to ST segment value at rest and maximum ST depression (greater depressions with atenolol).

Reviewer: For the primary endpoint, no superiority over atenolol was demonstrated. In addition, for ST segment value at rest, as well as maximum ST depression, there were significant treatment by investigator interactions of these measurements (p=0.001) indicating heterogeneity of results.

Heart rate: A significant decrease in heart rate was seen with respect to atenolol-treated patients compared to those on placebo. The mean difference for ranolazine-placebo was 1.5 bpm (p=NS). A significant (p< 0.001) treatment by investigator interaction was noted. Similar results were obtained with respect to heart rate at the end of exercise.

Blood Pressure (BP):

The mean ranolazine-placebo difference for resting systolic BP was -0.5 mm Hg (p=NS) and for diastolic BP 0.2 mm Hg (p=NS); there was a statistically significant reduction, vs. placebo, in resting SBP and DBP for atenolol-treated patients. At end of exercise, mean SBP was higher with ranolazine compared to placebo. The mean R-P difference was 4.7 mm Hg (95% CI 0.8, 8.7; p=0.02). The treatment by investigator interaction was significant at p < 0.001. For DBP the mean R-P difference was 0.6 mm Hg (p=NS).

Rate Pressure Product (RPP): Compared to placebo, the mean RPP was significantly reduced with atenolol and mildly (not significantly) increased with ranolazine. At end of exercise, the RPP was significantly increased in the ranolazine group (mean difference vs. placebo was 1261 bpm*mmHg, p=0.005) and significantly decreased in the atenolol group (mean difference vs. placebo was -6797 bpm*mm Hg, p<0.001). The treatment by investigator interaction was significant (both at rest and end of exercise) at p < 0.001).

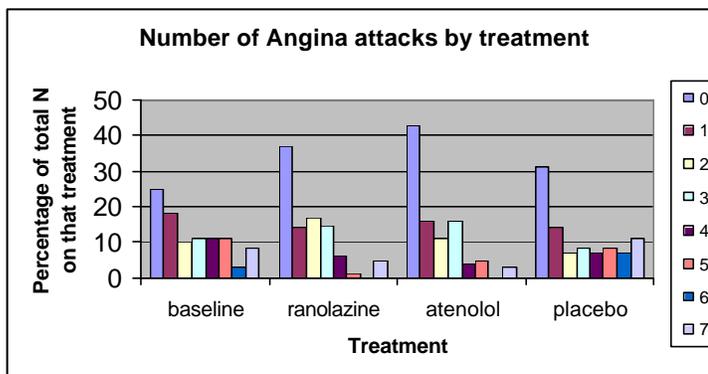


Figure 4. Angina attacks by treatment.

The legend refers to number of anginal attacks. No adjustments were made to allow for different lengths of time on treatments.

¹⁶ The p-values were calculated from pairwise comparisons from ANOVA models appropriate to 3 period crossover design; no adjustments were made for multiple comparisons.

¹⁷ Dr. Cocco's study site was also noted in Study RAN 081.

¹⁸ In fact, if one looks at the data from Dr. Cocco's site, the mean baseline exercise duration is 389 (149.3) seconds. The group on atenolol experienced a mean exercise duration of 389.1 (139.6) seconds.

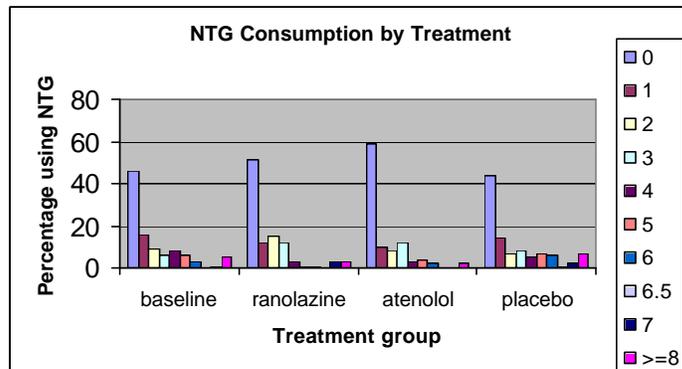


Figure 5. Nitroglycerin consumption by treatment

The legend refers to the number of NTG used. No adjustments have been made to allow for differing lengths of time on treatment.

Plasma Levels:

There were a total of 143 plasma concentrations from the 155 patients on ranolazine IR. The mean plasma concentration was 2039 ng/ml (range < 5 to 5750 ng/ml). One patient (number 199) had a concentration below detection. For 9 patients, no plasma concentrations were available because of interfering peaks in the samples. Three patients did not provide plasma samples.

Forty patients (28%) were on concomitant diltiazem; the overall mean plasma concentration for this group was 2529 (range 47-5750) ng/ml. One hundred three (72%) were not taking concomitant diltiazem. The overall mean plasma concentration was 1850 (range <5 – 4340) ng/ml for this group.

Reviewer comments:

1. This was a placebo-controlled, 3-way crossover study of one week of ranolazine IR 400 mg TID vs. atenolol vs. placebo. No interim washout period was used.
2. Two different exercise methods were used and may have confounded some of the results.
3. In some of the efficacy variables, treatment differences were not consistent in all centers and there were significant treatment by investigator interactions.
4. Ranolazine significantly improved the time to angina at approximately 1 hour post-dosing (primary endpoint) compared to placebo. The first period analysis supported this finding and was also statistically significant.
5. Ranolazine did not demonstrate superiority over atenolol with respect to the primary endpoint. A significant improvement in exercise duration (all patients but not evaluable population) was seen with respect to ranolazine vs. atenolol.

RAN 1514:

Title: A Double-Blind, Placebo-Controlled, Extended-Period Crossover Study to Assess the Efficacy and Safety of Three Dosing Regimens of Ranolazine in Patients with Chronic Stable Angina Pectoris (Vol. 317-318) (Final Protocol May 1, 1992).

Primary Objective: Determine, in patients with chronic stable angina, the trough effect on treadmill time to onset of angina of the following doses of ranolazine: 267 mg tid, 400 mg bid, and 400 mg tid.

Secondary Objectives:

1. Compare, in patients with chronic stable angina, the peak effect (1 hour postdose) of these 3 dosing regimens on treadmill time to onset of angina, as well as effects at peak and trough on total duration of exercise and time to 1 mm ST depression or change;
2. In addition, analysis of the following parameters was planned: plasma ranolazine concentration at trough and peak (1 hour postdose); number of anginal attacks/week; number of sublingual nitroglycerin tablets consumed/week.

Patient population: Patients with stable effort angina pectoris responding to medical therapy.

Study Summary:

This multicenter, Latin square, crossover study consisted of two phases: a single-blind placebo qualifying phase (2-7 weeks) and a placebo-controlled double-blind treatment phase (total of 5 weeks). Each patient received single-blind placebo for 2-7 weeks; during this time, patients were taken off one or more of their antianginal medications, beginning with long-acting nitrates, and underwent treadmill testing at each visit. Only patients whose time to angina shortened by at least 1 minute upon discontinuation of one or more antianginal therapies was allowed into double-blind. When a third drug was discontinued to meet the time decrease criteria, one of the three drugs should have been associated with a reduction in time to onset of angina of a minimum of 30 seconds. During double-blind, three regimens of ranolazine (as noted above, under primary objective) and placebo will be administered, each for one week, with the fourth period repeated during a fifth period; trough and peak treadmill performance was assessed at each visit. Blood samples were collected for trough and peak ranolazine levels.

In addition, information regarding anginal episodes and nitroglycerin consumed/week was collected.

Table 1. RAN 1514: Schedule of Assessments

Phase	Single-blind placebo			Double-blind phase					Early withdrawal***
	1	2¶	3	4	5	6	7	8	
Week	0	1-2	2-7	8	9	10	11	12	
Consent	X								
History	X								
Physical	X							X	X
Concom. Meds (chge)		X		X	X	X	X		
Concom. Meds (all)			X					X	X
AE		X	X	X	X	X	X	X	X
AP freq/NTG use		X	X	X	X	X	X	X	X
ETT screening	X								
ETT qualifying		X	X						
ETT peak									
ETT trough									X
Plasma peak/trough				X	X	X	X	X	X**
12-lead ECG	X	X	X	X	X	X	X	X	X
Lab tests*	X			X	X		X	X	X

*Liver panel at trough only at Visits 4, 5, 6, 7. Urinalysis at Visits 1 and 8 or upon early withdrawal.

**Plasma trough level only upon early withdrawal (only if patient has received double-blind medication).

¶ If the time to angina on the second stress test is not at least 1 minute shorter that that seen on the first stress test, Visit 2 can be repeated up to 2 additional times.

***Only if early withdrawal occurs after patient received double-blind medication.

Exercise Treadmill Test (ETT):

All patients underwent treadmill tests, done 7-10 am (prior to am dose for the trough study) and 1 hour post-dose (peak study). Each patient was to have ETT done at the same time of day throughout the study; patients were required to stop smoking 2 hours before testing, wear similar clothing for each test, and avoid sublingual nitroglycerin 60 minutes prior to testing. A light breakfast was allowed up to 1 hour prior to testing. A modified Bruce protocol was used.

Trough was defined as either 8 hours post-dose for the tid regimen and 12 hours post-dose for the bid regimen.¹⁹

Table 2. RAN 1514: Inclusion/Exclusion criteria

Inclusion criteria	Exclusion criteria
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¹⁹ The reviewer has questioned how the different regimens of exercise testing, including timing of trough ETT, affected “blinding.” During double-blind, patients took 1 capsule four times a day. According to the sponsor (verbal communication), ETT at trough was done 8 hours after the last dose.

<p>Single-blind placebo phase:</p> <ol style="list-style-type: none"> 1. At least 21 years old; 2. At least 3 month history of chronic stable effort angina relieved by rest/sublingual nitroglycerin and improved (by symptoms or ECG signs of ischemia) with medical therapy (beta blocker, calcium channel blocker and/or long-acting nitrate); 3. Signed approved informed consent. <p>Double-blind phase:</p> <ol style="list-style-type: none"> 1. Time to angina during first exercise test (before any antianginal med is discontinued) is at least 3 and not more than 13 minutes; 2. After withdrawal of \geq one antianginal medications, the patient shows a decrease in ETT time to angina of at least 1 minute; if a 3rd drug is discontinued, discontinuation of at least one of these drugs should have resulted in a reduction in time to angina of a minimum of 30 sec. 3. Definite ECG signs of ischemia ($>$ 1 mm ST depression in one lead) during the ETT that meets the 1 minute time criteria as above; 4. ETT time to angina for the last 2 consecutive qualifying ETT(t2 and t3) does not differ by more than 15% of t2; 5. Reason for stopping ETT should be angina; 	<ol style="list-style-type: none"> 1. Factors interfering with ECG interpretation or causing false positive result; 2. NYHA Class III-IV CHF; 3. Significant valvular heart disease or septal defects; 4. Unstable angina; 5. 2nd or 3rd degree AV block or uncontrolled arrhythmia other than sinus or occas. extrasystoles; 6. MI within past 3 months; 7. Ongoing acute myocarditis/pericarditis; 8. Cardiomyopathy; 9. Condition likely to hinder or confuse follow-up; 10. Significant lab abnormality; 11. Cannot discontinue digoxin or long-acting nitrates; 12. Participation in another investigational drug study within 1 month of entering this study; 13. Pacemaker; 14. Labile diabetic or subject to hypoglycemia; 15. Childbearing potential.
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Efficacy Parameters:

The primary efficacy parameter was time to onset of angina at trough. Duration of exercise will be used if angina is not attained.

Secondary efficacy parameters:

1. Time to onset of angina at peak; duration of exercise will be used if angina is not attained;
2. Duration of exercise at both peak and trough;
3. Time to 1 mm ST depression or change from rest, at both peak and trough; duration of exercise will be used if ST change is not attained;

Analysis Plan:

According to the protocol, the primary analysis was an analysis of all patients contained in complete (evaluable) squares. All continuous treadmill data was to be analyzed using an extended-period Latin Square ANOVA model with the following effects: investigator, patient within investigator, period, previous treatment, treatment, investigator by period interaction, investigator by previous treatment interaction, and investigator by treatment interaction. For the primary and secondary parameters at trough, a first period analysis, including only those patients with valid baseline and first period double-blind treatment data was planned. There were prespecified criteria for pooling.

Sample Size: 240 patients planned in order to obtain 192 evaluable patients.

Protocol Amendments:

1. June 5, 1992: Added as exclusions: supine DBP $>$ 100 mm Hg or SBP $<$ 100 mm Hg; labile diabetic or subject to hypoglycemia (otherwise, changes appeared to be minor);
2. April 28, 1993: 1) Analysis changed from “all patients with valid data during double-blind” to all patients who had any data during double-blind.” 2) Added supplemental complete squares analysis of monotherapy patients (with different pooling criteria).

Results:

Patient Disposition: Forty nine sites (42 in US, 5 in Canada, 2 in Mexico) enrolled 318 patients. A total of 29 patients (9.1%) withdrew prematurely. The mostly common reason for withdrawal was adverse event/new or worsening illness/lab abnormality (total of 15 patients, 3 on placebo and 12 on a treatment of ranolazine).

Baseline characteristics: Majority (72%) male, 86% Caucasian (7% Black), about half were 65 years and older; mean age was 64.2 years, mean weight 82 kg, 83% were nonsmokers and 96% had a history of noncardiovascular disease at entry. Patients had a history of angina for a median of 5.8 years; 43% had a history of MI, 32% underwent prior CABG, and 100% had used cardiovascular medication during the last month. Forty-one patients in this study were taking concomitant diltiazem.

Of the 318 patients, 312 had both trough and peak ETT data and were included in the all-patients analysis. Of those 312 patients, 260 and 248 patients were considered evaluable for the ETT per-protocol analyses at trough and peak, respectively.

Efficacy:

Results of the primary efficacy parameter are shown below. While mean time to angina, duration of exercise and time to 1 mm ST depression trend in favor of ranolazine (ie, mean differences are positive vs. placebo), the primary endpoint does not achieve a statistically significant result and the null hypothesis is not rejected. The only statistically significant trough parameter is a pooled “all ranolazine regimens” vs. placebo for time to 1 mm ST depression. The per-protocol complete squares analysis was similar, except the time to 1 mm ST depression did not make statistical significance for all ranolazine vs. placebo (p=0.06, trend in favor of ranolazine).

Table 3. RAN 1514: Trough Endpoint ETT Pairwise Treatment Comparisons (all patients analyses)

Parameter	Statistic	Ran 400 BID-DB placebo	Ran 267 TID-DB placebo	Ran 400 TID-DB placebo	All ranolazine regimens-DB placebo
Time to onset angina (min)	Mean difference (SE)	0.18 (0.12)	0.19 (0.12)	0.07 (0.12)	0.15 (0.10)
	95% CI	-0.06, 0.42	-0.05, 0.43	-0.17, 0.31	-0.05, 0.34
	p-value	NS	NS	NS	NS
Duration of exercise (min)	Mean difference (SE)	0.05 (0.09)	0.06 (0.09)	0.10 (0.09)	0.07 (0.07)
	95% CI	-0.13, 0.23	-0.11, 0.24	-0.08, 0.27	-0.07, 0.21
	p-value	NS	NS	NS	NS
Time to 1 mm ST depression (min)	Mean difference (SE)	0.19 (0.13)	0.18 (0.13)	0.27 (0.13)	0.21 (0.11)
	95% CI	-0.07, 0.45	-0.08, 0.44	0.01, 0.53	0.003, 0.42
	p-value	NS	NS	NS	0.047

Source: Sponsor, Table 18. All statistics based on ANOVA. Significant investigator and period effects were seen with regard to the primary endpoint and duration of exercise (all p < 0.01); significant investigator effects were seen with regard to time to 1 mm ST depression (p<0.01) (Source: Table 16) DB placebo= double-blind placebo

Results at peak levels of ranolazine are shown in the following table. The per-protocol complete squares analysis showed improvements in mean time to angina that were only significant for the “all ranolazine” regimen column vs. placebo.

Table 4. RAN 1514: Peak Endpoint ETT Pairwise Treatment Comparisons (all patients analyses)

Parameter	Statistic	Ran 400 BID-DB placebo	Ran 267 TID-DB placebo	Ran 400 TID-DB placebo	All ranolazine regimens-DB placebo
Time to onset angina (min)	Mean difference (SE)	0.32 (0.13)	0.39 (0.13)	0.32 (0.13)	0.34 (0.10)
	95% CI	0.07, 0.57	0.14, 0.64	0.07, 0.57	0.14, 0.55
	p-value	0.013	<0.01	0.012	<0.01
Duration of exercise (min)	Mean difference (SE)	0.07 (0.09)	0.20 (0.09)	0.17 (0.09)	0.18 (0.07)
	95% CI	-0.01, 0.34	0.03, 0.38	-0.002, 0.34	0.04, 0.32
	p-value	NS	NS	NS	0.013
Time to 1 mm ST depression (min)	Mean difference (SE)	0.28 (0.12)	0.41 (0.12)	0.36 (0.12)	0.35 (0.10)
	95% CI	0.05, 0.52	0.17, 0.65	0.13, 0.60	0.16, 0.55
	p-value	0.02	<0.01	<0.01	<0.01

Source: sponsor, Table 27. All statistics based on ANOVA. DB placebo= double-blind placebo. Significant period effects ($p < 0.01$) were seen with regard to duration of exercise and time to 1 mm ST depression; a significant investigator x treatment effect ($p = 0.03$) was seen with regard to time to onset angina (Source: Table 28).

According to the sponsor, there were no significant carryover effects for either peak or trough analyses. Significant period effects, however, were seen for the duration of exercise and time to 1 mm ST depression at times of peak ranolazine concentration.

A first-period analysis showed no statistically significant difference for peak or trough time to angina, exercise duration or time to 1 mm ST depression. No treatment-by-period analysis was submitted. Hence, a treatment-by-period interaction cannot be excluded by the reviewer.

Table 5. RAN 1514: Peak exercise treatment change from baseline to endpoint pairwise treatment comparisons: First period per-protocol analyses (n=304)

		Ran 400 mg bid vs. DB placebo	Ran 267 mg tid vs. DB placebo	Ran 400 mg tid vs. DB placebo
Time to Onset of Angina (min)	Mean difference (SEM)	0.78 (0.43)	0.59 (0.43)	0.43 (0.42)
	95% CI	-0.07, 1.63	-0.25, 1.43	-0.40, 1.27
Duration of exercise (min)	Mean difference (SEM)	0.39 (0.3)	0.29 (0.3)	0.13 (0.29)
	95% CI	-.20, 0.98	-0.29, 0.88	-0.45, 0.71
Time to 1 mm ST depression (min)	Mean difference (SEM)	0.40 (0.38)	0.94 (0.38)	0.48 (0.38)
	95% CI	-.35, 1.15	0.19, 1.68	-.26, 1.22

Statistics were estimated by the sponsor from ANOVA. The overall test was not significant.

Other efficacy parameters:

Other analyses were presented as per-protocol complete squares analyses. Trough ETT reasons for cessation are presented below (for peak ETT, 72-79.4% of ranolazine patients stopped due to angina, vs. 83.2% on double-blind placebo). The median difference in weekly rate of anginal attacks and nitroglycerin consumption was 0.0 for ranolazine treatment comparisons vs. placebo (hence no meaningful difference).

Table 6. RAN 1514: Trough ETT cessation reasons by treatment (per-protocol complete squares analyses) (n (%)) (reasons occurring > 3%)

	Placebo (single-blind)	Placebo (double-blind)	Ran 400 mg BID	Ran 267 mg Tid	Ran 400 mg TID
Total # ETT performed	260	325	325	325	325
Angina	260 (100%)	283 (87%)	274 (84%)	270 (83%)	274 (84%)
Fatigue	6 (2)	61 (19)	63 (19)	68 (21)	64 (20)
Dyspnea	6 (2)	28 (9)	29 (9)	24 (7)	27 (8)
ST deviation	9 (4)	13 (4)	11 (3)	10 (3)	11 (3)

Source: sponsor, table 31.

Hemodynamic data: For trough ETT results, investigator effects (ANOVA $p < 0.01$) were seen with regard to maximum workload double product and maximum workload heart rate. A significant treatment effect ($p < 0.01$) was seen for standing heart rate. The pattern of standing HR results was graphically similar to that seen with trough double-product (shown below); mean changes were < 2 beats per minute and no significant changes in standing heart rate were seen. Otherwise, no hemodynamic patterns were seen by the reviewer. Hemodynamic data for peak ETT showed decreases in maximum workload double product, heart rate and SBP, as well as standing double product, heart rate and SBP for all ranolazine doses vs. double-blind placebo. Statistical significance was only achieved in the “all ranolazine regimens” vs. placebo for maximum workload double product and SBP.

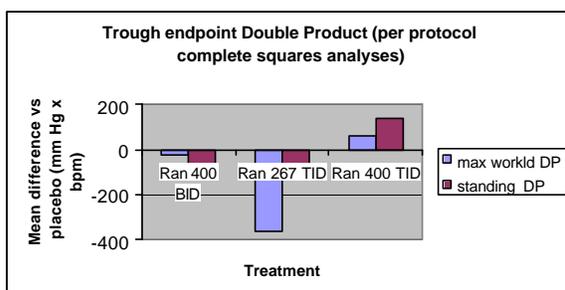
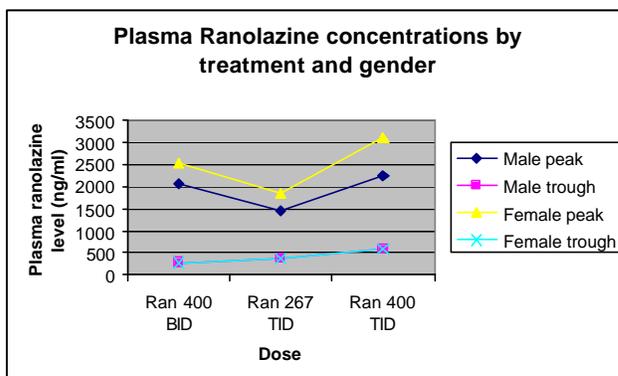


Figure 1. Trough ETT double product comparison vs. placebo (per protocol complete squares analysis)

Figure 2. Ranolazine peak/trough levels by treatment and gender



The sponsor’s analysis of plasma ranolazine levels showed an increase in peak levels for females but not males (trough levels for both genders are superimposable per figure).

Additional analysis: A gender subgroup analysis showed statistically significant improvements in all ranolazine groups (peak ETT per protocol complete squares analyses) for males but confidence intervals that crossed zero for all ranolazine doses for females (parameters measured included: time to angina, duration of exercise and time to 1 mm ST depression).

Safety: please see the Safety Review.

Reviewer Comments:

1. This was a placebo-controlled crossover study comparing IR ranolazine 400 mg BID, 267 mg TID and 400 mg TID.
2. There was no statistically significant improvement in the primary efficacy parameter vs. placebo. Mean comparisons vs. placebo for the primary efficacy parameter trended toward improvement with ranolazine.
3. Significant period and investigator effects were seen ($p < 0.01$) with regard to the primary endpoint.
4. Statistically significant results were seen with respect to time to onset of angina and time to 1 mm ST depressions at peak. However, a significant period effect were seen with respect to the time of onset of angina at peak, and the first period analysis did not show a statistically significant treatment effect. No treatment-by-period analysis was submitted. A treatment-by-period interaction cannot be excluded.

RAN 081

Title: An Evaluation of the Long-Term Efficacy and Safety of Ranolazine in Patients with Angina Pectoris. (protocol date November 21, 1991; protocol amendments: December 19, 1991, January 22, 1992, May 14, 1992, March 8, 1993).

Objectives:

1. safety and tolerability of long-term ranolazine (IR) administration over a one year open-label phase. Appropriate patients may be continued for a second year;
2. assess effects of ranolazine withdrawal after stabilization of patients on their maximum tolerated dose of ranolazine on anginal symptoms and exercise capacity by performing a one-week, double-blind, withdrawal phase.

Study Summary: This study was designed as a follow-on from study RAN 080, which evaluated short-term ranolazine efficacy compared with atenolol. This study consisted of an open-label titration phase to achieve optimal medical control of anginal symptoms. One month after stabilization of therapy, an ETT at peak will be performed before and after a one week double-blind withdrawal period during which patients will be randomized to either ranolazine or placebo. All patients will then continue on ranolazine for up to 1 year. Hematology and chemistry labs will be done entry into RAN 080 and after 2 weeks in RAN 081, at 3, 6 and 9 months, at the end of the double-blind withdrawal phase and at one year. Twelve-lead ECGs were planned at both withdrawal visits as well as Week 2, and Months 3, 6, and 9.

All ETT were planned at 1 hour post-dose and, depending on the center, were either treadmill (modified Bruce protocol) or bicycle (starting load 20 watts, increasing by 20 watts every minute until ST depression and angina occur).

Allowed concomitant medications: short-acting nitrates were permitted as escape medication, long-acting nitrates and calcium channel blockers were allowed as background therapy if used during RAN 080. Beta blockers were not permitted.

Patient population: up to 108 eligible patients will be entered.

Inclusion criteria: successful completion of RAN 080 with reasonable compliance and without severe adverse events.

Notable Exclusion criteria: clinically significant arrhythmias or CHF, unstable angina/MI less than one month prior to RAN 080, pregnant/breastfeeding women, investigation drug use other than ranolazine in past 28 days, hepatic/renal dysfunction, significant lab abnormalities in RAN 080, cerebral hemorrhage/thrombosis/aneurysm, pulmonary hypertension, COPD, pacemaker.

Efficacy data: these data were obtained following the two exercise tests performed before and after the 1-week double-blind withdrawal period:

Time to angina, Exercise duration, Time to 1 mm ST depression, Maximum ST depression, Integrated ST depression.²⁰

Hemodynamic data included: Heart rate, SBP and DBP, Rate pressure product²¹.

Other: nitroglycerin consumption and number of angina attacks were collected from diary cards.

Analysis plan:

According to the protocol, the time to angina (peak) was listed as primary analysis. For this variable, those patients failing to reach angina pre- and post-withdrawal phase were to be excluded; for patients failing to reach angina on one of the two days, exercise duration may be substituted for time to angina. A planned secondary analysis would substitute exercise duration for all patients failing to reach angina on any study day; if there were a large number of protocol violators/noncompliant (< 70%) patients, this secondary analysis would be repeated, excluding those patients.

All statistical tests were two-tailed, with a 5% level of significance. The statistical significance of within-treatment group changes would be tested using the paired t-test. Between treatment group changes were compared using ANOVA with terms for center, treatment (during double-blind withdrawal) and treatment by center interaction.

Safety: adverse events, laboratory tests

Protocol amendments:

1. (Dec. 1991): added chemistry tests at months 3, 6, and 9.
2. (Jan. 1992): minor changes.
3. (June 1992): added hemodynamic data collection for each ETT; added hematology and chemistry testing prior to ETT;
4. (March 1993): added option to continue ranolazine for a second year.

Results:

According to a Syntex Interim Report dated December 1994 (study period March 1992-December 1993), 135 patients in 9 centers (119 males and 16 females), aged 41-77 years, received open-label ranolazine. Of this group, 66 received ranolazine and 60 placebo during the double-blind withdrawal period; nine patients were not randomized. Sixty-six ranolazine and 59 placebo patients were included in the safety analyses for double-blind withdrawal period and the "all patients" efficacy analyses. Fifty nine ranolazine and 50 placebo patients were evaluable for efficacy analysis of double-blind withdrawal period.

Six centers used treadmill for exercise testing. The other 3 centers used bicycle testing.

Baseline characteristics: Mean pulse was lower in the placebo (N=59, mean pulse 68 bpm) group compared to patients on ranolazine (N=66, mean pulse 72.5 bpm). Otherwise, no obvious differences in baseline characteristics (gender, mean age, weight, SBP, DBP) were noted across treatment groups. The population was 100% Caucasian. The median time on double-blind treatment was 7 days for both ranolazine and placebo.

Also of note, 22 patients (2/3) in one site (Dr. Rousseau) were started on background beta blocker during the titration phase. Of the 31 patients in this site, 20 had zero angina attacks during double-blind treatment, regardless of study medication. Four other sites had a majority of patients with zero angina attacks during double-blind.

²⁰ Integrated ST depression was calculated as the area under the ST depression/time curve.

²¹ Rate pressure product was calculated as heart rate x SBP.

Primary efficacy parameter:

For the time to onset of angina at ‘peak’ (all patients), the pre- and post-withdrawal means for ranolazine were similar (391.7 and 390.7 seconds, respectively) while the pre-and post-withdrawal means for placebo were 428.9 and 364.7 seconds, respectively. The treatment by investigator interaction was significant (p=0.005) for between-treatment comparison of changes, indicating heterogeneity of results by site (interactions between investigator (p=0.0001) and treatment (p=0.002) were also significant). The calculated treatment difference (R minus P), adjusted for imbalance in the number of patients receiving each treatment in each center was 53.61 (SE 16.6) seconds with a 95% CI of 20.7 to 86.5 seconds (not crossing zero). Although the decrease on placebo was consistent, there were also differences in mean change according to exercise method used.

In the all patients analysis, it should be noted that 50% and 43% of the data points in the ranolazine and placebo groups respectively were substituted data (ie, exercise duration substituting for time to onset of angina).

Table 1. RAN 081: Time to onset angina at peak (sec) (all patients) by method of exercise (All patients)

	Ranolazine N=59	Placebo N=50
Treadmill N	43	36
Mean change (post-pre) (SEM)	-2.09 (12.96)	-82.64 (24.44)
Bicycle N	23	23
Mean change (post-pre) (SEM)	0.96 (7.12)	-35.43 (10.55)

Results were similar for the evaluable population (although mean change for treadmill (post-pre) was +3.12).

Dr. Cocco’ site²²: The mean treatment difference in favor of ranolazine seen in Dr. Cocco’s center was much higher than those seen in other centers. In Dr. Cocco’s center, a mean decrease of 9 seconds in time to onset of angina was seen for patients on ranolazine and a mean decrease of 210 seconds for patients on placebo (the adjusted mean across all centers was 48.41 sec). Large decreases were seen for 3 patients on placebo at that site (# 198: 545 seconds; # 199: 540 seconds; #204: 403 seconds). At baseline, all 3 patients did not reach angina during exercise lasting 10 minutes 5 seconds, 11 minutes, and 9 minutes 43 seconds respectively. During the post-withdrawal test, the onset of angina occurred after 1, 2 and 3 minutes respectively for the three patients.

An imbalance was also seen in Dr. Cocco’s site regarding mean weekly angina attacks (3.3 in the placebo vs. 1.56 observed in the placebo group across all centers during the double-blind phase).

Exercise duration at peak:

Exercise duration decreased for both ranolazine (mean change = -10 sec) and placebo (mean change = -25.91 sec) during the withdrawal period (p=ns). There was a significant investigator interaction (p=0.001). The magnitude of effect varied by method of exercise.

Table 2. RAN 081: Exercise duration at peak (sec) (all patients)

	Ranolazine	Placebo
Treadmill N	43	36
Mean change (post-pre) (SEM)	-15.49 (12.99)	-40.72 (21.97)
Bicycle N	23	23
Mean change (post-pre) (SEM)	-5.96 (6.37)	-19.09 (4.72)

Time to 1 mm ST depression: As in the previous analyses, results varied by method of exercise. In addition, there was a significant treatment by investigator interaction (p=0.015). The mean change for

²² Dr. Cocco’s site is also mentioned in study RAN 080.

ranolazine was 13.96 sec (increase) while the mean change for placebo was -42.4 sec (decrease). Results for evaluable patients were similar.

Heart rate, SBP, DBP: Evaluation of heart rate, SBP and DBP at rest and at end of exercise did not reveal any clinically meaningful differences between ranolazine and placebo for either analysis population (all patients vs. evaluable population).

Rate Pressure Product (RPP): There was no statistically significant difference between ranolazine and placebo with regard to RPP at rest and at end of exercise. A statistically significant investigator effect was noted for RPP at rest (evaluable patients).

Table 3. RAN 081: Weekly rates of angina attacks and nitroglycerin consumption

	Whole study	Double-Blind withdrawal phase	
		Ranolazine	Placebo
<i>Angina attacks</i>			
N	135	66	59
Mean (SD)	0.8 (0.97)	1.22 (1.7)	1.56 (1.82)
<i>NTG use</i>			
N	135	66	59
Mean (SD)	0.39 (0.63)	0.6 (0.94)	1.15 (1.72)

The above table shows week rates of angina attacks and nitroglycerin consumption, with higher rates in both groups (higher on placebo) compared to rates for the whole study.

Safety: For a detailed safety discussion please see the safety review.

Reviewer Comments:

1. This was an open-label study with a one-week double-blind IR ranolazine vs. placebo period to assess withdrawal from therapy. The primary efficacy variable was time to angina. All exercise testing was performed at peak.
2. About 50% of the time to angina data represented substituted data (exercise duration).
3. Decreases in time to angina, total exercise duration, and time to 1 mm ST depression were seen in the placebo-treated patients; also seen were increases in angina attacks and nitroglycerin use.
4. There was a heterogeneous response with regard to the primary efficacy variable. In particular, one site showed large decreases in time to onset of angina (210 sec mean decrease in Dr. Cocco's site, compared to an adjusted mean of 48.41 seconds across all centers).
5. There was no statistically significant difference in exercise duration between ranolazine vs. placebo.
6. Imbalances were noted in terms of background therapy.
7. No meaningful changes were seen with regard to hemodynamic parameters (heart rate, BP, RPP).

RAN 015.

Title: A Crossover Study of Two Doses of Ranolazine 120 mg and 180 mg TID and Placebo in Coronary Artery Disease (Volume 245) (Protocol date: March 18, 1987)

Objective (listed as 'aim'): evaluate, using exercise tolerance, anginal frequency and nitrate consumption, whether 120 mg and 180 mg RS 43285 (ranolazine IR) administered three times daily are well tolerated, give effective antianginal control and whether there is a dose relationship.

Study Summary: This was a double-blind, 3-way crossover study using a Latin square design in patients with stable angina. After a 1 week washout period, where previous therapy was withdrawn, patients entered a 2-4 week placebo washout (Phase 1). On two days during the second week of Phase 1 (one of

these days being Day 14), patients underwent a treadmill ETT; if the time to onset of angina did not differ by more than 15% between these two tests, the patient proceed to Phase 2 (double-blind treatment) where either ranolazine 120 mg, 180 mg or placebo would be given tid. Efficacy was evaluated primarily by ETT 1.5 and 8 hours post-dose in each treatment phase; in addition, anginal frequency and nitroglycerin consumption would be evaluated.

Sublingual nitroglycerin was allowed if used as treatment for angina (not prophylactically).

Sample Size: The enrollment planned for 30 patients randomized in order to achieve 24 completed patients. The sample size was based on an assumed standard error of the difference of about 0.4 min, based on results with other antianginal drugs, with a 70% power to detect a 1 minute difference in exercise times, and a 95% power to detect a difference of 1.5 minutes.

Table 1. RAN 015. Inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
<ol style="list-style-type: none"> 1. Males and females, 25-65 years old, incapable of conception; 2. At least 6 month history of stable effort angina relieved by rest/nitroglycerin; 3. If measured, resting EF \geq 50%; 4. On standard ETT: a) difference in exercise time between last 2 ETT at baseline placebo must be less than 15% of the longer time; b) time to onset angina must be within 2-10 minutes; c) evidence of ischemia must be present in a standard ECG lead (J point depression \geq 1 mm and ST depression \geq 1 mm 80 msec after J point) with normal or interpretable resting ECG; 5. Patients under treatment for angina will be admitted only if their response to such treatment is inadequate or complicated by unwanted effects;²³ 6. Verbal informed consent. 	<ol style="list-style-type: none"> 1. Presence of factors associated with false positive stress test; 2. Uncompensated CHF; 3. Significant valvular heart disease/septal defects; 4. Unstable angina; 5. Second/third degree AV block/uncontrolled arrhythmia other than sinus arrhythmia or occas. extrasystoles; 6. MI within past 3 months; 7. Acute myocarditis/pericarditis; 8. High grade left main disease; 9. SBP < 95 mm Hg; 10. Condition likely to hinder/confuse follow-up; 11. Abnormal pretreatment renal/hepatic/thyroid/potassium tests or anemia; 12. Unable to discontinue long-acting nitrates/beta blockers/calcium blockers. Digitalis is not permitted; 13. Significant disease requiring medical therapy or supervision (other than angina); 14. Inability to undergo ETT; 15. IDDM; 16. Female subjects capable of conception.

Principal Efficacy variables: 1. Total exercise time; 2. Heart rate, BP, and rate-pressure product at end of exercise; 3. Workload at termination of treadmill. Additional variables: angina attacks/week; nitroglycerin consumption/week.

Pharmacokinetic samples will also be drawn.

Safety monitoring: adverse events, vital signs, ECG, laboratory tests.

Protocol amendments: no substantive changes.

Results:

Twelve (2 female, 10 male) patients, 41-64 years old, were enrolled and 11 patients completed all phases of the study. The study was terminated prematurely due to slow progress. One patient withdrew prematurely due to adverse event during placebo run-in and prior to randomization.

Baseline characteristics: The study population (n=12) was 100% Caucasian. Mean age was 53 years old, weight 79 kg, height 171 cm.

²³ Not further defined.

Efficacy: For the key endpoints, neither 120 or 180 mg ranolazine showed effects greater than placebo. For nitroglycerin consumption/week and anginal attacks/week, ranolazine showed no improvement compared to placebo.

Safety: Seven adverse events were reported in three patients (3/7 were reported while on placebo). One patient on ranolazine 120 mg complained of listlessness and intermittent nausea, dizziness and musculoskeletal pain (4 adverse events).

Reviewer comments:

1. This study does not support efficacy of ranolazine IR at the doses and regimen used.
2. The sample size was smaller than originally planned and this change in size may have impacted results.

RAN 020:

Title: A Double-Blind Crossover Study of Ranolazine (RS-43285) 60 and 120 mg tid versus Placebo in Patients with Angina Pectoris (Protocol date: March 1987) (Volume 246).

Primary Objective (listed as “aim”): evaluate, using exercise tolerance, anginal attack frequency and nitrate consumption, the relative efficacy and tolerance of two weeks dosing with RS 43285 60 and 120 mg tid.

Secondary Objective:

Patient population: Males and females with stable effort angina (see Inclusion criteria). The protocol called for 15 enrolled or 12 completed patients..

Study Summary: This was a double-blind, 3-phase crossover study in patients with stable angina. After a one week washout followed by a placebo run-in, patients were randomized to ranolazine 60 mg tid, ranolazine 120 mg tid or matching placebo for a period of 2 weeks each; there were no washout periods between the active phases.

Two ETT were planned at the end of placebo run-in; both tests were to be performed at the same time (either 1.5 or 7.5 hours post-dose). If the time to onset of angina did not differ by more than 20% they were to proceed directly into active treatment. Otherwise, patients were to continue on placebo for up to 2 more weeks during which time they further trained on the treadmill.

Patients not satisfactorily treated (this was not further defined) on long-acting nitrates and beta blockers were to have these drugs tapered off and discontinued before the end of the 1 week washout.

Concomitant medication: Sublingual nitroglycerin was allowed as treatment for anginal attacks.

Prophylactic use of any form of nitrate necessitated withdrawal from the study.

Table 1. RAN 020: Inclusion/Exclusion criteria:

Inclusion criteria:	Exclusion criteria:
1. Males and females, 21-70 years old, incapable of conception;	1. Presence of factors associated with false positive stress tests (e.g. IVCD, WPW, LBBB, etc);
2. At least 3 month history of classic stable effort angina pectoris relieved by rest/nitroglycerin;	2. Uncompensated CHF;
3. Difference in treadmill exercise time (last 2 ETT prior to active treatment) must be less than 20% of the longer time;	3. Clinically significant valvular disease;
4. Ischemia (J point depression \geq 1mm and ST	4. Unstable angina;
	5. Second/third degree AVB/ uncontrolled arrhythmia other than sinus arrhythmia;
	6. MI within past 3 months;

²⁴ This point is not further defined in the protocol. It is not clear whether “inadequate response” means that the patient was given adequate or maximal doses of a particular medication.

<p>depression \geq 1mm at 80 msec after J point) resulting from the ETT must be present in a standard lead. Resting ECG should either be normal or not interfering with interpretation of ST changes.</p> <ol style="list-style-type: none"> 5. Maximal exercise time at end of placebo phase must be 3-10 minutes; 6. If the patient has had a coronary angiogram, 50% or greater occlusion in a single view of a major coronary artery or one of its primary branches must be evident; 7. Patients who are currently under treatment for angina will be admitted to this study only if their response to treatment is inadequate or is complicated by unwanted effects;²⁴ 8. Must give consent. 	<ol style="list-style-type: none"> 7. Acute myocarditis/pericarditis; 8. High grade left main disease; 9. SBP < 95 mm Hg or sitting BP > 165/110 mm Hg; 10. Any condition likely to hinder/confuse follow-up; 11. Abnormal pretreatment renal, hepatic function, potassium levels, anemia; 12. Patients unable to discontinue therapy with long-acting nitrates, beta blockers, antihypertensive medication, calcium channel blockers or any investigational drug. Digitalis was not permitted during this study. Diuretics were permitted if continuous throughout study; 13. Inability to undergo ETT; 14. IDDM, systemic infection, female subjects capable of conception.
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Efficacy assessments:

All patients were to have treadmill ETT under uniform conditions at the same time of day at each visit. Time to angina, 1 mm ST depression, 2 mm ST depression and maximal exercise capacity were noted for all ETT. No smoking or sublingual nitroglycerin was allowed on the morning of the clinic visit where ETT was scheduled.

Forms for 2 weekly diaries were given to patients in order to record time of angina attack, number of nitroglycerin tablets used and time of study medication.

No primary efficacy variable was specified in the protocol. Principal efficacy variables to be compared among dosage regimens included: angina attacks/week; nitroglycerin consumption/week; total treadmill time; heart rate/BP and rate-pressure products at the end of exercise; workload at termination of treadmill exercise.

Safety: Safety monitoring included vital signs, ECGs, laboratory testing, adverse reactions and withdrawals.

Analysis Plan: No analysis population was prespecified in the protocol.

Amendments/changes in the conduct of the Study: Amendment 1 (April, 1987) increased enrollment to 30 patients or until 24 have completed. Amendment 2 (June, 1987) included one day of 24 hour ECG monitoring at the end of each active treatment phase. Otherwise, there were no substantive changes to the study.

Results:

Patient Disposition:

Baseline characteristics: Mean age was about 63 years. The total patient population (n=36) was 86% male, 72% Caucasian, 22% Asian, 28% smokers and 78% admitted to alcohol consumption. The patients deemed “valid for efficacy” were divided into 6 groups (P/60/120 (n=4); P/120/60 (n=4); 60/P/120 (n=3); 60/120/P (n=4); 120/P/60 (n=4); 120/60/P (n=5)). The baseline characteristics for each group are too small to permit comparisons. The total N deemed valid for efficacy was 24. Of the 12 patients excluded from analysis, 2 dropped out prior to active treatment (Phase 1), 5 were inappropriately enrolled, 2 did not meet ETT criteria for inclusion, 2 were protocol violators via noncompliance, and 2 patients required prohibited medication.

Of the 2 premature terminations during active treatment, one patient dropped out of ranolazine 120 mg tid due to unsatisfactory response (worsening of angina). The other patient on ranolazine 120 mg tid was withdrawn due to inappropriate enrollment.

Efficacy:

Nitroglycerin consumption/angina frequency: Mean angina attacks and nitroglycerin consumption for all patients valid for efficacy decreased from baseline for all groups but active treatment was either the same as or slightly worse (less of a decrease) than placebo. No statistical analysis was done by the sponsor.

ETT: There were no significant or meaningful differences in exercise time, time to angina, and time to 1 mm ST depressions between ranolazine 60 or 120 mg tid and placebo for the 1.5 or 7.5 hour exercise studies. Carryover effects were seen for: changes in mean SBP at onset of angina (pre-test values to post-test values); changes in double product at onset of angina from pretest to 1.5 hour ETT; ranked times to 2 mm ST depression for 1.5 hour ETT.

Several statistically significant findings were noted; according to the study report these findings were felt to result from the large number of analyses and no statistical corrections were made to accommodate this factor.

Safety: Please see the safety review for a detailed safety discussion.

Reviewer comments:

1. This was a 3-way crossover study of ranolazine 60 and 120 mg tid and placebo. Only sublingual (prn) nitroglycerin was allowed as a concomitant medication. There was no interim washout period between treatments.
2. This study does not support efficacy of ranolazine IR 60 or 120 mg po tid as given in this trial.

RAN 054.

Title: A Double-Blind Crossover Study of Ranolazine 120 and 240 mg TID Versus Placebo in Patients with Angina Pectoris. (Volume 248) (Protocol date: April 1988)

Primary Objective (listed as ‘aim’): evaluate relative efficacy and tolerance of 4 weeks dosing with ranolazine 120 and 240 mg tid, using exercise testing, anginal attack frequency and nitrate consumption.

Study Summary: This was a double-blind, 3 phase crossover study in patients with stable angina. After a 1 week washout period (previous therapy withdrawn), patient entered a single-blind placebo phase (phase 0, 2-4 weeks). On 2 days, several days apart, during the second week of placebo (phase 0), patients were given ETT to determine eligibility (see Inclusion criteria for difference in ETT time). Following the placebo phase, patients were given ranolazine 120 mg tid, 240 mg tid or placebo tid each—in random order—for a period of 4 weeks. There was no interim washout period between treatments. ETT were performed during the initial placebo period as well as 60 minutes and 7.5 hours post-dose between days 24 and 30 of each treatment phase.

Sample size: A total enrollment of 120 planned to achieve 100 completed patients. The sample size was based on an 80% power to detect a 10% difference in exercise time with a 95% level of significance.

Table 1. RAN 054 Inclusion/exclusion criteria

Inclusion criteria:	Exclusion criteria:
1. Males and females, 21-75 years old, incapable of conception;	1. Presence of factors which may cause false positive stress test;
2. At least 3 month history of stable effort angina relieved by rest/nitroglycerin;	2. CHF;
3. Difference in ETT exercise time (last 2 ETT prior to active treatment) must be less than 20% of the longer time;	3. Unstable angina in the past 4 weeks;
4. Evidence of ischemia during baseline ETT must be	4. Second/third degree AV block or uncontrolled arrhythmia other than sinus arrhythmia or occasional extrasystoles;
	5. MI within psat 3 months;

<p>present in a standard ECG lead (≥ 1 mm J point depression and ≥ 1 mm ST depression at 80 msec after the J point and occurring within 9 min of the start of the 2 tests). Resting ECG should be normal or of such pattern as not interfere with interpretation during angina;</p> <p>5. Onset of angina within placebo phase must be within 9 min or less;</p> <p>6. If the patient has had a coronary angiogram, 50% or greater occlusion in a single view of a major coronary artery or one of its primary branches must be evident;</p> <p>7. Patients under treatment for angina will be admitted only if their response to treatment is inadequate or complicated by unwanted effects;</p> <p>8. Written consent.</p>	<p>6. Acute myocarditis/periocarditis;</p> <p>7. High grade left main disease;</p> <p>8. SBP < 95 mm Hg or sitting BP > 165/110 mm Hg;</p> <p>9. Any condition likely to hinder/confuse follow-up;</p> <p>10. Abnormal pretreatment renal/hepatic/ potassium tests or anemia;</p> <p>11. Inability to discontinue long-acting nitrates, beta blockers, ACE inhibitors, calcium channel blockers or investigational drug. Digitalis is not permitted. Diuretics are permitted if use is continuous throughout the study;</p> <p>12. Systemic infection;</p> <p>13. Inability to undergo ETT;</p> <p>14. IDDM;</p> <p>15. Females capable of conception.</p>
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Concomitant medication: Sublingual nitroglycerin was permitted only as treatment for anginal attacks. The use of prophylactic nitrates necessitated withdrawal from the study. Initiating or changing therapy with antihypertensive or antiarrhythmic therapy also necessitated study termination.

Efficacy analyses: No primary efficacy variable was prespecified in the protocol. The principal efficacy variables to be compared among dosage regimens were: anginal attacks/week; nitroglycerin consumption/week; total treadmill time plus time to exercise induced angina; heart rate, BP and rate-pressure product at end of exercise; workload at treadmill termination.

According to the Statistical Report (Appendix D, dated October 1992) the primary efficacy variable of interest was peak (1 hour) total exercise time. Pooling of centers, while not prespecified in the protocol, was done for those centers who did not recruit at least one patient into each of the 6 possible treatment centers.

All patients were to undergo treadmill testing under uniform conditions, at the same time of day at each visit.

For documentation of anginal attacks, forms for 2 weekly diaries were provided to all patients.

Protocol Amendments:

1. Nov. 1988: added inclusion criterion that patients needed at least 2 angina attacks/week, on average, during placebo run-in.
2. March 1989: added a review of results, without statistical analysis, once 60 patients completed the trial.
3. July 1989: changed exercise testing to Bruce (rather than modified Bruce) protocol;
4. Sept. 1989: excluded antiarrhythmics from this study;
5. May 1991: added calculation for workload (in order to define workload at treadmill termination).

Study Conduct:

A 3-page document entitled Practical Conduct of the Study was included in the submission (Appendix A-2). It was noted that the clinical phase of the study ran from October 1988-April 1990 and the process of data discrepancy resolution and reporting took until October 1992.

1. Methodologies for the various measured parameters varied across the centers. Recording equipment for treadmill ETT varied from fully automated systems to manual ones; this difference impacted most significantly (according to the sponsor) on measurement of ST depression. BP was recorded using a standard sphygmomanometer in all centers except one (Stephen) which used a Hawksley random zero recorder.
2. Pre-trial and end of phase ECG were recorded under varying conditions (supine, sitting, upright) according to center.
3. Clinical chemistry and hematology results were generated at 4 different laboratories.

Results:

Patient Disposition: A total of 144 patients were enrolled at 8 centers. Of those enrolled, 7 were not randomized (leaving 137 randomized patients) and another 8 patients never entered the active treatment phase. One patient was excluded due to poor compliance. Another 13 patients had less than 2 phases worth of data. According to the statistical report (although not found in the protocol) the criteria for inclusion in the analysis stipulated that each patient should have at least 2 phases worth of data. One patient failed to meet the requirement for 3 full phases and it was deemed appropriate (not clear how this decision was made) to increase the requirement to 3 phases and not include that patient in the efficacy analysis.

Therefore, 114 patients were included in the sponsor’s Full patients analysis. Of these 114 patients, 90 patients were included in the Valid Patients analysis (24 were excluded because of noncompliance).

A total of 16 patients withdrew due to adverse events (4 during placebo run-in, another 4 on double-blind placebo); of the patients on ranolazine, 2 withdrew while receiving 120 mg tid (one with worsening angina associated with hypertension/headache, and another with sudden death) and 6 withdrew while on 240 mg tid (2 with headache/vasodilatation, 1 with chest burning/depression, 1 with hip pain, 1 with infection and 1 with chills/fever).

Baseline Characteristics: In the all patients group, mean age was 59 years; mean height 171 cm; mean weight 77 kg without imbalances across centers. History of MI ranged from 18% to 32% in one center (Raj); a similar imbalance was seen with respect to history of hypertension. Heterogeneity across centers was seen with respect to baseline aspirin use (13-64%) and diltiazem use (1-27%).

Efficacy:

According to the study report, “the exercise data presented some problems with data verification and analysis which meant that the analysis as planned in the protocol had to be considerably altered.”

For ST depression, there was variation between centers in the method used to calculate ST depression, failure of some investigators to use a standardized lead, changing of the protocol from modified Bruce to Bruce (removing Phase) leading to inappropriateness of data to time periods, and loss of monitoring manpower due to sickness. Therefore, the sponsor has stated that this dataset (ST depression, time to 1 and 2 mm ST depression) could not be rendered sufficiently accurate and reliable.

Diary card data for nitrate use/number of angina attacks was suspect because patients/investigators were unclear about which point should be used to represent the end of one phase and beginning of the next.

Rate pressure product was not calculated and analyzed because measurements of BP and HR prior to ETT was not sufficiently controlled for posture, and it was concluded by the sponsor that the uncontrolled addition of this variable would make interpretation of baseline and change from baseline unreliable.

Table 2. RAN 054: Selected efficacy parameters (Full patients analysis- complete data in all 3 phases: N=114)

Parameter	Ran 120 mg – placebo	Ran 240 mg - placebo
Total exercise time (min) (peak: 1 hr) (treatment by center interaction p=0.002, period effect p=0.01)		
LSM difference from baseline (SEM)	0.09 (0.12)	0.22 (0.12)
95% CI	(-0.15, 0.33)	(-0.02, 0.45)
p-value	NS	NS
Total exercise time (min) (trough: 7.5 hr) (treatment by center interaction p=0.04; period effect p=0.06)		
LSM difference from baseline (SEM)	0.19 (0.13)	0.24 (0.13)
p-value	NS	NS
Time to angina (peak: 1 hr) (treatment by center interaction NS; period effect p=0.0001)		
LSM difference from baseline (SEM)	0.17 (0.19)	0.11 (0.19)
95% CI	(-0.2, 0.55)	(-0.26, 0.48)
p-value	NS	NS
Time to angina (trough: 7.5 hr) (treatment by center interaction NS; period effect p=0.08)		

LSM difference from baseline (SEM)	0.32 (0.18)	0.42 (0.17)
95% CI	(-0.03, 0.67)	(0.08, 0.76)
p-value	0.08 (NS)	0.02
Angina attacks per week (treatment by center NS)		
LSM difference from baseline (SEM)	-1.35 (0.46)	-0.73 (0.45)
95% CI	(-2.26, -0.43)	(-1.62, 0.17)
p-value	0.004	NS
NTG consumption per week (treatment by center NS)		
LSM difference from baseline (SEM)	-0.55 (0.35)	-0.66 (0.34)
p-value	NS	NS

Source: sponsor. P-values based on ANOVA model

For the valid patients analysis (N=75 for total exercise time, N=88 for time to angina) patients on ranolazine 240 mg experienced a statistically significant improvement in total exercise time vs. placebo (both peak and trough: statistically significant period effect $p < 0.05$). The time to angina was significantly longer for peak ranolazine 120 mg but not 240 mg (period effect $p = 0.0008$) and for both doses at trough (period effect $p < 0.05$).

End of Exercise heart rate:

Slight increases in heart rate were seen pre-exercise (peak and trough) in ranolazine vs. placebo. Variations in heart rate were 3 beats per minute or less and were not statistically significant. Pre-exercise mean systolic and diastolic BP were not different between treatment groups. Post-exercise heart rate was significantly higher in the ranolazine 240 mg group (both peak and trough) vs. placebo

Safety: One death during the study (Patient 414, on ranolazine 120 mg) was noted. According to narratives, this was a 62 year old man, on ranolazine 120 mg tid for one month, who experienced intermittent chest pain, unresponsive to nitroglycerin over 7, and then developed severe chest pain (ambulance called) and found to be in asystole when the crew arrived.

Another death (DT 415) was noted 2 days post-completing the study. A 57 year old man who completed ranolazine 120 mg tid (last phase) collapsed and died.

Reviewer Comments:

1. This was a randomized, double-blind, 3 phase crossover study comparing patients with angina on ranolazine IR 120 mg tid, 240 mg tid and placebo. There were no interim washout periods.
2. Primary efficacy variable and analysis population was mentioned in the statistical report but not prespecified in the protocol.
3. There were difficulties in the conduct of this study, including changing the exercise protocol (modified Bruce to standard Bruce), heterogeneity in ST segment interpretation, issues regarding monitoring, and recording of ECGs and vital signs under different conditions.
4. For several efficacy variables, there were significant treatment by center and period interactions.
5. For total exercise time at peak, the results of "all patients analysis" and "valid patients analysis" were not consistent. In addition, there was a significant treatment by center interaction, with heterogeneity by center.
6. For all patients analyzed, there were slight improvements in total exercise time (favorable for ranolazine) that were not statistically significant.
7. Two deaths (one during the study and another 2 days post-study) in ranolazine-treated patients were noted.

RAN 1490.

Title: Double-Blind Parallel Dose-Scheduling Study of RS-43285 Versus Placebo in Patients with Chronic Stable Angina Pectoris. (Protocol volume 265) (Protocol date: May 28, 1987).

Objective: evaluate efficacy and safety of RS-43285 as treatment of chronic stable angina, and to provide an estimate of the optimal total daily dose and dosing interval.

Sample size: The study was originally planned for 48-72 patients, to be determined by the number of dose levels tested. However, due to slow enrollment, a decision was made to discontinue the study after 12 patients had enrolled. Eleven completed the study; one withdrew prematurely.

Study Summary: This was a double-blind, randomized, placebo-controlled, dose ranging and scheduling trial. Eligible patients would receive 2 weeks of single-blind placebo prior to double-blind randomization. Treadmill ETT was planned 2 days after starting placebo (Visit 3) and at end of run-in (Visit 4). If the duration of exercise from these 2 baseline tests did not differ by more than 15% of the duration of the longer test, then patients qualified for double-blind and were randomized to receive 5 days of study medication or placebo. ETT was performed on Day 5 at peak (2 hours following the first morning dose) and on Day 6 at trough (one full dosing interval post-dose). Medication was taken every 12 hours (if bid), every 8 hours (if tid) and every 6 hours (if qid). The study consisted of 4-6 substudies, each involving 12 patients (4 patients given placebo and 8 patients given active treatment). These substudies involved ascending doses of ranolazine. However, only the first dosing group, 60 mg po tid, was given prior to the study being stopped.

Notable Inclusion criteria: Patients, 21-70 years old, with at least 3 month history of chronic stable effort angina relieved by rest/nitroglycerin. The first ETT must not exceed 12 minutes and the reason for stopping must be angina, with ST depression (≥ 1 mm) in a standard lead. Time to angina for the last 2 ETT prior to double-blind must not differ by more than 15% of the duration of the longer test. Resting ECG must be normal or not interfere with ETT interpretation.

Notable Exclusion criteria: pregnant/breastfeeding women, factors associated with false positive stress test, CHF, unstable angina, MI within past 2 months, myocarditis/pericarditis/cardiomyopathy, high-grade AV block, nonobstructive CAD, SBP < 95 mm Hg, significant lab abnormality, inability to discontinue anginal medication or undergo ETT, labile DM or IDDM.

Efficacy Parameters:

Primary efficacy parameter: duration of treadmill exercise to maximal tolerated angina or other limiting symptomatology.

Secondary efficacy parameters: exercise time to onset of angina, specified amounts of ST depression and changes in severity of angina and ST changes at maximal work loads.

Results:

Patient Disposition:

5 women and 7 men, mean age 62 years, were randomized; 8 were given ranolazine 60 mg tid and 4 were given placebo.

Efficacy: Because only 12 patients from the first group entered the study, no formal analysis was done by the sponsor.

The reviewer looked at the data listings (nitroglycerin consumption, anginal attacks, and treadmill data at peak/trough) and did not note any striking pattern.

Reviewer Comments: No efficacy conclusions can be drawn from this study.

RAN 1513.

Title: Double-blind Parallel Efficacy and Safety Study of Various doses of Ranolazine vs. Placebo in Patients with Chronic Stable Angina Pectoris (Protocol volume 265, dated April 19, 1989; six Amendments between June, 1989-February, 1990).

Objective: evaluate safety and cardiac anti-ischemic properties of ranolazine 30, 60, 120 mg tid or placebo tid as treatment for patients with chronic stable angina who may also have silent ischemia.

Primary Objective: assess change in duration of treadmill exercise to maximum tolerated angina or other limiting symptoms.

Secondary Objectives:

1. Change in number of angina attacks;
2. Change in number of episodes of ST depression as documented by 48 hour Holter monitors (at the end of 4 weeks treatment);
3. Change in duration of episodes of ST depression.

Sample Size: 284 planned (four groups of 71 patients).

Study Summary: This was a double-blind parallel-group randomized placebo-controlled dose-finding study. Eligible patients entered a 5 day washout period where antianginal medications were withdrawn (except prn sublingual nitroglycerin), followed by a one week single-blind placebo period prior to double-blind medication.

On Day 0 of the placebo run-in, patients underwent laboratory testing and 48 hour Holter monitoring; on Day 2, the Holter was removed and, following removal, a treadmill ETT was performed. A second treadmill ETT was done 2-10 days following the first ETT; in order to qualify for double-blind, there must be at least 36 hours of interpretable ECG on Holter (read by a central Holter lab), the duration of exercise of the two ETT must be 3-9 minutes and not differ by more than 15% of the duration of the longer test, and the reason for stopping must be angina. The final ETT during single-blind placebo will be considered to be the baseline test. The patient must also have reported at least one anginal episode in a diary the week before randomization. Eligible patients were then randomized to receive 30, 60, 120 mg ranolazine tid or placebo tid for 4 weeks; medication was to be taken q 8 hrs.

Two days before the end of week 4, the am dose was given in clinic; one hour post-dose, a serum sample was drawn and the patient underwent an ETT at peak. Following the ETT, another 48 hour Holter monitor was done. After 48 hours, the Holter monitor was removed, a trough plasma sample was drawn and the final ETT at trough was performed.

Table 1. RAN 1513. Inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
1. ≥ 21 years old;	1. Women of childbearing potential;
2. At least 3 month history of chronic stable effort angina relieved by rest/nitroglycerin;	2. Presence of factors associated with false positive ETT;
3. At least 1 subjective attack of angina recorded in their diary during the week prior to randomization;	3. Uncompensated CHF;
4. Qualifying ETT: Primary reason for stopping must be angina, duration of test must be 3-9 minutes, exercise time (time to angina) for last 2 consecutive tests (prior to double-blind) must not differ by more than 15% of duration of the longer test. All ETT were planned according to Bruce protocol; all ETT must show evidence of ischemia, ≥ 1 mm ST depression, measured 80 msec from J point, in a standard lead ;	4. Valvular heart disease; septal defects; unstable angina; second/third degree AV block; uncontrolled arrhythmia; acute myocarditis/pericarditis; cardiomyopathy; pacemaker.
5. Resting ECG should not interfere with interpretation of ST changes during angina;	5. Nonobstructive CAD;
6. Patients with intermittent atrial fibrillation during the Holter must have 36 hours of readable tape without atrial fibrillation;	6. High grade left main coronary disease;
7. Patients must have telephone and sign informed consent.	7. MI within the past 2 months;
	8. Standing SBP < 95 mm Hg;
	9. Any condition likely to hinder/confuse follow-up;
	10. Clinically significant lab abnormality;
	11. Inability to discontinue long-acting nitrates, calcium channel blockers, beta blockers, or any investigational drug. Digitalis is not permitted in this study;
	12. Inability to undergo ETT;
	13. Labile DM/subject to hypoglycemia;
	14. Participation in investigational drug study within previous month.

Efficacy Analysis: Using Fisher's Least Significant Difference procedure, all ranolazine doses would be tested vs. placebo if the overall treatment effect was significant at the 0.05 level. All efficacy variables will be tested using ANOVA including effects of treatment, center, and treatment by center interaction.

Primary Efficacy variable: exercise duration at peak.

Secondary Efficacy variables: (2-6 measured at peak and trough).

1. Exercise duration at trough;
2. Time to onset of angina (duration of exercise will be used if angina does not occur);
3. Time to 1 mm ST depression from rest; duration of exercise will be used if 1 mm ST depression is not attained;
4. Standing heart rate on treadmill and at maximum workload;
5. Standing SBP on the treadmill and at maximum workload.

Diary card data:

1. Number of anginal attacks;
2. Number of nitroglycerin tablets taken.

Holter data:

Of the two ECG leads used per patient, the lead giving the maximum total duration of ischemia during the 48 hour qualifying phase will be chosen for statistical analysis. The same lead will be used for subsequent analyses. The following tertiary parameters were obtained from a 48-hour Holter monitor:

1. Number of silent ischemic attacks;
2. Number of subjective attacks;
3. Total duration of ischemic attacks over the 48-hour period (silent and subjective);
4. Median of the areas of the individual attacks, where the area is defined as the integral of ST shift over time.

Holter analysis will only include patients with documented ischemia on the baseline Holter. Documented ischemia is defined as at least 3 episodes of ST depression, ≥ 1 mm, lasting ≥ 30 seconds and separated from other events by at least one minute or at least one episode lasting 3 minutes or longer.

Results:

Patient Disposition:

A total of 319 patients were enrolled. The “all patients” analyses (N=299) included patients who had both baseline and endpoint data; the per-protocol analyses (N=258) included patients without protocol deviations who had both baseline and endpoint data. The safety analysis included all enrolled patients (N=319).

Thirty-one (9.7%) of 319 patients prematurely terminated the study. Adverse events, new illness or laboratory abnormalities led to premature terminations for 5 of 81 patients (6.2%) in the RAN 30 group, 2 of 81 patients (2.5%) in the RAN 60 group, 3 of 78 patients (3.8%) in the RAN 120 group, and 5 of 79 patients (6.3%) in placebo. Unsatisfactory response led to premature termination in 0-2 patients per treatment arm with no preponderance in any treatment group.

Baseline characteristics:

Regarding all randomized patients, as well as the patients included in the primary efficacy parameter analysis, an imbalance was seen with respect to congestive heart failure history (0 in the RAN 120 group versus 5 (or 7%) in the placebo group. Treatment by center imbalances (indicating heterogeneity by site) were seen with regard to history of rest angina, myocardial infarction, prior CABG as well as enrollment by gender. Otherwise, no imbalances were seen. The mean age (all randomized patients) was 64-66 years, and the study population was about 79% male and 86% Caucasian, with 13-19% reporting tobacco use and over 80% reporting at least 2 anginal attacks per week.

Efficacy:

Of the randomized patients, at least 74% achieved baseline and follow-up endpoints for duration of exercise, time to angina onset and time to 1 mm ST depression for peak and trough. Key ETT parameters are shown in the table below. There were no statistically significant differences between the placebo group and the three ranolazine dose groups in any key ETT parameter. There also were no statistically significant treatment effects in the per-protocol analyses of key ETT parameters, diary and Holter data.

Table 2. RAN 1513: Efficacy results: Ranolazine vs placebo comparisons from ANOVA for the change from baseline (all patients analysis)**

Mean (SEM) change from baseline (vs. Placebo)	Ran 30 mg	Ran 60 mg	Ran 120 mg
<i>Peak:</i>			
Exercise duration (min)*	-0.15 (0.21)	0.13 (0.21)	-0.04 (0.17)
Time to angina onset (min)	0.08 (0.27)	0.39 (0.27)	0.15 (0.26)
Time to 1 mm ST depression (min)	0.03 (0.29)	0.36 (0.29)	0.09(0.29)
<i>Trough:</i>			
Exercise duration (min)	-0.23 (0.24)	-0.06 (0.24)	-0.13 (0.24)
Time to angina onset (min)	a	0.15 (0.29)	-0.20 (0.28)
Time to 1 mm ST depression (min)	0.16 (0.31)	0.43 (0.31)	0.26 (0.30)

*Primary efficacy parameter. **Mean, SEM and between treatment p-values were estimated from ANOVA models which include treatment, center and treatment by center factors. Source: sponsor.

Other parameters:

Reasons for stopping exercise: There were no significant differences between treatments in reasons for stopping exercise (“angina vs. not angina” or “all individual reasons”) for either peak or trough ETT .

Hemodynamic data: There were no statistically significant changes from baseline (either peak or trough ETT) in resting heart rate, heart rate at maximum workload, SBP at rest and at maximum workload.

Pharmacokinetics:

In this study, trough plasma levels increased proportionally with dose; however, peak levels were not proportional with dose (p <0.05). According to the sponsor, the spread in sample collection time for peak concentration ranged from 10 minutes to 1.5 hours, resulting in variability in concentration during the absorption phase. (?saturation of cytochrome P450 3A4 enzyme). No correlation between efficacy variables and plasma ranolazine levels were noted.

Safety: There were no deaths in this study. Most frequently reported adverse events (for ranolazine-treated patients) were headache, dizziness, and asthenia. For further discussion please see the safety review.

Reviewer comments:

1. There were no statistically significant treatment effects of ranolazine, compared to placebo, in any measured efficacy parameter, peak or trough, in this study.
2. In this trial, peak ranolazine levels were not proportional with dose.

RAN 2240.

Title: A Double-Blind, Placebo-Controlled, Parallel-Design Study of the Effect of Ranolazine SR 1000 mg bid on Utilization of Elective Revascularization Procedures in Patients with Refractory Chronic Stable Angina Pectoris Referred for Percutaneous Transluminal Coronary Angioplasty (PTCA). (volume 365).

Study period: February-October, 1994.

Primary Objective: Determine whether ranolazine SR 1000 mg bid prolonged time to revascularization (PTCA or CABG) compared to placebo in patients referred for elective PTCA to relieve refractory symptoms of chronic stable angina.

Secondary Objectives:

1. Determine whether ranolazine SR 1000 mg vs. placebo prolonged time to 1. First occurrence of revascularization or cardiovascular death; 2. First occurrence of revascularization, nonfatal MI or cardiovascular death.
2. Determine whether ranolazine SR decreased medical care utilization for which a diagnosis of angina was made.

Study Summary: Patients with angina refractory to maximal medical therapy, within 2 weeks post-coronary angiography resulting in recommendation for PTCA, were randomized to receive either ranolazine SR 1000 mg bid or placebo. Throughout the trial, background medications were kept constant. Patients were followed via clinic visits after 2 weeks, 1 month, 3 months, and every 3 months until revascularization with ECG monitoring, QOL questionnaire, laboratory tests, and assessments of medical care utilization. After revascularization, study medication was discontinued and limited follow-up continued for collection of data concerning concomitant anginal medications, medical care utilization and QOL.

Because of low enrollment at the study center, a decision was made in August, 1994 to discontinue the trial.

Patient population: Patients were at least 21 years old and had angina refractory to medical therapy; all had undergone coronary angiography within 2 weeks of randomization. Patients were excluded if they had left main or severe proximal triple-vessel disease, had a large amount of myocardium in jeopardy, or had unstable angina within 4 weeks of beginning the trial or had Class III-IV CHF.

Results: A total of 11 patients, aged 46-76, 10 males and 1 female, entered the trial. Nine patients were Caucasian and 2 were Hispanic. Seven patients received placebo and 4 received ranolazine SR 1000 mg bid. Two patients terminated double-blind because of adverse events (1 out of 2 underwent revascularization), 8 patients terminated the double-blind phase of the study because of unsatisfactory response and underwent revascularization, and one patient (on placebo) terminated the study because of sponsor termination of the study. Ten of 11 patients participated in the post-revascularization phase of the trial and terminated follow-up when the sponsor (Syntex) discontinued the trial. At the time that the trial was discontinued, 9 patients had taken double-blind medication for 4-92 days.

Safety: No deaths were reported during the trial. Thirteen adverse events were reported by 6 patients in the trial. For the 3 of 4 patients reported adverse events on ranolazine SR, the adverse events were: musculoskeletal should pain (#1002), dizziness, sweating and myocardial infarction (#1004), urinary incontinence, polyuria, headache, and nausea (#1008). Patients #1004 and 1008 withdrew prematurely due to adverse events.

Reviewer Comments: No conclusions can be drawn from this study.

Pharmacodynamic Studies:

RAN 003.

Title: A Single-Dose Tolerance Study to Investigate RS-43285 (ranolazine) in Subjects with Ischemic Heart Disease (Protocol date: June 20, 1985) (Study started September, 1985-completed February 1986).

Objective: determine safety, tolerance, invasive cardiac hemodynamic effects and pharmacokinetic features of single intravenous doses of RS 43285 over the dose range 25-200 µg/kg in patients with coronary artery disease undergoing diagnostic cardiac catheterization.

Study Summary: This was initially a single-dose, open-label, ascending dose study. After the first patient received 25 µg/kg and completed the study, the design was changed to become single-blind, placebo-controlled, ascending dose. The second patient received a dose of 25 µg/kg and two patients were dosed at each subsequent dose (50, 100, 150 and 200 µg/kg). Each dose of ranolazine was preceded by a single intravenous dose of placebo (saline); approximately 20 minutes was allowed between injections. Prior to and 10 minutes after both placebo and ranolazine administration, hemodynamic measurements were taken. Patients were to receive no cardioactive drugs except for: calcium blockers/beta blockers up to 48 hours prior to catheterization; long-acting nitrates up to 12 hours prior to study; and sublingual nitroglycerin up to 2 hours prior to procedure.

Symptoms and ECGs were monitored throughout the procedure. Blood was collected for pharmacokinetic analysis as well as routine screens.

Patient Population: Males and postmenopausal women, 21-75 years, with a clinical diagnosis of stable angina based on a positive exercise test or history of MI. The planned sample size was 10 patients, 2 at each dose level.

Notable Exclusions: congenital/valvular disease; LV dysfunction (PCWP > 18 mm or EF < 40%); Prinzmetal's or unstable angina; MI within 12 weeks; bradycardia/LBBB/high-grade AV block; SBP < 95 or DBP > 100 mm Hg; contraindications to cardiac catheterization.

Hemodynamic Measurements: Two catheters, one venous and one arterial, were used. The venous (Swan-Ganz) catheter, via femoral vein, was advanced to the pulmonary capillary wedge position and used to measure right heart and pulmonary pressures as well as cardiac output (via thermodilution). A double lumen arterial catheter, via femoral artery, was used for systemic arterial pressure as well as angiography. Hemodynamic parameters included: right atrial pressure, pulmonary artery pressures, cardiac output, heart rate, systemic arterial pressures, left ventricular pressures, left ventricular end diastolic pressure (LVEDP), pulmonary capillary wedge pressure, left ventricular dp/dt, left ventricular Vmax.

Results: Ten patients, mean age 53 years, mean weight 77 kg, entered and completed the study. The diagnosis of stable angina was based on a positive stress test in 9 patients, and a history of MI in one patient. Two patients received furosemide throughout the study.

Hemodynamics:

The data presented are limited by the fact that pre- and post-dose values exist only for placebo. For ranolazine-treated patients only post-dose values are represented. A review of the available hemodynamic data showed no appreciable effect of ranolazine (at these dose levels, compared to pre- and post-doses for saline) on mean right atrial pressure, mean pulmonary artery pressure, pulmonary artery systolic and diastolic pressures, PCWP, systemic/pulmonary vascular resistance, LV dp/dt, cardiac output, left ventricular Vmax.

There was a suggestion of increased LV EDP with ranolazine (from 6 mm Hg pre-saline to 11 mm Hg post-saline, to 16 mm Hg post-ranolazine), only seen at the 200 µg/kg dose level. Whether this represents a drug effect or (in the absence of a concurrent placebo group) some other effect is unclear.

Pharmacokinetics: Plasma profiles were obtained from only one subject at 150 and 200 µg/kg. Peak levels were seen at 5-10 minutes post-administration.

According to the sponsor, ranolazine plasma concentration declined in a biexponential manner following intravenous administration. The distribution phase half-life ranged from 1-8 minutes (mean 4 minutes) and the terminal elimination ranged from 1-6 hours (mean 2.4 hours).

The sponsor concluded that single intravenous doses of ranolazine had no effect on cardiac preload, afterload, cardiac output, and LV function including contractility.

Reviewer Comment:

1. With the data available, results did not show ranolazine effects on cardiac output, right-sided pressures, systemic/pulmonary vascular resistance, indices of LV contractility or systemic pressures. There was a suggestion of increased LVEDP at the highest dose level; however, the meaning of this single finding is unclear.
2. According to the sponsor, pharmacokinetic results are consistent with a two compartment model with elimination from the central compartment. No dose dependency was noted for either clearance or terminal half-life although there was significant intersubject variation.

RAN 003B.

Title: A Study to Investigate the Potential Anti-Anginal Efficacy of Intravenous Ranolazine (RS 43285) in Subjects with Ischemic Heart Disease

(Protocol date: February 12, 1986) (Study started: April, 1986-completed February 1987)

Objective: determine safety, tolerance, pharmacokinetic features, hemodynamic and cardiac metabolic effects of ranolazine 200 µg/kg in patients with ischemic heart disease undergoing atrial pacing.

Study Summary: This was a single-dose, single-blind study. Males with a clinical diagnosis of angina received a saline injection first, followed by administration of intravenous ranolazine 200 µg/kg. Prior to and 20 minutes after saline and 20 minutes after ranolazine dosing the patient was to undergo atrial pacing. The effect of the compound will be assessed by measurements of: coronary sinus blood flow, coronary sinus oxygen, lactate and pyruvate content, systemic arterial oxygen, lactate and pyruvate content, time to pacing-induced angina, BP/HR.

If a coronary sinus catheter could not be successfully inserted, then a pacing wire would be inserted and only BP, HR and time to pacing-induced angina would be measured.

In addition, symptoms/ECGs would be monitored, and blood for pharmacokinetic analysis/safety screened were to be obtained.

Study Population: Males, 21-75 years, undergoing cardiac catheterization or atrial pacing test, with a clinical diagnosis of angina based on a positive exercise test or history of MI. Patients must not have received cardiac drugs for one week prior to the study, except for: calcium blockers/beta blockers up to 48 hours prior to the study; long-acting nitrates up to 12 hours prior to the study; sublingual nitroglycerin up to 2 hours before the study.

Notable Exclusions: Please see Study RAN 003 (identical exclusions).

Procedures:

Atrial pacing: Atrial pacing was performed pre- and 20 minutes post-saline and 20 minutes post-active dosing. Starting at 100 beats per minute the rate was to be increased gradually by 10 beats/minute and each rate held for 3 minutes. The criteria for discontinuation was: chest pain or 1 mm ST depression below resting; upsloping ST depression was to be measured 0.08 seconds after the J point.

Coronary sinus (CS) blood flow: This parameter was measured using a continuous thermodilution technique. During the third minute at each level of pacing CS flow will be calculated 3-4 times over consecutive 10-15 second intervals. The recorded flow values on the case report form will represent the average of measurements obtained over the one minute interval. CS flow will also be measured in a similar manner before the start of pacing (baseline) and during the 5 minutes after pacing has stopped. Blood samples for myocardial oxygen uptake, pyruvate levels and % lactate extraction will be obtained from the arterial catheter and CS during the 3rd minute but 15-30 seconds after each flow measurement.

Hemodynamic data:

Blood pressure was obtained by sphygmomanometry. Duplicate recording was planned at each time point. Hemodynamic measurements were planned during the 3rd minute at each level of pacing; in addition, values would be obtained before pacing (baseline) and during the 5 minutes after pacing. Central hemodynamic measurements would be obtained by averaging the values from at least 5 consecutive heart beats.

ECG: Six-lead ECGs were obtained prior to, catheterization; at least two leads will be continuously monitored throughout the study. A 6-lead ECG will be recorded within 1-4 hours after the procedure, and a 12-lead ECG will be obtained on the morning following catheterization.

Angiographic data:

Left ventriculography and coronary angiography were to be performed in the usual manner, if clinically indicated, after the completion of post-dosing hemodynamic measurements. The findings were to be recorded in the case report form.

Pharmacokinetic sampling:

Venous blood samples were to be taken prior to ranolazine dosing, 2, 5, 10 and 20 minutes after dosing, and immediately and 5 minutes after completion of post-drug pacing measurements.

Other data:

The following will be analyzed if the data are available: cardiac index, stroke volume, systemic vascular resistance, left ventricular dP/dt, left ventricular Vmax, total coronary resistance (mean aortic pressure/coronary sinus flow), coronary arteriovenous (AV) oxygen content difference (coronary artery minus CS oxygen content), coronary AV lactate difference, coronary AV pyruvate difference, myocardial oxygen uptake index (coronary AV oxygen difference x CS flow).

Results:

Eleven males, mean age 57 years, entered and completed the study. One patient (#6) was excluded from some of the analyses because the point at which he experienced anginal pain was not well-defined. All patients had a clinical diagnosis of angina and documentation (via coronary angiography) of occlusion in at least one major coronary artery. Another patient (#7) completed the drug assessment (and was included in the analysis) but did not complete angiography due to multiple vessel spasm occurring with the injection of contrast. A third patient (#4) had an elevated LV EDP (38 mm) pre-saline; all other patients met eligibility criteria.

Four patients took concomitant medication (3 took nitrates) throughout the study.

Time to Pacing-Induced Angina:

The mean time to angina was 418 sec (pre-saline), 448 sec (post-saline), and 550 sec (post-ranolazine). The mean increase from baselines were: (pre/post saline) 30 sec (p=NS); and (post-ranolazine/post-saline) 102 sec (95% CI 1.03, 1.42, p < 0.05).

Hemodynamic results: There were no significant or meaningful changes in mean SBP, DBP, or mean BP post-ranolazine compared to pre- or post-saline. Slight increases post-ranolazine were seen. Mean resting HR was 3 bpm higher post-ranolazine compared to post-saline; HR at end of pacing was 133 bpm post-ranolazine compared to 124 bpm post-saline and 120 bpm pre-saline.

Table 1. RAN 003B: hemodynamic parameters (mean)

	Pre-saline	Post-saline	Post-ranolazine
Systolic BP (mm Hg)			
Rest	139	144	139
End of pacing	146	144	141
Heart rate (bpm)			
Rest	66	67	70
End of pacing	120	124	133
Change	54	57	63
Double Product (mm Hg.bpm)			
Rest	9276	9782	9765
End of pacing	17,668	18088	19029
Change	8392	8306	9264

Measurements of LV systolic pressures and contractility were taken only at rest. LV systolic and end-diastolic pressures were similar between pre-saline, post-saline and post-ranolazine values. LV dp/dt (minus Patient #10 post-ranolazine) showed a lower (1602 mm Hg/sec, p=NS) mean compared to pre-saline (1673 mmHg/sec) and post-saline (1645 mm Hg/sec); Vmax/sec post-ranolazine was calculated as 35.1 compared to 33.9 post-saline and 30.8 pre-saline.

Metabolic results:

There were no significant treatment effects of ranolazine on mean pH, mean hemoglobin levels, mean pCO₂ levels, mean % hemoglobin O₂ saturation, mean pO₂ levels, noradrenaline levels, mean lactate levels or mean free fatty acid levels. There was one statistically significant result, namely, the change over pacing in coronary sinus mean adrenaline (nm) levels post-ranolazine compared to post-saline, reflecting a greater increase in coronary sinus adrenaline during pacing in the post-ranolazine group compared to the post-saline group. Given the lack of consistency in other metabolic effects, the meaning of this finding (to this reviewer) is unclear.

Ranolazine plasma assay results:

The submitted data contain more than one data point for only 2 patients; therefore, the available data are limited for analysis. From the limited data available, there does not seem to be an apparent plasma relationship.

Reviewer Comments:

1. This was a small, single-blind, single dose study. The placebo control was not concurrent but always preceded ranolazine dosing.
2. There was a statistically significant increase in the time to pacing-induced angina in the post-ranolazine group; however, the contribution of a training or sequence effect cannot be excluded.
3. An increase in heart rate and double-product at the end of pacing was noted in the post-ranolazine group (p=NS).
4. An increase in adrenaline levels following pacing was seen in the ranolazine group; the meaning of this finding is unclear.
5. No ranolazine effects were seen with respect to BP, lactate, free fatty acids, O₂, CO₂.

RAN 004

Title: A Study to Investigate the Potential Anti-Anginal Efficacy of Intravenous Ranolazine (RS-43285) in Subjects with Ischemic Heart Disease

(Protocol date: November 13, 1985) (Study start date: April 1986; Study completed: April 1987)

Objective: determine safety, tolerance, pharmacokinetic features, invasive cardiac hemodynamic and metabolic effects at rest and after exercise of RS 43285 dosed at 200 µg/kg intravenously in patients with ischemic heart disease.

Study Summary: This was a randomized double-blind placebo-controlled single-dose study of 10 male patients with angina pectoris undergoing diagnostic cardiac catheterization. In this cohort, 4 subjects received placebo and 6 received ranolazine 200 µg/kg. The following parameters were tested pre- and post-exercise prior to and 30 minutes after dosing: mean right atrial pressure (RAP), mean and phasic pulmonary artery pressure (PAP), mean pulmonary capillary wedge pressure (PCW), cardiac output (CO) by thermodilution, phasic and mean systemic arterial pressure (SAP), heart rate, left ventricular (LV) systolic pressure, LV end diastolic pressure (LVEDP), coronary sinus lactate content, time to exercise induced angina.

In addition, symptoms and EKGs were to be monitored. Blood for pharmacokinetic analysis and safety screens and urine for safety tests would be obtained.

After the pre-dose exercise schedule, hemodynamic parameters were allowed to return to baseline prior to dosing with active compound or placebo.

Inclusion criteria: Males, 21-75 years, with classic angina history, ischemic resting EKG, positive stress test, or remote (≥ 3 month) history of MI. Patients must not have received cardiac drugs for one week prior to the study except for: calcium channel blockers and beta blockers up to 48 hours prior to catheterization; long acting nitrates up to 12 hours prior to the study; and sublingual nitroglycerin for up to 2 hours before the procedure.

Exclusions: congenital heart disease; significant valvular heart disease; LV dysfunction (PCW > 18 mm Hg or EF < 40%); left main coronary stenosis; Prinzmetal's/unstable angina; recent MI; bradycardia/LBBB/2nd or 3rd degree AV block; resting SBP < 95 mm Hg or supine DBP > 100 mm Hg, history of MAOI, tricyclic, reserpine or investigational drug use within one month prior to study; DM/hepatic/renal disease; any abnormal laboratory test that would preclude catheterization.

Exercise testing: Supine bicycle testing was planned pre- and 30 minutes post-dosing.

Results:

Patient Disposition: Ten males, 36-71 years old, undergoing diagnostic cardiac catheterization for clinically diagnosed angina, were enrolled. One patient developed a transient ischemic attack (presumed to be related to the catheterization procedure) and was withdrawn prior to receiving study medication. Nine patients (6 on ranolazine, 3 on placebo) completed the trial.

Efficacy:

After dosing, the mean time to exercise-induced angina increased by 5% in the ranolazine-treated group (n=5) and increased by 28% in the placebo-treated group (n=3). Overall exercise times were reduced by 6% in the ranolazine-treated group but increased after placebo.

Pharmacokinetic results: Ranolazine plasma levels fell from a mean (sd) of 675(17.2) ng/ml after 2 minutes to 197 (43.2) ng/ml after 20 minutes.

Hemodynamic measurements: A review of the central hemodynamic measurements, pre and post dosing, showed up to 4% increase in Cardiac Output (CO) with ranolazine, compared to a 10% increase with placebo; after exercise there was a 13% reduction in CO compared to a 51% increase with placebo. Cardiac Index (at rest, after 60 watt exercise load and peak value during exercise) change after dosing by +8%, -22% and -13% with ranolazine, compared to +29%, +186% and +129% for placebo.

Heart rate, peak LV systolic pressures, and mean pulmonary artery pressure changes were similar between ranolazine and placebo.

There were slight decreases in SBP (mean decrease 12 mm Hg for ranolazine, 7 mm for placebo) in both ranolazine and placebo-treated groups.

Mean aortic lactate content before and after dosing increased by 148% (ranolazine) and 78% (placebo) at rest and fell by 18% at a work load of 60 watts (increased 11% after placebo); mean coronary sinus lactate levels increased after ranolazine dosing by over 5 fold at rest (49% increase after placebo) and fell by 9% after exercise (increased 14% after placebo).

Safety: No adverse events were reported after the time of study drug administration. Interpretation of laboratory results was confounded by the high level of missing data. For further safety discussion of ranolazine, please see the safety review.

Reviewer Comments:

1. The sponsor concluded that this study has not generated evidence for a hemodynamic or metabolic basis for ranolazine use as an antianginal agent.
2. The hemodynamic data suggest that ranolazine is associated with decreases in Cardiac Output/Index and decreases in coronary sinus/aortic lactate with exercise; however, this study is too small to generate definitive conclusions.

RAN 006A.

A Study to Investigate the Potential Anti-Anginal Efficacy of Intravenous RS 43285 in Subjects with Ischemic Heart Disease (protocol date: September 2, 1985)

Objective: establish a dose of ranolazine which demonstrates potential anti-anginal efficacy (defined as an increase in time to pacing induced angina of 10% or more).

Study Summary: This was an open-label, ascending dose study of subjects with clinically diagnosed angina who were undergoing diagnostic cardiac catheterization. Fifteen males were to receive a single dose of intravenous ranolazine, 5 at each of the dose levels 50, 100 and 200 µg/kg. Prior to and 20 minutes after dosing the patient would undergo right atrial pacing; hemodynamic parameters, symptoms and ECGs would be monitored and blood/urine samples for pharmacokinetics/safety would be obtained.

Right atrial pacing was planned to start at 100 beats/minute, increasing by 10 beats/minute with each rate held for 3 minutes. The criteria for discontinuation was chest pain or ST depression (measured 0.08 after the J point) of 1 mV below the resting level.

Patient Population: Males, 21-75 years, with clinical diagnosis of angina (positive exercise test or history of MI), who have not received cardiac drugs for one week prior to study, except for: calcium channel blockers/beta blockers up to 48 hours prior to catheterization; long acting nitrates up to 12 hours prior to study; sublingual nitrates up to 2 hours prior to procedure.

Notable Exclusions: congenital/valvular heart disease, LV dysfunction (PCWP > 18 mm or EF < 40%), left main stenosis, Prinzmetal's/unstable angina, MI within 12 weeks, bradycardia/LBBB/greater than 1st degree AVB, SBP < 95 mm or DBP > 100 mm, DM/hepatic/renal disease.

Results:

Fourteen males, mean age 55 years, mean weight 85 kg, entered the study. Six had a history of MI, one had angina, one had intermittent claudication, one had a positive stress test and in 5 the diagnosis was not stated.

Four patients received ranolazine at 50 mcg/kg; 5 received ranolazine at 100 mcg/kg and 5 received 200 mcg/kg.

The duration of pacing in the pre-dose and post-dose assessments is shown below.

Table 1. RAN 006A: Duration of pacing prior to and after dosing

Dose	N	Mean duration (min:sec)	Range (min: sec)
Pre-Dose			
50 µg/kg	4	4:15	1:56-6:03
100 µg/kg	5	5:20	1:30-9:35
200 µg/kg	5	7:13	4:24-11:15
Post-Dose			
50 µg/kg	4	7:31	5:00-10:14
100 µg/kg	5	8:15	3:52-14:20
200 µg/kg	5	9:38	6:00-14:59

Hemodynamics:

Heart rates during pacing appear to reflect pacing rather than drug effect. Both diastolic and systolic mean BP increased during pacing except for the 200 mcg/kg dose, where mean SBP decreased by 0.8 mm Hg.

Pharmacokinetics: Mean plasma ranolazine levels are shown below. The 50 and 100 mcg/kg doses do not appear to be dose-proportional

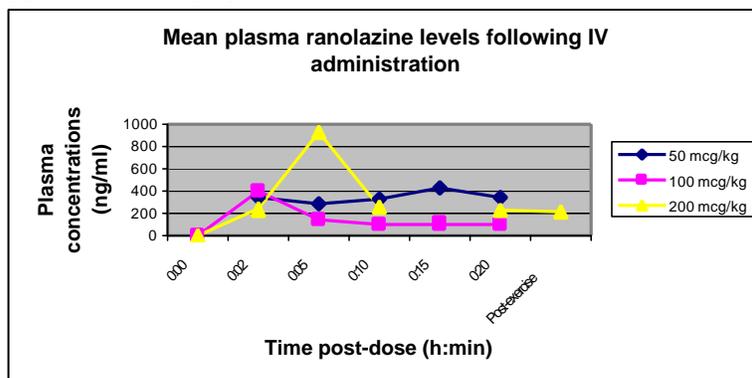


Figure 1. Mean plasma ranolazine levels following iv administration

Safety: For further safety discussion, please see the safety review.

Sponsor conclusions:

The sponsor concluded that the results are of uncertain clinical significance but might support that ranolazine has anti-anginal efficacy. The study failed to identify an appropriate dose for further examination. However, the doses utilized here were not associated with any significant adverse events or disturbances in laboratory parameters. There appeared to be no significant changes in ECG recording during the study period.

Reviewer Comments:

Without a concurrent placebo control it is difficult to interpret the post-dose increase in duration of pacing.

RAN 007.

Title: A Study to Investigate the Potential Anti-Anginal Efficacy of RS 43285 in Subjects with Ischemic Heart Disease (protocol date: December 23, 1985)

Note: Study Terminated Prematurely—see below

Objective: Establish a dose of RS 43285 which demonstrated potential anti-anginal efficacy. In addition, assess hemodynamic, pharmacokinetic, tolerance and safety features of the administered doses.

Study Summary: This was a double-blind placebo-controlled crossover trial of males with stable angina. Eligible patients with a stable baseline treadmill exercise test will receive, on 4 consecutive days, single doses of placebo and 10, 20 and 30 mg RS 43285 administered according to a double-blind crossover schedule. Prior to and ninety minutes after dosing a treadmill ETT will be performed. In addition, hemodynamic monitoring, ECGs, and blood for pharmacokinetic analysis/safety would be obtained.

Patient Population: Males, 21-75 years, with clinical diagnosis of stable angina and positive exercise test (limited by angina) or history of MI. Patients must be off cardiac drugs except for: calcium/beta blockers up to to 48 hours prior to any study day; long-acting nitrates up to 12 hours prior to any study day; and sublingual nitroglycerin up to 2 hours prior to dosing on any study day. Patients must be pretrained 2 days prior to the study, with 2 consecutive treadmill exercise tests showing exercise tolerance differences of less than 15%.

Notable Exclusions: congenital/valvular heart disease, LV dysfunction (PCWP > 18 mm or EF < 40%), left main stenosis, Prinzmetal's/unstable angina, MI within 12 weeks, bradycardia/LBBB/greater than 1st degree AVB, SBP < 95 mm or DBP > 100 mm, DM/hepatic/renal disease.

Exercise testing: A multistage exercise test according to the standard Bruce protocol was planned prior to and 90 minutes after dosing. Testing was to stop for: symptoms of angina, reduction in SBP \geq 10 mm Hg, ECG effects/arrhythmia/high grade heart block.

ECGs: Twelve-lead ECGs were recorded prior to and within 1-4 hours after dosing on each day of the study.

Protocol Amendment: (November 4, 1986): Because 5 patients experienced minimal effects at 10 and 20 mg ranolazine, the doses were increased to 20, 40 and 60 mg.

Results:

A total of 12 patients, mean age 58 years, mean weight 85 kg, were enrolled. After 5 patients received the original doses, an additional 7 patients received doses of 20, 40 and 50 mg ranolazine and placebo in random order.

The study was apparently terminated prematurely because of slow progress or the lack of clear hemodynamic or antianginal effects. No efficacy data were provided and no details were given for the incompleteness of data.

Plasma Levels: Mean (sd) ranolazine concentrations after 90 minutes were: 28.1 (13.7), 60.5 (35.1) 88.1 (48.3), 179 (57.7) and 239 (41.1) ng/ml for 10, 20, 30, 40 and 60 mg, respectively.

Reviewer Comment: No efficacy data have been presented in this study. According to the study report, no evidence is available to support the pharmacologic activity of ranolazine in the 10-60 mg range.

RAN 010.

Title: A Pilot Dose-Finding Study of Oral RS 43285 (ranolazine) in Stable Angina Pectoris (Protocol date: September, 1986)

Objective: Determine efficacy and tolerability of 3 dose levels of RS 43285 compared with placebo.

Study Summary: This was a double-blind, randomized, placebo-controlled study. After a 7 day withdrawal period from cardiac medications, patients entered a 1 week placebo run-in period followed by randomization to placebo or 10, 30 and 50 mg RS 43285 tid. On the 7th day of each week the patient underwent a side effect questionnaire as well as treadmill exercise test. Patients who fail to produce at least 1 mm ST deviation within 15 minutes (or 240 watts) on treadmill exercise, or fail the compliance check on Day 7 of the placebo period, will be discharged, not included in the analysis, and replaced.

No concomitant medications were permitted in placebo or active treatment periods. Short-acting nitrates was allowed only for treatment of angina attacks.

A daily record of angina attacks and nitrate consumption was planned.

Patient Population: Males or females, 21-70 years old, with at least 3 month history of stable angina, > 50% stenosis in one or more major coronary arteries, normal LV function (EF > 50%) and sinus rhythm.

Notable Exclusions: MI within 3 months; CHF; hypertension (DBP > 95 mm Hg); cardiac arrhythmia; left main disease; pregnant/lactating women; significant laboratory abnormality.

Exercise Testing: The exercise test, done 60 minutes after the morning dose, followed the Bruce protocol to the maximum work tolerance. Reasons for stopping the test included: 1. More than 15 minutes; 2. Angina; 3. Dyspnea/fatigue without chest pain; 4. Other; 5. Arrhythmia or other contraindication to continuing.

Other measured parameters for 15 minutes after testing included: time to 1 mm ST change; time to 2 mm ST change; maximum ST change; time from end of exercise to ST segment returning to isoelectricity; summed ST change (ST deviation to nearest 0.5 mm from start of test to 15 minutes after end of exercise test).

Side Effect Questionnaire: This was completed in English by the physician and involved frequency, severity and relationship of side effect to study drug.

Results:

Twenty-five patients were enrolled in the study; one patient, a protocol violator (age 78), was still included in the analysis. The trough exercise test was not performed by a proportion of patients; in addition, some

safety laboratory tests were lost. Of the twenty-five patients, 6 patients were on no pre-study anginal therapy, had no anginal attack during placebo run-in, and therefore did not stop the exercise test due to angina.

Baseline characteristics: The study population was mostly male, mean age 55-61 years, mean weight 67-79 kg, 20-50% smokers.

Anginal attacks/NTG consumption: On placebo, anginal attacks fell from a mean 3.8/week during run-in to 2.3/week during the second week. Mean anginal attacks and NTG consumption increased, compared to placebo, in the 10 mg TID ranolazine group and decreased, compared to placebo, in the 50 mg tid group; missing data were noted in the ranolazine 30 and 50 mg tid groups.

Exercise times:

Mean exercise times at both peak and trough (Day 14) were higher in the placebo group (10.64 and 9.95 sec, respectively) than for ranolazine 50 mg tid (9.34 and 8.54 sec, respectively). The change from baseline for the peak study was also higher for placebo than ranolazine 50 mg tid. The other measured parameters (time to 1 mm ST deviation, time to 2 mm ST deviation, maximum ST depression, recovery time) did not show a consistent pattern.

Pharmacokinetic data:

Serum samples for ranolazine were apparently mishandled and therefore not available for analysis.

Reviewer Comments: No evidence of antianginal efficacy was seen in this study.

RAN 011.

Title: A Study of RS-43285 (Ranolazine) on Myocardial Metabolism. (Protocol date: June, 1987)

Objective: Study the metabolic changes induced by I.V. RS 43285 (ranolazine) in the human myocardium

Study Summary: This was an open-label, nonrandomized study comparing pre-treatment and post-ranolazine data without the use of a concurrent placebo control. Ten male patients with angina and at least 50% LAD stenosis will be selected; another 10 males with chest pain, and normal coronary arteries, exercise tests, hyperventilation responses and echocardiography will also be studied. A preliminary 12-lead ECG bicycle test (starting at 50 watts, increasing by 50 watts every 3 minutes) must show at least 1 mm ST depression in the patients with coronary artery disease.

All cardio-active medication, except for short-acting nitrates and diuretics, were to be withdrawn at least 7 days prior to study. On the day prior to study, patients will be admitted, receive screening laboratory tests, and undergo post-midnight fasting. Patients with normal screening laboratory tests will be sent to the catheterization laboratory to undergo insertions of: femoral artery (BP/arterial samples) catheter, coronary sinus catheter (coronary sinus blood flow (CSBF) and sampling), pulmonary artery catheter via femoral vein (PAS, PAD, PAP), and venous cannula for drug administration. In addition, a single lead ECG would record heart rate and ST changes (ST segment deviation will be measured at 30 second intervals).

Two test sequences would then follow, with about 45 minutes between each sequence. The first would be without drug, and the second sequence would occur after a 2 minute bolus of RS 43285 (140 µg/kg) followed by a steady state infusion of 1.2 µg/kg/min RS 43285 by syringe pump. Ranolazine will be started 7 minutes before the test sequence and will continue throughout the test sequence.

Each test sequence would consist of a base phase (5 minutes at sinus rate) followed by a pacing phase (150 bpm), followed by a recovery phase (10 minutes at sinus rate). Each test sequence will be preceded by determination of HR and BP, and the sequence not started until 3 consecutive readings do not differ by more than 10%.

In the basal phase, and in the first and second minutes following onset of angina in the pacing phase, and in recovery, CSBF, CS and arterial samples will be obtained and HR, arterial BP and pulmonary artery pressures will be measured. If the CAD patient does not experience angina with ST changes in the first (control) test sequence they must be discharged from the study. Time to onset of angina in the first

sequence must be noted and the patient paced to the same time in the second (drug) sequence. Pacing should stop once angina is established and should not last longer than 10 minutes.

Patients with normal coronary arteries will be paced for a maximum of 10 minutes if no angina occurs.

Arterial and CS samples will be analyzed for: oxygen (for MV02), lactate, citrate, alanine, glutamic acid, free fatty acids, glucose, xanthine and hypoxanthine.

Patients will remain supine from admission until completion of study. Each pacing phase will be preceded by 0.5 mg atropine IV. Prior to pacing and after recovery a plasma sample for RS 43285 will be drawn.

Patient Population: 1. Males with CAD, effort angina and at least one 50% stenosis on coronary angiogram in 1 or 2 vessels, one of which must be the LAD.; 2. Males with atypical chest pain with normal exercise tests, echocardiography, angiograms, normal hypoventilation responses and metabolic profiles.

Notable Exclusions: left main disease, contraindications to exercise testing, clinical significant ECG/laboratory abnormality, contraindications to the procedure, single RCA disease.

Analysis Plan: According to the protocol, a 5% level of significance will be used in the study analysis; the statistical methods will be decided after preliminary review of the data. No primary efficacy variable was prespecified in the protocol.

Protocol Amendments: There were 4 protocol amendments that: specified basal phase hemodynamic/metabolic measurements at 2 time points (2 and 3 minutes) and measured hypoxanthine/xanthine at one time point during basal, pacing and recovery periods; doubled ranolazine loading dose and infusion; changed ranolazine dosing and regimen (200 µg/kg iv bolus + 20 µg/kg/min) so that loading and infusion doses would occur simultaneously (goal was plasma concentrations of 500 ng/ml occurring 20 minutes after the start of dosing).

Results:

Disposition and Baseline Characteristics:

Seventeen males (9 with CAD and 8 with normal coronaries) were enrolled and completed the study. Mean age in the CAD group was 55 years compared with 45 years in the group with normal coronaries. Mean weight in the group with CAD was 78 kg; mean weight in the normal group was 85 kg. Eight patients in the CAD group were Caucasian and one was Asian. In the normal group, half were Caucasian and half were Asian. There were no differences between the two groups in mean atrial/ventricular rate, PR, QRS and QT intervals.

The mean total (mg) IV ranolazine dose received was 32.7 mg in the CAD group and 31.7 mg in the normal group.

Metabolic Results: The following calculations were used:

MV(myocardial uptake or release) = (arterial minus coronary sinus) x CSBF

Extraction = $\frac{\text{arterial minus coronary sinus}}{\text{arterial}} \times 100\%$

ANOVA, including group (CAD or normal), phase (control or treatment) and stage (ie basal, pacing 1 and 2, recovery 1-4),, as factors and interaction terms, was used to compare control and treatment phases. Due to the large amount of missing xanthine and hypoxanthine data, calculated values were not analyzed.

Myocardial oxygen uptake during control and treatment phases is graphically depicted (Figure 1). It should be noted that results of the two groups, during the control (pre-drug) phase, are not superimposable. During the treatment phase, values consistently increased in the normal group and decreased in the CAD group. According to the sponsor, a statistically significant group by treatment interaction (p=0.043) was seen for MV oxygen.

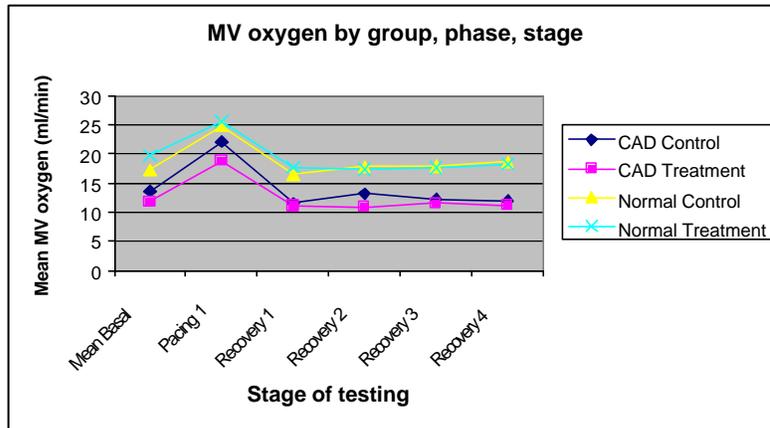
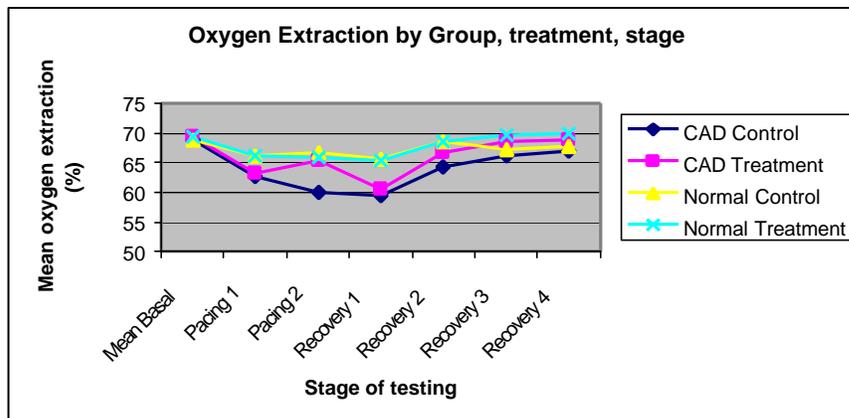


Figure 1. Myocardial oxygen uptake by group (CAD or normal), phase, sequence (control or drug).

Oxygen extraction is also depicted graphically (Figure 2). According to the sponsor, a statistically significant difference was seen between control and treatment ($p=0.02$).

Figure 2. Oxygen extraction by group, treatment, phase.



Other statistically significant differences were noted for glutamic acid extraction ($p < 0.001$) and free fatty acid uptake (MV FFA) ($p=0.01$). There was no statistically significant difference seen for MV citrate; for MV lactate, MV glucose and glucose extraction, values were lower with treatment with differences yielding $p=0.06$ to 0.07 range. Myocardial lactate production (negative arterio-coronary sinus difference in lactate concentration) was seen in 3 patients only during control pacing.

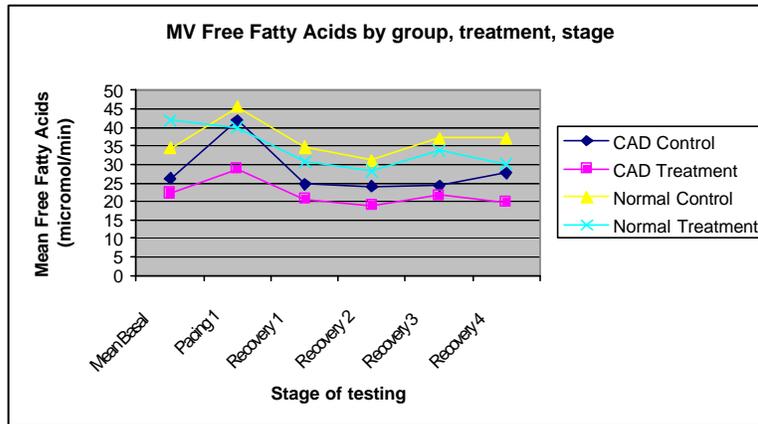


Figure 3. FFA Uptake ($\mu\text{mol}/\text{min}$).

Reviewer: The mean basal levels are not superimposable; there is about a 2-fold difference between normal treatment and CAD treatment. Except for the normal treatment group, MV FFA increased with pacing and decreased toward baseline during recovery 1 and 2. In both CAD and normal groups there is a decrease in MV FFA with treatment (see above, according to the sponsor this difference was statistically significant). According to the sponsor, the phase x stage interaction was not statistically significant.

Pacing Results: There were no statistically significant differences between control and treatment values for time to onset of angina, time to 1 mm ST depression, time to maximum ST depression and duration of pacing. Maximum ST depression was statistically significant between control (median = -2 mm, range -4 to -1 mm) and treatment (median = -1 mm, range -2 to -0.5 mm) phases ($p=0.02$).

Reviewer: Given the lack of other statistically significant differences (e.g., time to angina, duration of pacing) with pacing, the meaning of one positive finding, maximum ST depression, is unclear.

Hemodynamic Results:

Examination of heart rates and DBP did not reveal any meaningful differences between control and treatment groups.

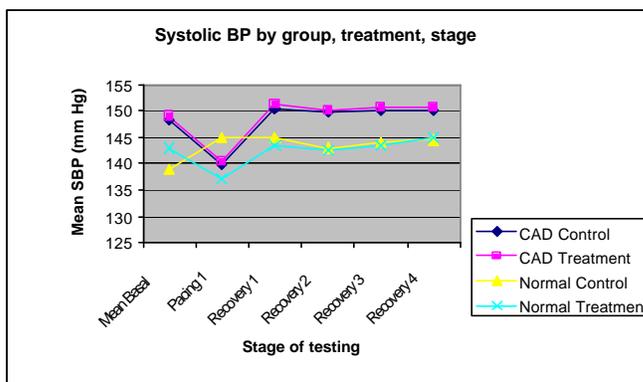


Figure 4. SBP

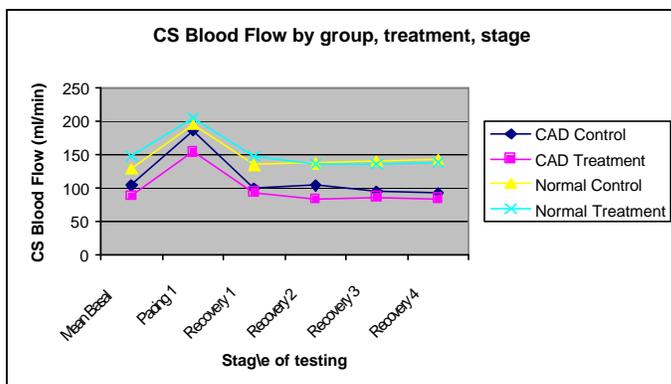


Figure 5. CS Blood Flow

Results of CS Blood flow and SBP are shown. Differences between “normals” and patients with CAD seem more apparent compared with differences between control and treatment.

Ranolazine plasma levels:

Table 1. RAN 011: Ranolazine plasma levels

Mean (SD)	140 mcg/kg iv bolus + 1.2 mcg/kg/min iv infusion	200 mcg/kg iv bolus + 2.0 mcg/kg/min iv infusion
Baseline	<10	<10
12 minutes	312 (112)	498 (374)
18 minutes	214 (63.9)	581 (243)

Safety: For safety discussion, please see the Safety Review

Reviewer Comments:

1. This was a small, open-label, nonrandomized study of males with either atypical chest pain and normal coronary arteries or effort angina and CAD. There was no placebo control group. No primary efficacy parameter or statistical method of analysis was prespecified. Method of analysis, according to the protocol, was decided after preliminary review of the data.
2. There appear to be differences between normal and CAD patients in myocardial oxygen uptake, coronary sinus blood flow and SBP. Differences between normal and CAD patients may confound several results in this study.
3. In this study without a concurrent placebo group, a reduced FFA uptake is noted with ranolazine treatment compared to baseline. Given the ranolazine plasma levels achieved, along with the lack of several anti-anginal treatment effects (ie, time to angina, pacing duration, time to 1 mm ST depressions), it is unclear whether what role this effect (reduction in FFA uptake) plays in anti-anginal treatment benefits of ranolazine.

RAN 012.

Title: A Single-Blind Study of Ranolazine (RS 43285) versus Placebo in Patients with Angina Pectoris (Protocol date: November 6, 1986) (Study dates: November 1986-May 1987)

Objective: evaluate, using anginal attack frequency, nitrate consumption and exercise tolerance, the 2 week efficacy of ranolazine 30 mg and 60 mg tid.

Study Summary: This was a single-blind single-site study of the safety and efficacy of ranolazine 30 mg po tid and then, if tolerated, 60 mg po tid; both doses would be administered for two weeks each. A one week washout period and 2 week placebo period preceded the active treatment phases. There was no washout period in between the two active treatment periods.

Efficacy of each treatment would be evaluated by comparing each patient's ETT performance during washout, at the end of placebo and each active treatment phase. Efficacy was also measured by assessment of daily patient recordings of anginal frequency and nitroglycerin consumption.

Safety evaluations consisted of AE monitoring and laboratory testing. In the event of an increase in frequency or severity of anginal symptoms during placebo run-in or active treatment periods, patients may be advanced into the next treatment period as an alternative to withdrawal. If the patient had continued medication to that point, the ETT must be done first.

Concomitant medication: Use of sublingual nitroglycerin was allowed only as treatment for anginal attacks.

Sample size: 15 enrolled or 12 completers.

Inclusion criteria:

1. Males and nonpregnant females, 21-75 years old, with at least 3 month history of stable effort angina relieved by rest/nitroglycerin;
2. The difference in exercise time (on ETT) between the first 2 exercise tests, prior to active treatment, must be less than 20% of the longer time; in addition, evidence of ischemic (i.e. ST depression \geq 1mm at 80 msec after J point) must be present in a standard ECG lead;
3. Maximal ETT at the end of placebo phase must be 3-10 minutes;
4. If the patient has had a coronary angiogram, 50% or greater occlusion in a major coronary artery (or one of its primary branches) must be present;
5. Patients currently under treatment for angina will be admitted only if their response to such treatment is inadequate or complicated by unwanted effects;²⁵

Notable Exclusions:

1. Presence of factors associated with false positive stress test;
2. Uncompensated CHF;
3. Valvular heart disease/septal defects;
4. Unstable angina within the last 4 weeks;
5. Second or third degree AVB or any uncontrolled arrhythmia other than sinus arrhythmia/occasional extrasystoles;
6. MI within the past 3 months;
7. Acute myocarditis/cardiomyopathy/acute pericarditis;
8. SBP < 95 mm Hg or sitting BP > 165/110 mm Hg;
9. Abnormal renal/hepatic tests/potassium/anemia/IDDM.
10. Inability to discontinue long-acting nitrates, beta blockers, antihypertensive medication, calcium channel blockers or any investigational drug. Digitalis was not permitted in this study. Diuretics were allowed if continuous throughout the study.

Exercise Tolerance Tests:

Time to angina, time to 1 mm ST depression, time to 2 mm ST depression and time to maximal exercise capacity were recorded for all ETT. All exercise tests were performed on a motor-driven treadmill under uniform conditions, at the same time of day at each visit. The exercise protocol will be determined by the principal investigator and would be the same for all patients in the study.

Each patient would undergo an ETT at the end of washout, 90 minutes post-dose on the first day of ranolazine 30 mg tid (phase 2), and the end of placebo, ranolazine 30 and 60 mg tid treatment periods (phases 1, 2, and 3) and 7 hours post-dose at the end of each phase.

Patients were to refrain from smoking or sublingual nitroglycerin use on the morning of the clinic visit or within 2 hours prior to ETT.

²⁵ It is not stated whether or not patients needed to be on maximal therapy.

Criteria for stopping ETT: signs of vasoconstriction (pale, clammy skin), atrial fibrillation/tachycardia, dyspnea, electrical alternans, SBP \geq 230 mm Hg, fatigue, faintness, musculoskeletal pain/discomfort, progressive angina/ BP drop/ST changes/QRS widening/increase in PVCs/ventricular tachycardia.

Angina frequency/nitroglycerin consumption: These events were recorded by patients on weekly diary cards.

Results:

Patient Disposition: Sixteen patients were recruited; 15 patients received at least one dose of active treatment and 12 completed all phases of the study. One patient withdrew from active treatment due to chest pain requiring hospitalization. Another patient did not meet entry criteria. Two patients were withdrawn from placebo (because of ineligibility and noncompliance, respectively).

Baseline characteristics:

Twelve males and four females, mean age 59 (range 39-74) years, 100% Caucasian, were enrolled.

Ranolazine plasma levels:

According to the sponsor, a freezer malfunction damaged a number of stored samples (for example, for patients 2 and 3, only 2 plasma samples were available). The mean plasma level 1.5 hours following the first dose of ranolazine 30 mg was 113 ng/ml. On Day 28, the mean ranolazine concentration was 167 ng/ml (1.5 hours after the last dose of ranolazine 30 mg tid) and 29.2 ng/ml (7 hours after the same dose). On Day 42, the mean ranolazine concentration was 354 ng/ml (1.5 hours after the last dose of ranolazine 60 mg tid) and 73.3 ng/ml (7 hours after the same dose).

Drug Accountability:

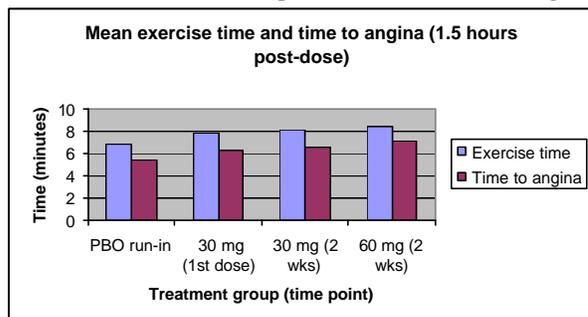
According to the sponsor, it was discovered, during one of the monitoring visits, that written records were not being kept of drug dispensing and accounting for treatments issued to patients. Drug accountability records were then performed retrospectively from the returned drugs and tablet count data. No data were provided on the assessment of patient compliance.

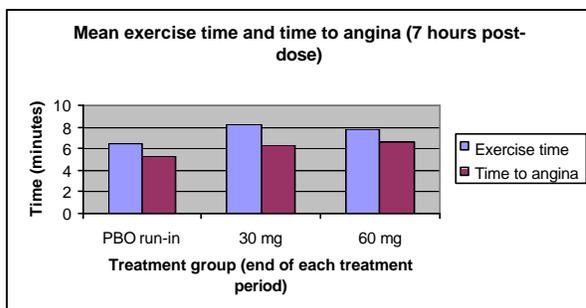
Efficacy:

Anginal attacks/nitroglycerin consumption: During placebo, mean number of anginal attacks and nitroglycerin (ntg) consumption were 12 ± 4 and 11 ± 4 , respectively. During the ranolazine 30 mg phase, mean number of anginal attacks and ntg consumption were 10 ± 4 and 10 ± 4 , respectively; during the ranolazine 60 mg phase, mean number of anginal attacks and ntg consumption were 6 ± 2 and 3 ± 1 , respectively. These differences were not statistically significant.

ETT:

Exercise time and time to angina are depicted graphically for the 1.5 and 7 hour post-dosing timepoints. It should be noted that the time to angina was similar between peak and trough times for placebo and the ranolazine 30 mg tid groups. Significant p-values were calculated for exercise time and time to angina (each active treatment vs. placebo) but not for 30 mg vs. 60 mg dosing.





Figures 1 and 2. Mean exercise time and time to angina at peak and trough

The sponsor has noted that methodology for ST depression measurement was not always uniform (ie, the first ETT for patient #13 was recorded manually; recordings for patient #15 were performed on the “Mark 12” equipment). On the Mark 12 equipment, “peak” was defined at end of exercise (not necessarily the same time as maximum ST depression). In addition, the initial exercise tests did not always agree with the $\pm 20\%$ entry criterion as defined in the protocol.

Hemodynamic measurements: Heart rate at rest and peak exercise, resting and peak SBP and rate pressure product (peak exercise) showed no appreciable changes at peak and trough times in this study.

Safety: For safety discussion, please see the safety review.

Reviewer Comments:

1. This was a small, single-blind, ascending dose pilot study. There was no concurrent placebo control.
2. Improvements in exercise time and time to angina may have been related to sequence effects rather than a true treatment effect.
3. The dose-concentration relationship appears to be linear in this dose range.
4. In this dose range and treatment period, there were no meaningful ranolazine effects on resting and peak heart rate and SBP as well as peak rate pressure product.

RAN 014.

A Study of the Effects of RS-43285 on Coronary Blood Flow, Myocardial Metabolism and Left Ventricular Function in Patients with Angina Pectoris (Protocol date: April, 1987)

Objectives (listed as aims): 1. Determine if RS 43285 improves myocardial biochemistry in patients with angina pectoris under resting conditions and during transient high demand ischemia; 2. Determine dose/response relationship of these effects in patients; 3. Determine effects of the compound on global coronary hemodynamics (coronary vascular resistance, coronary sinus flow) and left ventricular function.

Study Summary: This was an open-label, non-randomized, ascending dose study without a placebo control. Patients with angina underwent hemodynamic and metabolic measurements first in the basal state in sinus rhythm and then after increasing the heart rate up to an average of 115 bpm by atrial pacing. These measurements, at basal state and with pacing, were then repeated 20 minutes after intravenous ranolazine administration. The dose of ranolazine was 50 $\mu\text{g}/\text{kg}$ in the first 5 patients, 100 $\mu\text{g}/\text{kg}$ in the next 5 patients, and 150 $\mu\text{g}/\text{kg}$ in the last 5 patients. In addition, C-14 lactate was infused continuously during the study at a rate of 12 $\mu\text{Ci}/\text{hour}$ after a priming bolus of 10 $\mu\text{Ci}/\text{hour}$, in order to determine the net transcardiac lactate production.

In order to account for “spontaneous variation,” ten patients were to be restudied after 20 minutes in the absence of drug treatment.

Patients were instrumented as follows: left heart catheterization (Judkins) with LV pressure recording, arterial pressure, right heart catheterization (thermodilution) with pacing electrodes in the coronary sinus, arterial and coronary venous blood samples. Hemodynamic and ECG were digitized and processed off-line to derive heart rate, LV systolic and end-diastolic pressure, dP/dt max and min (dp/dt/DP40)²⁶, T1, T,²⁷ ejection time, systolic/diastolic/mean arterial pressures, coronary sinus blood flow (CSBF), coronary vascular resistance²⁸. In addition, blood samples were analyzed for lactate-glucose plasma levels, alanine, glutamine, glutamic acid, free fatty acids and C-14 lactate. A venous blood sample for plasma ranolazine was taken after each drug phase.

Patient Population: Males and females, 35-75 years old, with angina pectoris and angiographic evidence of CAD.

Notable Exclusions: LV dysfunction, abnormal impulse generation/conduction, MI within 3 months of study, pregnant/lactating females, significant laboratory abnormality.

Analysis: No primary efficacy parameter was prespecified in the protocol. A 5% level of statistical significance was prespecified. The statistical method used will be decided after preliminary review of the data.

Concomitant medication: All cardioactive drugs except short-acting nitrates were to be stopped at least 2 days before study and no premedication will be used.

Protocol Amendment: One protocol amendment (June, 1988) replaced exclusion criterion of “LV dysfunction” with “evidence of congestive heart failure,” and added sampling for pyruvate and safety laboratory tests.

Results: Fifteen patients (14 males), 38-68 years (median 53 years) were enrolled and completed the study; no side effects were reported. Two patients had a history of MI within 3 months of study entry but were included in the analysis; another patient received isosorbide dinitrate on demand and did not stop other cardiovascular medication until the day prior to study entry.

Coronary hemodynamics, LV function, Systemic arterial pressure: Mean coronary sinus blood flow increased and coronary vascular resistance decreased with pacing in all groups; there were no statistically significant differences between treatment vs. control in either basal or pacing state. In addition, heart rate, diastolic pressure, mean arterial pressure increased and LV systolic pressure, arterial systolic pressure, decreased in all groups with no statistically significant difference between treatment vs. control in either basal or pacing state. Mean LVEDP decreased with pacing in all groups; there was a statistically significant difference (p=0.04) between treatment vs. control in the basal state only (ie, the basal values in the treatment sequence were lower compared to basal values in the control group). There were no statistically significant differences between treatment vs. control in dP/dT indices or in the indices of relaxation. A statistically significant decrease was seen (treatment vs. control) in the basal state (p=0.03) with regard to mean transcatheter oxygen extraction (arterial minus coronary sinus oxygen); however, no statistically significant difference was seen (during basal or pacing states) with regard to mean myocardial oxygen consumption.

Reviewer: Other than a lower basal mean LVEDP, no statistically significant consistent changes were seen with regard to hemodynamics.

²⁶ As indices of inotropic state, maximum of the first derivative of LV pressure (dP/dt Max) and dP/dt measured at a developed pressure of 40 mm Hg and normalized for this pressure [(dP/dT)/DP40] were used.

²⁷ Time-constants of the early (0-40 ms) and late (0-80 ms) exponential of LV pressure decrease during relaxation and dP/dt Min were used as indices of relaxation.

²⁸ Coronary vascular resistance was defined in the study report as the ratio of mean aortic pressure/mean coronary blood flow.

Metabolic data: Median lactate uptake and percent lactate extraction showed no significant difference between treatment and control.

The median C-14 lactate uptake ($\mu\text{mol}/\text{min}$) showed a difference (treatment minus control) of -4.6 at the basal state ($p < 0.001$); no significant difference was seen with pacing.

The percentage C14 lactate extraction showed no statistically significant differences between treatment vs. control.

Median lactate production ($\mu\text{mol}/\text{min}$) also was significantly lower (treatment minus control) at the basal state (difference of 5.3 , $p < 0.01$); no significant difference was seen with regard to pacing.

Median myocardial glutamic acid uptake ($\mu\text{mol}/\text{min}$) showed a statistically significant increase with pacing (but not at basal state); the median difference (treatment pacing minus control pacing) was 1.27 ($p=0.04$).

Myocardial metabolism of alanine, glutamine, free fatty acids or pyruvate showed no significant changes in the basal state or during pacing.

Plasma ranolazine levels:

Mean levels at 20 minutes post-dosing ranged from $51 \text{ ng}\cdot\text{ml}^{-1}$ in the ranolazine $50 \mu\text{g}/\text{kg}$ group to $217 \text{ ng}\cdot\text{ml}^{-1}$ in the ranolazine $150 \mu\text{g}/\text{kg}$ group.

Reviewer comments:

1. This was a small, open-label, nonrandomized study without a placebo control in a population with angina and CAD.
2. The only statistically significant finding during pacing was an increase in median myocardial glutamic acid uptake; the significance of this isolated finding, in the absence of other positive findings for pyruvate, free fatty acids, etc. is unclear.
3. Statistically significant differences at the basal state were seen (ranolazine vs. control) with regard to: mean LVEDP, median C-14 lactate uptake, median lactate production; the significance of these findings is unclear.

RAN 017.

A Single-Dose Placebo-Controlled Study of Ranolazine (RS-43285, 120 and 240 mg) on Ischemic Burden

Primary Objective: compare effect of two single doses of ranolazine (120 and 240 mg) with placebo on ST displacement profile during bicycle ergometry and during recovery.

Study Summary: This was a double-blind randomized placebo-controlled crossover study in patients with stable exertional angina receiving no anginal medication other than short-acting nitrates (which were prohibited for 2 hours prior to exercise testing). Each patient attended on two test days, at an interval of 3 + 1 days, where they performed bicycle ergometric exercise testing at baseline (0), and 2 and 6 hours following a single dose of ranolazine or placebo. Plasma samples were obtained at 2 and 6 hours post-dose. Patients were excluded if there was not at least 0.1 mV ST depression in one of the standard ECG leads during the baseline exercise test.

The original protocol (March 17, 1987) specified only the 120 mg dose; this protocol was amended (February 16, 1988) after an “informal interim analysis” to allow 240 mg to be studied in a further series of patients. A minimum of 10 patients was required to be studied at each dose level.

Study Population: Males, 21-75 years, with stable, classic exertional angina, ischemic heart disease (confirmed by at least 75% stenosis in one coronary artery, history of MI, or history of angina with ST depression on exercise), normotensive, sinus rhythm with no evidence LV impairment, and at least 0.1 mV ST depression in one lead during the baseline test on day 1.

In an amendment (November 17, 1987) postmenopausal or surgically sterilized females, up to 75 years old, were allowed to enroll.

Notable exclusions: Patients on antianginals which could not be withdrawn prior to study; presence of clinically significant disease requiring continuing medical therapy or supervision; significant laboratory abnormality.

Sample size: 12 per dose level. Evaluable patients were required to complete the full test day protocol (6 hours) on both dose occasions.

Exercise testing: Symptom-limited bicycle testing was performed, starting at 25 watts, increasing by 25 watts every 2 minutes. ECG recordings were taken in the last 10 seconds of every minute; BP was measured every 2 minutes. After cessation of exercise, BP and ECG were monitored each minute for up to 10 minutes. The permitted difference in duration between the two baseline tests (test day 1 and 2) was \pm 20%.

Analysis: Two dose groups were entered in this study, the second dose group beginning after completion of the first. A double-blind two-period crossover study was carried out within each dose group. No randomization was carried out between doses and the random code supplied for the 120 mg group was repeated for the 240 mg dose.

The primary variable of interest was ST depression during exercise and recovery. This was calculated as the summed ST depression during exercise, during recovery and for the total period. Summed ST depression at 2 and 6 hours was analyzed separately, and the difference from the pre-dose exercise test was analyzed as well.

An analysis of variance was used, with treatment sequence, between-patient error, treatment effect and the treatment by sequence interaction (period effect) included in the model.

Results:

Patient Disposition: Ten patients were entered in the 120 mg group and 12 in the 240 mg group. However, 3 of the patients in the 240 mg group had already entered and completed the study in the 120 mg group and were excluded from the efficacy analysis for the 240 mg group. Therefore, 9 patients were included in the efficacy analysis for 240 mg. One patient in the 120 mg group received ranolazine and placebo in the wrong order (as shown by plasma levels) and was therefore included in the placebo/ranolazine, rather than ranolazine/placebo group.

Study days were 2-5 days apart.

Baseline characteristics: Sixteen males and 3 females with median age 63-66 years (range 49-74 yrs). Median number of angina attacks were 3.5-4 per week. A majority (12 patients) had NYHA Class III symptoms.

Efficacy:

The comparison of summed ST depression during exercise showed no significant benefit of ranolazine over placebo. This was true for both doses and at both time points.

During recovery, no significant effect of ranolazine compared to placebo was seen at 2 hours. A significant improvement in the rate of ST segment return to baseline was seen in the 120 mg group ($p=0.04$) but not confirmed in the 240 mg dose group.

Plasma ranolazine levels ranged from mean (sd) 310 (78) ng/ml (2 hours after 120 mg) and 742 (240) ng/ml (2 hours after 240 mg) to 104 (68) ng/ml (6 hours after 120 mg) and 44 (84) ng/ml (6 hours after 240 mg) and did not correlate with ST changes.

Reviewer comments: Ranolazine did not affect ST depression in this study.

RAN 070.

Title: A Study of the Effects of Ranolazine on Coronary Blood Flow, Myocardial Metabolism and Left Ventricular Function in Patients with Angina Pectoris (protocol date: December, 1988).

Objectives (listed as 'aims'):

1. Determine if RS 43285 improves myocardial biochemistry in patients with angina pectoris under resting conditions and during transient high demand ischemia;
2. Determine effects of the compound on global coronary hemodynamics (coronary vascular resistance, coronary sinus flow) and left ventricular function.

Study Summary:

This was a single-blind, randomized, parallel-group study of twenty patients with angina pectoris and CAD. Ten patients were to receive saline and ten receive RS 43285. Hemodynamic measurements and blood sampling were planned in resting sinus rhythm and during an increase in oxygen demand induced by increasing heart rate (pacing rate 130 bpm).

After control measurements in sinus rhythm, atrial pacing would be started at an average rate of 135 ± 5 bpm for 5 minutes. Measurements would then be made in the last 2 minutes of pacing. Following pacing, there was a recovery period (variable according to individual); then, the period in sinus rhythm and pacing period were repeated during drug administration.

C-14 glutamate was infused continuously during the study at a rate of $12 \mu\text{Ci/hr}$ after a priming bolus of $10 \mu\text{Ci}$, in order to determine the net transcardiac glutamate production. Ranolazine was dosed as an IV bolus $250 \mu\text{g/kg}$ over 2 minutes followed by a $2 \mu\text{g/kg/min}$ infusion administered to the end of the study; this was predicted to give a steady-state level of 250 ng/ml .

Patients were instrumented as follows: Left heart catheterization (Judkins), Millar Micromanometer (LV pressure), arterial pressure, right heart catheterization (thermodilution catheter) with pacing electrodes in the coronary sinus, arterial and coronary venous blood samples.

Hemodynamic/ECG data were digitized and processed off-line to derive heart rate, LV systolic and end-diastolic pressure (LVEDP), $dP/dt \text{ Max}$, $dP/dt \text{ Min}$, $(dP/dt)/DP \text{ 40, T, T1}^{29}$, systolic/diastolic/mean arterial pressure, coronary sinus flow, coronary vascular resistance. In addition, blood samples were analyzed for lactate, plasma glucose, alanine, glutamine, glutamic acid, plasma glutamate and free fatty acids. Venous samples for ranolazine levels were also collected.

Study Population: Males and females, 35-75 years, with angiographic evidence of CAD.

Notable Exclusions: CHF or abnormal impulse generation/conduction, MI within 3 months of study, pregnant/lactating women, clinically significant disease/laboratory abnormality.

Premature Terminations: All patients who withdraw should be replaced.

Concomitant Medications: All cardioactive drugs except short-acting nitrates were to be stopped at least 2 days prior to study and no premedication will be used.

Drug Supply: Ranolazine was supplied in open labelled ampules. Dextrose was supplied as matching placebo.

Analysis Plan: No primary efficacy variable was identified. Variables of primary interest were: MV oxygen, MV lactate and extraction, MV alanine, MV free fatty acids, MV glucose and extraction, MV glutamine, MV glutamate and extraction, MV C14 glutamate and extraction, glutamate production. Treatment groups were assessed for comparability during the control period. Formal statistical comparisons of the two groups were made at the two time-points when measurements were taken during the treatment period. Techniques such as the two-sample t-test or its non-parametric equivalent were planned and the 95% confidence interval for the difference between groups will be recorded. Measurements of hemodynamic variables were planned at the same time-points and same method of analysis used. All statistical tests were planned as two-tailed with a 5% level of significance.

²⁹ See Study RAN 014 for further explanation of these measurements.

Amendments to the Protocol: none

Results: Nineteen men and one woman with CAD, aged 41-68 years, who were undergoing diagnostic cardiac catheterization were enrolled and completed the study. The study population was 100% Caucasian. Mean weight was 83 kg in the placebo group and 75 kg in the ranolazine group. Ten patients were smokers and 19 patients drank alcohol (no gross imbalances across treatment groups). Two patients in the ranolazine group were protocol violators (no effort angina documented³⁰, and history of MI within 3 months) but were included in the analysis.

Hemodynamic Parameters: Coronary sinus flow, coronary vascular resistance, heart rate, left ventricular systolic and end-diastolic pressures, arterial systolic, diastolic, and mean pressures were not significantly different in patients treated with ranolazine or placebo. Indices of LV inotropic state and relaxation were not significantly different between ranolazine and placebo.

Metabolic Parameters: There were no significant differences between the ranolazine and placebo groups in the changes in arterial-coronary sinus oxygen levels, myocardial oxygen uptake, lactate uptake, lactate extraction, glutamate uptake or production, glucose uptake or extraction, alanine or glutamine uptake, or C14 glutamate uptake.

The only statistically significant finding was a median increase, during pacing, in free fatty acid uptake of 4.4 $\mu\text{mol}/\text{min}$ in the placebo group and decrease of 8.5 $\mu\text{mol}/\text{min}$ in the ranolazine group ($p=0.05$). Basal results for free fatty acid uptake were not significantly different between the two treatment groups.

Ranolazine plasma levels: Basal levels ranged from 165-315 (mean 254.1) ng/ml. During pacing ranolazine levels ranged from 162-252 (mean 215.3) ng/ml.

Safety: For detailed safety discussion, please see the Safety Review.

Reviewer Comments:

1. This was a small, single-blind, placebo-controlled, parallel-group study in patients with CAD. No primary efficacy variable was prespecified.
2. The only statistically significant difference between ranolazine and placebo was a median decrease in free fatty acid uptake in the ranolazine group compared to an increase in the placebo group. No significant differences were demonstrated in the other measured parameters.
3. It is unclear whether the decrease in free fatty acid uptake with pacing is consistent, or whether this explains the mechanism of action of ranolazine.

RAN 1789.

Title: A Double-Blind, Parallel Comparison of the Effects of Intravenous Ranolazine versus Placebo on Indices of Ischemia in Patients Undergoing Coronary Angioplasty (Protocol date: March 19, 1990. Eight amendments: June 22, 1990-February 21, 1992)

Objective: evaluate anti-ischemic effects on the myocardium of intravenous ranolazine vs. placebo in patients undergoing PTCA for therapeutic indications.

Study Summary (from protocol): This was a randomized, double-blind, placebo-controlled parallel-group single-dose intravenous ranolazine study. Eligible patients were stratified on the basis of the coronary artery to be dilated. Angiographic studies were planned with non-ionic contrast to minimize negative inotropic effects. Therapeutic angioplasty was then performed using prestudy balloon inflations to decrease the magnitude of coronary artery obstruction. If two or more vessels required angioplasty, the study was then conducted following successful angioplasty of the first vessel selected for the procedure.

³⁰ Effort angina was not listed under Inclusion/Exclusion criteria in the protocol.

Study inflation #1 was not performed until at least 60 seconds after the last contrast injection, or after contrast-induced alteration of ST-segments has disappeared.

Baseline measurements such as heart rate, aortic pressure, and 2D echocardiographic analysis of wall motion/ejection fraction (selected centers) was taken. After these measurements, pre-drug balloon occlusion (study inflation #1) was performed for 60 seconds with the following measurements: heart rate, aortic BP, maximum ST deviation on any surface EKG lead or on an intracoronary electrogram from the instrumented artery, time to ST change ≥ 0.1 mV on the same EKG to determine maximum ST change, time to angina, mean coronary wedge pressure in the instrumented artery. Those site performing echos would also perform segmental LV wall motion analysis with EF calculation. The EF wall motion score and percent area change for the LV segments affected by balloon occlusion was assessed at a central site.

In order to be randomized, a patient must develop at least 0.1 mV ST change on a surface or intracoronary ECG during study inflation #1. Eligible patients were randomized to iv placebo (5% dextrose solution) or ranolazine (700 mcg/kg) over 10 minutes via peripheral iv line. At the end of the 10 minute infusion period, a plasma sample was drawn to measure plasma ranolazine concentration. Immediately afterward, hemodynamic measurements (baseline #2) were taken to establish effect of ranolazine vs. placebo on resting hemodynamics. Study inflation #2 (60 seconds) ensued with similar measurements as during study inflation #1. The study was to end once the patient was comfortable and hemodynamics have returned to within 10% of baseline #1.

Thus, the protocol design was as follows: Initial inclusion criteria met? Prestudy therapeutic balloon inflations? baseline hemodynamics #1? Prestudy Inflation #1? Secondary inclusion criteria met? Placebo or ranolazine IV? Baseline hemodynamics #2? Postdrug study inflation #2.

Sample size: The study planned for 90 evaluable patients, divided into 2 similar groups, stratified based on lesion to be dilated.

Notable Initial Inclusion criteria:

1. Age 21-75 years;
2. Clinical indication for PTCA;
3. Normal ST segments on resting EKG within distribution of coronary artery to be dilated;
4. Successful prestudy balloon dilatation and clinically stable patient;
5. Thirty minutes must elapse between sublingual, intravenous or intracoronary nitrates and study inflation #1;

Echocardiographic Inclusion criteria:

1. Satisfactory 2-D visualization of LV segments in the distribution of the vessel to be dilated;
2. Normal to hypokinetic wall motion in the distribution of the vessel dilated.

Secondary Inclusion criteria (following Study Inflation #1):

1. A patient must develop ≥ 0.1 mV ST deviation (80 msec from the J point) on a surface or intracoronary ECG during study inflation #1;
2. An additional angioplasty balloon inflation is required for therapeutic reasons;

Notable Exclusions: Women of child-bearing potential; factors confounding ECG interpretation of ST changes; MI within 6 weeks of study; dilated cardiomyopathy/NYHA Class III-IV CHF/known EF < 30%; any condition interfering with performance of study; significant laboratory abnormality; participation in investigation drug or device study within previous month or during PTCA.

In addition, patients may not use concomitant digitalis for up to 5 days prior to or during study.

Concomitant Medication: Sublingual nitroglycerin for the treatment of angina attacks. However, sublingual, intravenous, or intracoronary nitrates were not to be administered within 30 minutes of study inflation #1 or during the protocol.

Ranolazine plasma levels: A blood sample for ranolazine concentration was planned, from the arm not receiving study drug infusion, immediately after completion of the intravenous infusion.

Primary Efficacy Parameter: Time to development of ST deviation 0.1 mV on any surface or intracoronary ECG. Duration of balloon occlusion will be used if 0.1 mV ST deviation is not attained during the study inflation.

Secondary Efficacy Parameters:

1. Maximum ST deviation during 60 seconds of balloon inflation on any surface or intracoronary ECG;
2. Percent change in maximum ST deviation during 60 seconds of balloon inflation on any surface or intracoronary ECG from study inflation #1 (predrug) to study inflation #2 (postdrug);
3. Time to development of angina. Duration of balloon occlusion will be used if angina does not occur during the study inflation;
4. Heart rate and mean aortic BP at 60 seconds of balloon occlusion;
5. Peak mean coronary wedge pressure;
6. Change in ejection fraction, wall motion score and the percent area change for the LV segments affected by balloon occlusion.

Sample size: A standard deviation of 20 sec for the change from baseline to postdrug was used for the calculation of sample size for this study. A sample of 45 evaluable patients per treatment group was required to achieve a significant difference of 12 sec between ranolazine and placebo with respect to the time to 0.1 mV ST deviation with 80% power and $\alpha = 0.05$. This calculation was based on a two-sided, two-sample t-test without accounting for the effects of center, treatment by center interaction, or stratum.

Stratification: Patients were stratified to one of three strata: left anterior descending (LAD), circumflex (circ), and right coronary artery (RCA).

Endpoint: Endpoint was defined as the measurement obtained during the postdrug study inflation. Within group comparisons will be made on measurements collected at study inflation #1 (predrug) vs. those collected at study inflation #2 (postdrug).

Efficacy Analysis: Patients will be excluded from efficacy analyses for gross protocol deviations. Primary and secondary efficacy parameters were analyzed via ANOVA model including effects of treatment, stratification factor, center, and treatment by center interaction. Patients undergoing RCA and CIRC dilatations will be collapsed into a single stratum, unless each site enrolls sufficient patients to permit separate adjustment. Percent change in maximum ST deviation will be analyzed by the van Elteren test, with the center as a blocking factor. All tests will be two-sided with 0.05 significance levels.

Protocol Amendments: There were 8 protocol amendments which do not appear to have influenced primary or secondary endpoints.

Results: A total of 95 patients were enrolled at five centers and randomized to placebo (n=45) or ranolazine (n=50). Forty-three patients in placebo and 48 in ranolazine completed the protocol. Five patients on ranolazine were excluded from the per-protocol efficacy analysis because of protocol deviations. A placebo-treated patient was excluded from per-protocol and all-patients analyses because of missing endpoint data.

Four patients (two per treatment group) withdrew prematurely. One safety-related ranolazine withdrawal was due to supraventricular tachycardia.

Baseline characteristics: Mean age 61-62 years, 67-81% male, about 90% Caucasian. Although there was a statistically significant difference between treatment groups with respect to prior CABG ($p=0.04$), the numerical difference was small (3) between treatment groups. Otherwise, no imbalances were seen across treatment groups. There were significant treatment by investigator interactions with respect to history of MI ($p=0.04$) and tobacco use ($p=0.01$).

The total number of patients receiving treatment and in the analysis was 89 (placebo=43, ranolazine=46). In the pre-protocol analysis of time to 0.1 mV ST deviation, 100% of patients in the analysis attained

baseline endpoint, and about 77-78% of patients in analysis attained follow-up endpoint. For the variable “time to onset of angina,” 47-54% of patients in analysis attained baseline endpoint and 33-44% of patients attained follow-up endpoint.

Efficacy Results:

There were no statistically significant differences between the two treatment groups with respect to the change from baseline to endpoint for any of the three angioplasty variables (time to 0.1 mV ST deviation, maximum ST deviation, time to onset of angina) ($p \geq .26$). An all-patients analysis also showed no significant treatment difference (ranolazine vs. placebo).

Per-protocol analysis of coronary wedge pressure, mean arterial pressure, and ejection fraction showed no significant differences between ranolazine vs. placebo. There was a statistically significant mean decrease from baseline in heart rate in the ranolazine-treated group (3.6 bpm, $p=0.01$) but the difference vs. placebo was not statistically significant.

Per-protocol analysis of echocardiographic data ($n=14$) showed mostly “no change” in wall motion segments (other possible choices were “improved” or “worse”).

Ranolazine plasma concentrations: Mean ranolazine concentration ($N=44$) was 658.2 ng/L. A correlation of 0.31 ($p=0.04$) was estimated by the sponsor between plasma levels and change in time to 0.1 mm ST deviation.

Safety: For a detailed discussion, please see the safety review.

Reviewer comments:

1. This was a 95-patient double-blind, placebo-controlled, single-dose study of effects of intravenous ranolazine on time to ST deviation and other hemodynamic parameters during angioplasty.
2. No statistically significant treatment effects were demonstrated.