

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-526

Medical/Statistical Review(s)

Medical-Statistical Review of Study CVT 3037:

Medical reviewer: Shari L. Targum, M.D.

Statistical reviewer: Valeria Freidlin, Ph.D.

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

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

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

Secondary objectives:

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

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

In the second phase of the study, eligible patients continued to receive amlodipine 10 mg daily, and were randomized to receive either ranolazine 500 mg or placebo twice daily for one week (double-blind initial phase). Patients completing this one week initial phase of double-blind treatment (visit 3) then entered the third phase (visits 4, 5), a 6 week treatment phase where, in addition to the amlodipine, the patients on ranolazine were up-titrated to receive ranolazine 1000 mg bid (in a blinded manner).

(Reviewer: this study did not include stress testing).

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

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

Prohibited Concomitant Medications/Food:

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

Allowed concomitant Medications:

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

Assessments:

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

Criteria for Withdrawal:

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

Statistical Analysis Plan:

The primary efficacy variable was each patient's average weekly rate of angina attacks during the 6-week double-blind treatment phase during which the treatments were ranolazine 1000 mg bid and placebo. Secondary efficacy variables were: 1. each patient's average weekly rate of nitroglycerin consumption during the 6-week double-blind Treatment Phase, and 2. the patient's score for each of the five dimensions of the SAQ score at the end of the 6-week double-blind Treatment Phase¹.

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

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

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

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

Protocol Amendments:

1. (May 13, 1994):
 - a. Allowed the use of long-acting nitrates (LAN) in the form of a patch or isosorbide mononitrate;
 - b. Extended the duration of the study from about 13 to up to 18 weeks, including the addition of a repeat Visit 1 for patients using a LAN;

¹ In the study report, the SAQ was mentioned as an exploratory analysis since it was not validated in Eastern Europe, the source for the majority of the study population.

- c. Modified exclusion criteria for end stage renal disease to specify “requiring dialysis;”
 - d. Specified that patients should take amlodipine at the same time of day throughout the study;
 - e. Added collection of the time of day of angina episodes;
 - f. Specified additional analyses of angina frequency, nitroglycerin use and SAQ scores by geographic region;
 - g. Specified that two original 12-lead ECGs should be printed out for every ECG performed;
 - h. Included the requirement of ECG submission to the sponsor for any ECGs collected as part of the cardiovascular adverse events
 - i. Added serum pregnancy tests to Visits 2-5;
 - j. Changed the dispensing for amlodipine;
2. Amendment 2 (October 26, 2004):
- a. Updated the Seattle Angina Questionnaire with a version available from the developer (JA Spertus).

Changes to the Planned Analyses:

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

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

Results:

A total of 627 patients entered the qualifying phase; of these, 565 patients satisfied entry criteria and were randomized into the double-blind phase of the study. Forty-two patients were ineligible because they no longer met inclusion/exclusion criteria and 20 patients had < 3 average weekly angina attacks.

Of the 565 randomized patients from 48 sites, only 3% (17 patients) were from sites in the USA (2 sites) or Canada (one site); the rest were recruited from sites in Eastern Europe. A

majority (64%, or 362 patients) were recruited from Russia. The rest of the study population was recruited from sites in Bulgaria, Romania, and the country of Georgia. As seen below (Table 1), the study population was mostly male and almost exclusively Caucasian.

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

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

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

Table 1. Baseline characteristics (all randomized patients)

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

Source: Table 14.3.1, Volume 19.

Table 1 displays baseline characteristics of the study population. The two treatment groups were balanced with respect to the demographic characteristics listed in the above table. Mean baseline weight was about 81 kg; mean height was 170 cm.

In terms of cardiovascular history, 19% of the safety analysis set (n=564) were diabetics (15-18% of the total had NIDDM); about 63% had previous MI; about 35-36% had unstable angina; about 51% had a history of CHF; and 10-12% of patients were post-CABG. In both the full analysis and safety populations, there was a small imbalance in patients with a single-vessel CABG (9% of ranolazine vs. 12% of placebo (10-12%) patients, CMH p-value =0.054) but the total percentage of patients with a CABG history was balanced across groups. In the full analysis set, about 21-25% of patients had a COPD history. About half (47-51%) of patients had a history of nitrate use. Few patients (< 4%) had a history of beta-blocker or calcium channel-blocker use; there was a baseline imbalance with respect to previous calcium channel-blocker use (4 patients on placebo; none in the ranolazine group; CMH p-value of 0.027, FAS²).

(Reviewer: It is unlikely that the 4 patient imbalance with respect to prior calcium channel blocker treatment will have affected the results. However, it is worth noting that this study population was not on maximal medical therapy for angina).

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

Table 2. Baseline Average Weekly Rate of angina attacks, nitroglycerin consumption and Seattle Angina Questionnaire (SAQ) scores—Full analysis set (FAS)

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

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

² Source: Table 14.3.9. CVT 3037 study report.

Baseline average weekly anginal attacks, nitroglycerin consumption and SAQ functional dimension scores are shown above.

Of note, baseline mean and median nitroglycerin consumptions are lower in ranolazine patients compared to those on placebo—although the differences are not statistically significant.

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

Table 3. Primary and secondary efficacy measurements: Frequency of angina attacks and nitroglycerin consumption (FAS)

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

Results confirmed by statistical reviewer.

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

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

The results for the secondary variable of nitroglycerin consumption are also shown above and support the results of the primary efficacy variable. Since a baseline imbalance was seen with respect to nitroglycerin consumption (see Table 2), the sponsor performed a sensitivity analysis adjusting for baseline differences; the results were consistent with the unadjusted analysis.

Table 4. Change in SAQ Scores from Baseline to the End of the 6-week Double-Blind Treatment Phase

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

Results confirmed by the statistical reviewer.

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

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

Analyses by Subgroup:

Concomitant use of long-acting nitrates (LAN):

Table 5. Average weekly rate of angina attacks during 6-week double-blind treatment by concomitant use of LAN

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

25 th -75 th percentile	1.34-3.76	1.15-3.35	
Mean (SEM)	3.26 (0.26)	2.84 (0.23)	

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

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

Gender:

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

Table 6. Efficacy variables by gender

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

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

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

†Effect size = (mean ranolazine-mean placebo)/standard deviation of ranolazine (source: statistical reviewer).

Age:

Table 7. Primary Efficacy Variable by Age

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

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

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

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

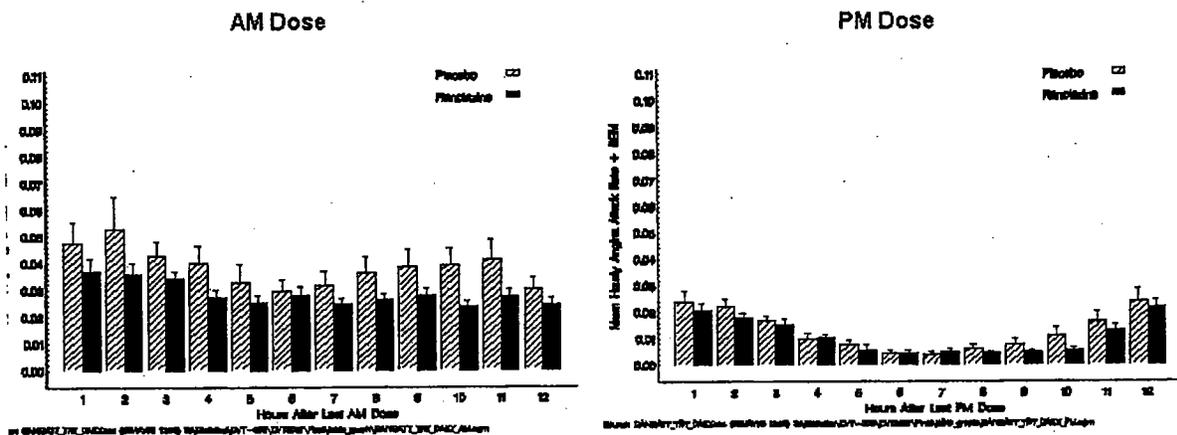
Geographic Region: There were too few patients outside Eastern Europe to allow for an adequate subgroup analysis. However, the median results of the primary efficacy endpoint were

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

Other Analyses:

Temporal Pattern of Angina Attacks:

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



reproduced from Section 14.4.3.4

Reproduced from Section 14.4.3.5

Figure 1. Mean Hourly Angina Attack Rate as a Function of Time since Last AM or PM Dose of Study Drug in the 6-week Treatment Phase.

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

Handling of Missing Data:

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

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

Safety:

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

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

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

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

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

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

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

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

Treatment-emergent adverse events:

Table 8. Treatment-emergent adverse events with an incidence of at least 1% and $\geq 1\%$ higher incidence in the ranolazine group vs. placebo (from randomization to study termination: safety analysis set)

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

Source: Table 14.7.1.3, Table 21

Adverse Events by Subgroup:

LAN use:

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

Table 9. Treatment-emergent adverse events by preferred term and concomitant use of LAN from randomization to study termination (safety analysis set); incidence $\geq 2.0\%$ in any ranolazine group

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

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

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

Table 10. Treatment-emergent adverse events by preferred term and gender (Randomization to study termination; Safety analysis set): incidence $> 4\%$ in any ranolazine subgroup

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

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

Adverse events by Age:

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

Table 11. Treatment-emergent adverse events by preferred term and age subgroup (Randomization to study termination; Safety analysis set): incidence > 4% in any ranolazine subgroup

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

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

Laboratory Tests:

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

Table 12. Serum creatinine shift table

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

Source: Table 14.8.1

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

Vital Signs:

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

decrease from baseline) without a statistically significant treatment effect. For standing systolic BP the mean change from baseline to endpoint was -2.9 mm Hg for ranolazine and -1.8 mm Hg for placebo (p=NS).

A review of postural vital signs (supine to standing) did not reveal a significant treatment effect.

ECG:

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

The sponsor also submitted available ECGs as follow-up in patients with cardiovascular events in study CVT 3037. Four ranolazine patients with cardiovascular AEs did not have available ECGs.

Reviewer: The ECGs are of adequate quality although several are missing grids (possibly due to the copy quality) for evaluation of conduction/repolarization. One patient (#8625-7006) was noted to have a QTc of 450 msec; atrial fibrillation (but not prolonged QTc) was coded.

Reviewer Comments/Conclusions:

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

Since the study was blinded and placebo-controlled, one would hope that the issues raised in points a. and b. will occur equally in both groups.

4. No significant treatment effect was seen in the female subgroup. The sponsor has noted that the female subgroup has a smaller sample size. While the sample size is smaller for the female subgroup, it is worth noting that the effect size for the primary endpoint is also smaller in females compared to the effect size in males.
5. A shift in creatinine was seen in the ranolazine group; however, no safety signal was seen in this study with regard to treatment-emergent or serious renal AE.

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

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/s/

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

Medical Reviewer: Shari L. Targum, MD
Statistical Reviewer: Valeria Freidlin, Ph.D.
Studies CVT 3033 and CVT 3031 were reviewed jointly by the medical and statistical reviewers.

Integrated Summary of Efficacy:

Table of Contents:

Statement of Conclusions:	2
General Approach to Review of the Efficacy of the Drug	2
Mechanism of Action:	5
Detailed Review of Angina Trials:	5
Efficacy in pivotal trials:	6
Dose-response/Drug concentration-response Relationship:	11
Onset of effect:	13
Maintenance of anti-anginal effect/Testing for Rebound effects:	13
Effects on heart rate and systolic blood pressure:	14
Interaction with Background Therapy:	14
Efficacy in Subgroups:	15
Individual Study Reviews:	21
Phase 3 Studies:	21
CVT 3033:	21
CVT 3031:	39
Other Efficacy Studies:	47
RAN 072:	47
RAN 080:	51
RAN 1514:	57
RAN 081:	63
RAN 015:	66
RAN 020:	68
RAN 054:	70
RAN 1490:	73
RAN 2240:	77
Pharmacodynamic Studies:	78
RAN 003:	78
RAN 003B:	79
RAN 004:	82
RAN 006A:	83
RAN 007:	85
RAN 010:	86
RAN 011:	87
RAN 012:	91
RAN 014:	94
RAN 017:	96
RAN 070:	98

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 2 weeks	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.

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: —	N=173 848.9 (55) Range: —	N=175 1959.2 (107.5) Range: —	N=170 3241 (150.9) Range: —
Peak plasma concentration (ng/ml) mean (SE)	N=173 35.2 (19.5) Range: —	N=169 1122.6 (55.9) Range: —	N=174 2476 (115.1) Range: —	N=166 3930.5 (161.3) Range: —

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 side 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.

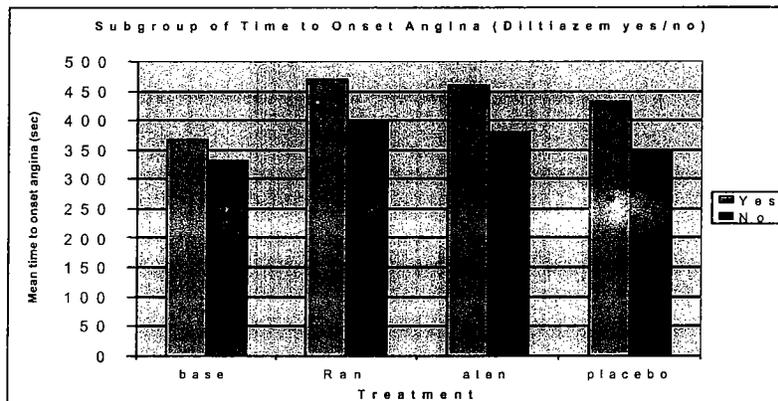
Heart rate:

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 beta 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).

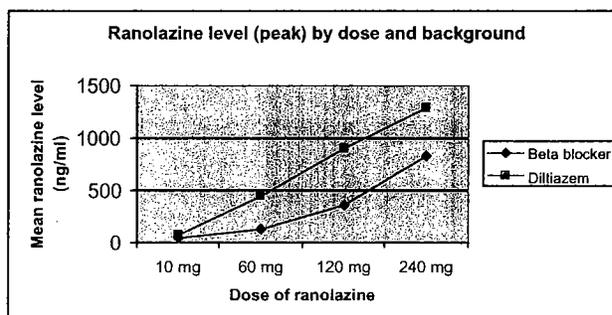


Blood Pressure Findings: Results for Systolic BP are graphically displayed. For diastolic BP, there was a statistically significant decrease in DBP at maximum exercise and recovery (calcium channel blocker group) in patients given placebo compared to ranolazine ($p=0.01$ and 0.03 , respectively). The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

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 (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 Max, dP/dt Min, (dP/dt)/DP 40, T, T1²⁹, 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.

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/s/

Shari Targum
8/28/03 11:21:04 AM
MEDICAL OFFICER

Valeria Freidlin
8/28/03 11:54:07 AM
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John- Please sign off the review (as requested by
Jim in his 8.25.203 email) and send to
George

John Lawrence
8/28/03 02:38:56 PM
BIOMETRICS

George Chi
8/28/03 03:06:27 PM
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