CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-526/S004

MEDICAL REVIEW(S)

NDA 21526
Medical reviewer: Maryann Gordon, M.D.
Study CVT 3036

RE: Ranolazine's effect on blood pressure in patients with low creatinine clearance.

Conclusion
There is no evidence that ranolazine increases the blood pressure in patients with creatinine clearance ≤ 30 mL/min.

Background
CVT 3036

The mean supine and standing blood pressures recorded periodically for subjects with creatinine clearance ≤ 30 mL/min are shown in the tables below.

Supine blood pressure

	placebo		ranolazine	
	# of subjects	mmHg	# of subjects	mmHg
baseline	50	133/69	52	135/72
Day 14	39	126/70	39	136/72
Month 8	22	133/76	23	139/74
Month 12	14	136/80	15	143/77

Standing blood pressure

	placebo		ranolazine	
	# of subjects	mmHg	# of subjects	mmHg
baseline	34	126/66	32	130/70
Day 14	33	126/71	33	136/73
Month 8	19	125/70	22	130/74
Month 12	12	135/79	15	136/74

14.3.7.6

In addition, the reporting rates of the adverse event "hypertension" for subjects with creatinine clearance < 60 mL/min were 5% for those randomized to placebo and 4% for those randomized to ranolazine.

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Maryann Gordon
11/3/2008 02:37:25 PM
MEDICAL OFFICER

NDA #21526
Review of document dated October 7, 2008
Medical reviewer: Maryann Gordon, M.D.

Conclusions

The sponsor recognized an error in the arrhythmia data for study 3036. The corrected results are not fundamentally different from what was presented in the original NDA. No changes to the primary medical review are required.

Background

Corrections to Arrhythmia Data for Study CVT 3036

Following completion of the CVT 3036 study report, an error was found in the program used by the Holter core lab to identify patients with VT $\geq$ 100 bpm lasting at least 3 beats (triplet). In the original results, patients who had more than one triplet (VT = 3 beats) and who did not have any VT $\geq$100 bpm lasting $\geq$ 4 beats were omitted. Thus, the corrected Holter results show the number of patients with VT $\geq$ 100 bpm that occurred for $\geq$ 3 beats (including all patients with multiple occurrences of triplets). A summary of the original and corrected data follows.

	Original Values			Corrected Values		
	Placebo	Ranolazine	p value	Placebo	Ranolazine	p value
Incidence of Clinically Significant Arrhythmias*	2650 (83.1%)	2330 (73.7%)	*< 0.001*	2786 (87.4%)	2525 (79.9%)	*< 0.001*
Any VT *100* bpm 3 beats	1211 (38.0%)	948 *(30.0%)*	--	1934 *(60.6%)*	1646 (52.1%)	--

* Among patients with Holter data (placebo = 3,189 and ranolazine = 3,162).

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Maryann Gordon
10/20/2008 09:17:15 AM
MEDICAL OFFICER

NDA #21526
Review of document dated October 2, 2008
Medical reviewer: Maryann Gordon, M.D.

Conclusion
There is no evidence from study CVT 3036 that ranolazine causes new cancers or the progression of existing cancers in subjects taking ranolazine.

Background
The currently approved Ranexa labeling contains a 'Warning' referencing the published results of a study by Suckow et al. with ranolazine in the APC (min/+) mouse model.

Results from study CVT 3036
The tumors reported in study CVT 3036 were 54 (1.6%) by subjects randomized to placebo and 63 (1.9%) by subjects randomized to ranolazine.

The tumors reported as serious were 34 (1%) in the placebo group and 37 (1.1%) in ranolazine group.

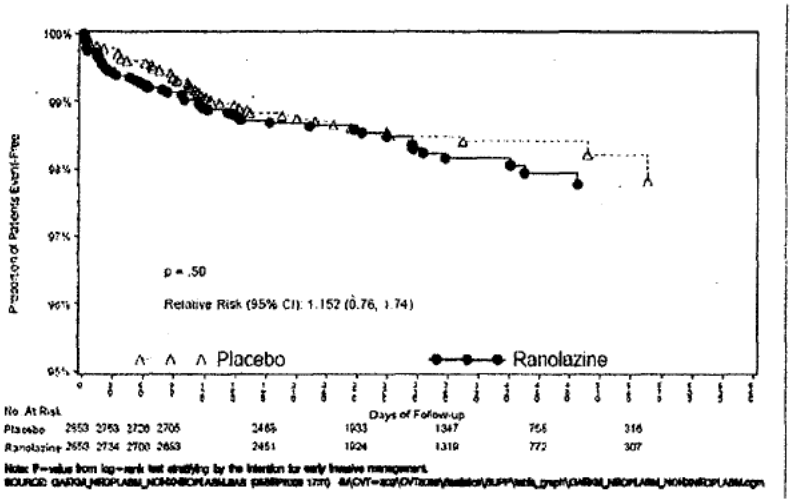
Cancer reports of any type by age group were as follows:
Less than 65 years: 21 (1%) placebo, 31 (2%) ranolazine
Between 65 and 74 years: 18 (2%) placebo, 22 (2%) ranolazine
Greater than 75 years: 15 (3%) placebo, 10 (2%) ranolazine.

The numbers of study subjects without a prior history of cancer who reported a cancer during the trial were 42 placebo and 48 ranolazine. The numbers with a prior history of cancer who reported cancer during the trial were 12 placebo and 15 ranolazine.

The time to reporting a cancer was consistent throughout the study for subjects who had a prior history of cancer regardless of treatment group.

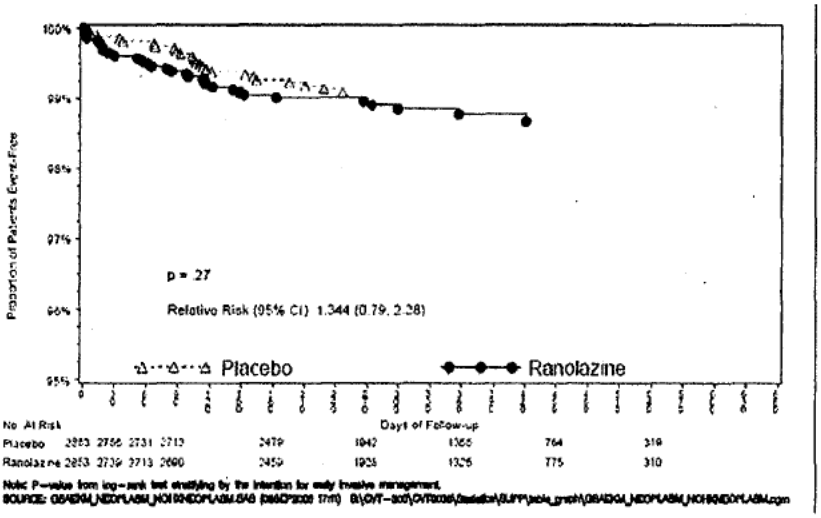
For those without a prior history of cancer, the time to reporting a cancer was greater for subjects who had been in the trial 180 days or less, regardless of treatment group, compared to those reporting cancer who were in the trial more than 180 days.

Figure 1 **Time from Randomization to Onset of New Neoplasm Reported as Treatment-Emergent Adverse Event in Patients without a Prior History of Neoplasm**



This pattern was similar for those reporting cancer as a serious adverse event.

Figure 2 **Time from Randomization to Onset of New Neoplasm Reported as Treatment-Emergent Serious Adverse Event in Patients without a Prior History of Neoplasm**



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Maryann Gordon
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MEDICAL OFFICER

NDA #21526
Review of document dated September 12, 2008
Medical reviewer: Maryann Gordon, M.D.

Conclusion

There is weak evidence that ranolazine decreases the incidence of ventricular tachycardia in subjects with unstable angina. This would need to be confirmed by additional clinical trials.

Background

The following table shows the incidence of ventricular tachycardia recorded during Holter monitoring for study CVT 3036.

Table 1 **Incidence of Ventricular Tachycardia Recorded During 7-Days of Continuous ECG (Holter) Monitoring in CVT 3036**

	Diltiazem or Verapamil			CYP3A4 or P-gp Other than Diltiazem or Verapamil		
	Placebo (n = 308)	Ranolazine (n = 350)	p value	Placebo (n = 135)	Ranolazine (n = 138)	p value
Patients with Holter Data	302	340		129	134	
Ventricular Tachycardia (≥ 100 bmp)						
≥ 3 beats	175 (58%)	166 (49%)	0.022	90 (70%)	71 (53%)	0.005
≥ 4 beats	89 (29%)	70 (21%)	0.006	53 (41%)	32 (24%)	< 0.001
≥ 8 beats	27 (9%)	16 (5%)	0.033	20 (16%)	7 (5%)	0.007
Sustained Ventricular Tachycardia (≥ 100 bmp lasting > 30 seconds)						
Monomorphic	0	0	--	2 (2%)	2 (1%)	0.95
Polymorphic	2 (< 1%)	2 (< 1%)	0.90	1 (< 1%)	0	0.29

Table 2 **Incidence of Symptomatic Documented Ventricular Tachycardias[a] in CVT 3036**

	Diltiazem or Verapamil		CYP3A4 or P-gp Other than Diltiazem or Verapamil	
	Placebo (n = 308)	Ranolazine (n = 350)	Placebo (n = 135)	Ranolazine (n = 138)
Ventricular Tachycardia	2 (< 1%)	4 (1%)	4 (3%)	1 (< 1%)

[a] Element of the composite safety endpoint of symptomatic documented arrhythmias recorded during the entire period of the study and adjudicated by the Clinical Events Committee

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Maryann Gordon
9/26/2008 10:47:23 AM
MEDICAL OFFICER

NDA #21526
Review of document dated September 3, 2008
Medical reviewer: Maryann Gordon, M.D.

Conclusion

There is no concrete evidence that ranolazine increases the mortality rate in patients with unstable angina who are also taking diltiazem or verapamil.

Background

There were 6 ranolazine and 2 placebo subjects taking concomitant diltiazem or verapamil who died in the hospital. The sponsor reports that there was no evidence of sustained ventricular tachycardia on the Holter recordings of the 6 ranolazine subjects.

The subjects discussed in the narratives were elderly with extensive cardiovascular disease. A brief description of each subject is shown in the table below.

Table 1 **Ranolazine and Placebo Patients Concomitantly Treated with Diltiazem or Verapamil Who Died in Hospital in CVT 3036**

Patient ID	Treatment	Days to Death Post Randomization	Sustained VT[a]		Non-sustained VT[b]			Holter Rhythm at Death	Cause of Death
			Mono	Polymorphic	Triplets	VT ≥ 4 beats	VT ≥ 8 beats		
7919-6007	Ran / Dilt	1	No	No	0	38	0	Bradycardia (CPR)	Sudden cardio-respiratory arrest[c] Ischemia, ST elevation[d]
5904-6040	Ran / Verap	2	No	No	0	0	0	Junctional rhythm Severe bradycardia Asystole	Acute MI[c] Ischemia[d]
6104-6019	Ran / Dilt	5	No	No	8	0	0	Bradycardia Asystole	Acute MI[c] Ischemia, ST depression[d]
4640-6002	Ran / Dilt	9	No	No	4	1	0	NA	Acute MI Post dipyridamole-thallium stress test[c]
6104-6014	Ran / Dilt	10	No	No	359	309	20	Bradycardia	Acute MI[c]
2104-6005	Ran / Dilt	16	No	No	0	1	0	NA	Post operative VF (Post CABG surgery)[c]
6106-6031	Pla / Verap	3	No	Yes	86	23	4	Polymorphic VT DC shock followed by agonal rhythm	Acute MI[c] Ischemia, ST elevation/ depression[d]
9401-6045	Pla / Dilt	9	No	No	33	0	0	NA	Cardiogenic shock[c] Asystole[d]

[a] > 30 sec
[b] ≥ 100 bpm and ≤ 30 sec
[c] Based on patient narrative
[d] Based on 7-day Holter

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Maryann Gordon
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MEDICAL OFFICER

NDA #21526
Submission dated July 31, 2008

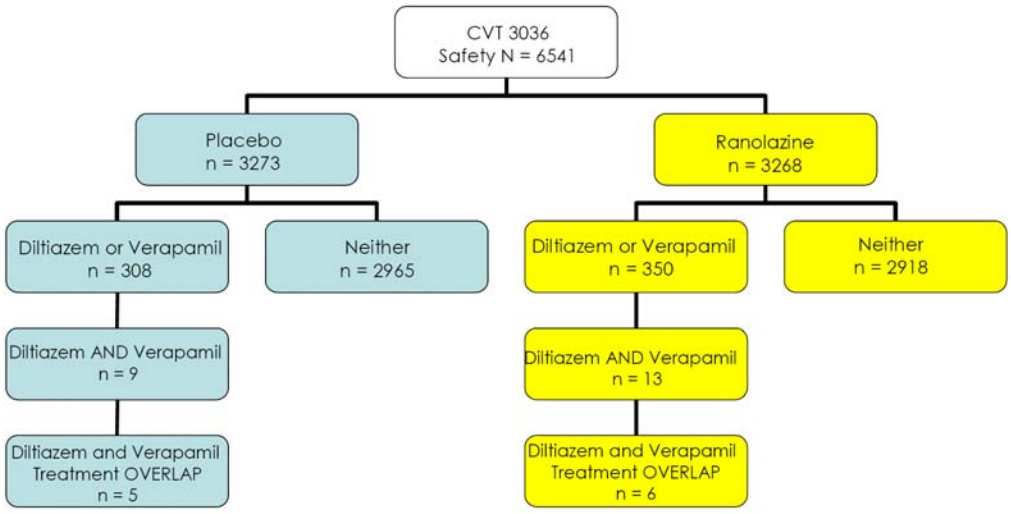
Conclusions
There is no convincing evidence that the co administration of diltiazem or verapamil increases mortality or serious adverse events in subjects taking ranolazine.

Background
In response to a discussion between CV Therapeutics (CVT) and the Division on July 28, 2008, CVT has submitted additional safety data obtained from Study CVT 3036 to determine whether co-administration of ranolazine with diltiazem or verapamil is associated with an increase in the incidence of deaths.

As requested by the Division, analyses of deaths occurring while patients were actively taking ranolazine, those occurring up to 7 days and up to 30 days following discontinuation of treatment with ranolazine, and all events occurring on or prior to the 14-day post-study follow-up period were provided.

The figure below shows the number of subjects randomized to placebo or ranolazine and the numbers of subjects who were also receiving diltiazem, verapamil, both drugs, or neither.

Figure 1 **Number of Patients Taking Diltiazem or Verapamil at Any Time in Study CVT 3036**



Overall, only ten percent of subjects were receiving one or both of these concomitant medications. These subjects were not randomized to these concomitant medications and the study was not stratified based on concomitant medications.

<u>Demographics</u>

The subjects who were randomized to ranolazine and received one or both of the above mentioned concomitant medications were older, were more likely to have had a previous MI,

heart failure, and/or experienced a resuscitated sudden death. They were an older, sicker population compared to the subjects who were randomized to placebo and received one or both of the above mentioned concomitant medications.

Results

The numbers and percents of subjects in this subgroup who died at various time points and of various causes of death are shown below.

Table 4 **All-cause Death, CV Death, and Sudden Cardiac Death in Patients with Diltiazem or Verapamil Use During or After Hospitalization**

	No. of Patients with Events		Proportion of Patients Experiencing an Event				Source
			360-day KM Estimate		30-day KM Estimate		
	Placebo	Ranolazine	Placebo	Ranolazine	Placebo	Ranolazine	
All-cause Death							
Including Events Occurring Up to Last Dose of Ranolazine	15 / 308	14[a] / 349	4.2%	4.5%	1.3%	2.5%	Appendix 4
Including Events Occurring Up to 7 Days Post Last Dose of Ranolazine	15 / 308	14 / 349	4.2%	4.4%	1.3%	2.4%	Appendix 5
Including Events Occurring Up to 30 Days Post Last Dose of Ranolazine	15 / 308	16 / 349	4.2%	5.0%	1.3%	2.6%	Appendix 6
Including Events over Duration of Study	15 / 308	23 / 350	4.2%	6.5%	1.3%	2.6%	Appendix 7
Cardiovascular Death							
Including Events Occurring Up to Last Dose of Ranolazine	13 / 308	13[a] / 349	3.5%	4.1%	1.3%	2.5%	Appendix 8
Including Events Occurring Up to 7 Days Post Last Dose of Ranolazine	13 / 308	13 / 349	3.5%	4.0%	1.3%	2.4%	Appendix 9
Including Events Occurring Up to 30 Days Post Last Dose of Ranolazine	13 / 308	15 / 349	3.5%	4.6%	1.3%	2.6%	Appendix 10
Including Events over Duration of Study	13 / 308	20 / 350	3.5%	5.4%	1.3%	2.6%	Appendix 11
Sudden Cardiac Death							
Including Events Occurring Up to Last Dose of Ranolazine	4 / 308	6 / 349	0.7%	1.9%	0.7%	0.9%	Appendix 12
Including Events Occurring Up to 7 Days Post Last Dose of Ranolazine	4 / 308	6 / 349	0.7%	1.8%	0.7%	0.9%	Appendix 13
Including Events Occurring Up to 30 Days Post Last Dose of Ranolazine	4 / 308	6 / 349	0.7%	1.8%	0.7%	0.9%	Appendix 14
Including Events over Duration of Study	4 / 308	7 / 350	0.7%	1.9%	0.7%	0.9%	Appendix 15

[a] Included patients 2104-6005 and 6720-6023 who died after stopping treatment with ranolazine for 2 and 6 days, respectively (see Table 3).

Overall, the numbers of deaths per group are very small and similar between the different treatment groups. Baseline differences between groups could account for any of the small imbalances.

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Maryann Gordon
9/24/2008 10:39:48 AM
MEDICAL OFFICER

NDA# 21526
Submission dated 8-26-08

Conclusions
There is no evidence that the use of ditiazem or verapamil increases the mortality rate in subjects receiving ranolazine.

As stated previously, the use of concomitant medication was not controlled. The analysis in this submission also confirmed the transient nature of medication compliance. Many subjects reported use of the drug (s) at only one visit.

There were only small insignificant differences between the percentages of reported deaths in the treatment groups. These differences could easily be the result of imbalances in the groups (such as mean age, extent of disease, to name two, and there are probably more).

Table 1 **Demographic and Baseline Characteristics Comparing the CVT 3036 Safety Population vs the Subset of Patients with Reported Use of Diltiazem or Verapamil**

Characteristic	Overall Safety Population		Patients with Reported Use of Concomitant Diltiazem or Verapamil	
	Placebo (n = 3273)	Ranolazine (n = 3268)	Placebo (n = 308)	Ranolazine (n = 350)
Previous documented MI	1094 (33%)	1114 (34%)	99 (32%)	130 (37%)
Previous documented episode of unstable angina	906 (28%)	889 (27%)	104 (34%)	127 (36%)
Angina pectoris	1775 (54%)	1785 (55%)	167 (54%)	204 (58%)
Ventricular arrhythmia	124 (4%)	119 (4%)	10 (3%)	16 (5%)
Prior coronary angiography	1101 (34%)	1112 (34%)	122 (40%)	153 (44%)
Percutaneous coronary intervention	636 (19%)	678 (21%)	74 (24%)	89 (25%)
Coronary artery bypass graft	379 (12%)	389 (12%)	46 (15%)	49 (14%)
Congestive heart failure	557 (17%)	537 (16%)	33 (11%)	59 (17%)
Peripheral vascular disease	295 (9%)	274 (8%)	50 (16%)	45 (13%)
Cerebrovascular disease	355 (11%)	355 (11%)	36 (12%)	49 (14%)
Resuscitated sudden death	16 (< 1%)	18 (< 1%)	2 (<1%)	7 (2%)
TIMI Risk Score				
0 – 2	882 (27%)	881 (27%)	82 (27%)	78 (22%)
3 – 4	1724 (53%)	1718 (53%)	156 (51%)	193 (55%)
5 – 7	667 (20%)	669 (20%)	70 (23%)	79 (23%)
Dyslipidemia	2018 (62%)	2022 (62%)	229 (74%)	242 (69%)
Diabetes	1117 (34%)	1098 (34%)	104 (34%)	126 (36%)
Age ≥ 75 yrs old	591 (18%)	559 (17%)	46 (15%)	69 (20%)

Concomitant drug use patterns

Patients were not randomized to the use of diltiazem or verapamil. The reports submitted by the sponsor indicate that the use of these drugs varied and was often intermittent. Approximately 26% of placebo patients and 31% of ranolazine patients reported use of diltiazem at only one study visit; a substantial percentage (19% placebo and 20% ranolazine) reported use only during the index hospitalization. The use of verapamil appeared to be more transient; the vast majority of patients (approximately 65%) reported its use at only 1 visit, with 57% of placebo patients and 60% of ranolazine patients reporting use only during the index hospitalization.

The summary of death by treatment groups are shown below.

Table 3 **Summary of All-cause Death, CV Death, and Sudden Cardiac Death over the Duration of the Study**

	No. (%) of Patients with Events		360-day KM Estimate		Source
	Placebo	Ranolazine	Placebo	Ranolazine	
All-cause Death					
All Patients	175 / 3273 (5.3%)	172 / 3268 (5.3%)	5.1%	5.3%	Appendix 15
Concomitant use of diltiazem or verapamil	15 / 308 (4.9%)	23 / 350 (6.6%)	4.2%	6.5%	Appendix 6
No concomitant use of diltiazem or verapamil	160 / 2965 (5.4%)	149 / 2918 (5.1%)	5.3%	5.1%	Appendix 6
Cardiovascular Death					
All Patients	148 / 3273 (4.5%)	147 / 3268 (4.5%)	4.4%	4.4%	Appendix 16
Concomitant use of diltiazem or verapamil	13 / 308 (4.2%)	20 / 350 (5.7%)	3.5%	5.4%	Appendix 10
No concomitant use of diltiazem or verapamil	135 / 2965 (4.6%)	127 / 2918 (4.4%)	4.5%	4.3%	Appendix 10
Sudden Cardiac Death					
All Patients	65 / 3273 (2.0%)	56 / 3268 (1.7%)	1.8%	1.7%	Appendix 17
Concomitant use of diltiazem or verapamil	4 / 308 (1.3%)	7 / 350 (2.0%)	0.7%	1.9%	Appendix 14
No concomitant use of diltiazem or verapamil	61 / 2965 (2.1%)	49 / 2918 (1.7%)	1.9%	1.7%	Appendix 14

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/s/

Maryann Gordon
9/24/2008 12:16:17 PM
MEDICAL OFFICER

NDA #21526
Review of document dated July 31, 2008
Medical reviewer: Maryann Gordon, M.D.

Conclusion

There is no evidence that the concomitant use of diltiazem or verapamil with ranolazine leads to an increased death rate compared to those taking diltiazem or verapamil with placebo.

Background

This document is in response to the question regarding the use of ranolazine with diltiazem or verapamil (drugs known to increase ranolazine plasma concentration by 2.3 fold) resulting in increased deaths in study CVT 3036 (placebo controlled trial).

Mortality for total study population

In my review dated April 21, 2008, the percent of deaths from any cause was 5.3% for both treatment groups (ranolazine and placebo). The percents of cardiovascular deaths were 10.4% and 12.6% for all placebo subjects and all ranolazine subjects, respectively.

Concomitant diltiazem and/or verapamil subpopulations

There were 308 placebo subjects (9.4%) and 350 (10.7%) ranolazine subjects taking concomitant diltiazem or verapamil at anytime during the trial. The groups were not randomized according to concomitant medications so imbalances in the groups were possible. The sponsor mentioned that there were more subjects in this ranolazine subpopulation, compared to the placebo subpopulation, who were at higher risk of an event including having

- a larger older age group (20% vs. 15% for those at least 75 years old),
- more with a history of previous MI (37% vs. 32%), history of CHF (17% vs. 11%), or resuscitated sudden death (2% vs. <1%).

There are probably more imbalances than those cited here.

Mortality for the concomitant diltiazem and/or verapamil subpopulations

There were 15 placebo deaths and 23 ranolazine deaths reported in these subpopulations. The p value for the treatment subgroup interaction was p=0.28).

All of the 23 ranolazine deaths are shown in the table below.

Table 3 **Listing of the 23 Ranolazine Patients, Reportedly Taking Concomitant Diltiazem or Verapamil, Who Died at Any Time**

Patient No.	Gender	Age (years)	Days to Death		Adjudicated Cause of Death
			from First Ranolazine Dose	from Last Ranolazine Dose	
Patients who died while receiving ranolazine or within 7 days following its discontinuation					
2104-6005	M	77	15	6[b]	CV non-sudden
4503-6011	M	85	26	0	CV sudden
4506-6017	M	94	193	0	Non-CV
4640-6002	F	73	8	0	CV non-sudden
4903-6009	M	69	146	0	CV non-sudden
4929-6010	M	65	173	0	CV sudden
5245-6001	M	63	8	0	CV sudden
5904-6040[a]	M	78	2	0	CV non-sudden
6104-6014	M	77	9	0	CV non-sudden
6104-6019	F	68	4	0	CV non-sudden
6720-6023	M	73	77	2[b]	CV non-sudden
7919-6007	F	69	0	0	CV sudden
8605-6001	M	69	468	0	CV sudden
8615-6082[a]	M	59	265	0	CV sudden
Patients who died following > 7 days of ranolazine discontinuation					
1318-6011	M	77	453	450	CV non-sudden
1417-6006	M	55	153	16	CV non-sudden
1512-6002	F	88	94	91	CV non-sudden
4101-6017	F	83	309	206	Non-CV
4621-6007	M	77	213	208	Non-CV
5243-6005	F	69	117	108	CV non-sudden
5244-6001	M	76	218	209	CV sudden
6207-6002	M	65	11	10	CV non-sudden
7931-6007	F	65	223	96	CV non-sudden

[a] Narratives for these patients are provided in Appendix 16; narratives for the other patients who died while receiving ranolazine or within 7 days following its discontinuation were included in the 13 July 2008 submission (Sequence No. 0031).

[b] Date of last treatment with ranolazine obtained from the data clarification form.

Of the 23 ranolazine deaths, 9 were reported to have occurred ≥7 days after last dose of ranolazine[1]. There were 14 reported ranolazine deaths in this subpopulation that occurred <7 days after the last dose of study drug.

The remaining 14 ranolazine deaths from any cause are nearly identical in number to the reported placebo deaths (15) from any cause. Therefore, there is no evidence from this trial that

[1] the terminal half life of ranolazine is 7 hours.

ranolazine taken with diltiazem or verapamil, leads to increased mortality in subjects hospitalized for non-ST elevation acute coronary syndrome.

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/s/

Maryann Gordon
9/22/2008 08:51:19 AM
MEDICAL OFFICER

NDA#21,526 supplement 004 (September 27, 2007)
Dated June 6, 2008
Financial disclosure

Medical reviewer's conclusion:
Financial disclosure statement by the sponsor indicates no unusual activity.

Background:
The sponsor provided financial interest information for the clinical investigators who participated in the studies CVT 3023 and CVT 3036, the studies that are included in this NDA Supplement. The sponsor submitted certification for the 457 principal investigators who participated in the main study (CVT 3036 known as MERLIN), as agreed with FDA on February 28, 2007 and June 27, 2007. The sponsor provided certification for the three principal investigators and 17 sub-investigators who participated in study CVT 3023.

The sponsor certified that it has not entered into any financial arrangement with any of the clinical investigators involved in the conduct of the covered clinical studies (Studies CVT 3023 and CVT 3036) whereby the value of compensation to the investigators could be affected by the outcome of the studies as defined in 21 CFR 54.2(a).

Lists of those investigators who participated in the two aforementioned trials were submitted with the signed Form FDA 3454 as part of the NDA.

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/s/

Maryann Gordon
6/6/2008 11:37:04 AM
MEDICAL OFFICER

NDA #21526 NDA supplement (S-004)
Name of Sponsor: CV Therapeutics, Inc.
Name of Finished Product: Ranexa®
Name of Active Ingredient: Ranolazine

Introduction

Chronic stable angina
This efficacy supplement proposes to change the use of Ranexa® from second-line to first-line of treatment for patients with chronic stable angina. The sponsor submitted the results of protocol CVT 3036 in the defense of this application.

Protocol CVT 3036 was reviewed as a special clinical protocol assessment (May 7, 2004, request, serial number 232). The study was designed to investigate the possible association of QT prolongation provoked by ranolazine and excess mortality. The Agency stated that

> [a well controlled, well conducted, adequately sized trial showing] "no adverse trend in death and arrhythmia would be assuring and could support approval of ranolazine as first-line therapy for long-term treatment of chronic angina. The interpretability of the safety results in this regard does not depend on the primary endpoint reaching statistical significance."

There were additional safety data submitted from six clinical trials (1 interaction trial with diltiazem, 1 trial in subjects with congenital long QTc[1], 1 trial with higher doses of ranolazine, 3 trials with uncontrolled long term safety information). There is little new information obtained from the results of these trials.

Decrease of clinically significant arrhythmias
There was a decrease in the incidence of clinically significant arrhythmias[2] found during the 7-day Holter monitoring period (83% and 74% for placebo and ranolazine, respectively; table 24 clinical study report). However, the analysis showing statistical significance is invalid because:

1. the original objective was not met so additional analyses are inappropriate;
2. the endpoint was not an efficacy endpoint but rather part of a long list of safety objectives[3].

In addition, this "finding" seems to occur in a vacuum: the incidence rates for sudden death were similar for the two treatment groups, there were no differences between placebo and ranolazine regarding other types of non fatal arrhythmias including those that were

[1] CVT 3114 was previous evaluated and is not discussed in this review.
[2] Defined as ventricular tachycardia ($\geq$ 3 beat), supraventricular tachycardia with ventricular rate of $\geq$ 120 bpm, new-onset atrial fibrillation, and bradyarrhythmia with ventricular rate of < 40 bpm or 3rd degree AV block.
[3] 1.1.4 of statistical analysis plan dated 8-25-2006.

symptomatic (table 23 of study report), and there were only minor differences between the treatment groups in the reporting of various arrhythmias as adverse events (14.3.1.4.1).

Currently, there is insufficient evidence that ranolazine decreases arrhythmias of any kind. A prospectively defined, placebo controlled study with the occurrence of symptomatic arrhythmias as the primary endpoint is, therefore, required.

Conclusions

Protocol CVT 3036 enrolled a total of 6556 subjects who were hospitalized for non-ST elevation acute coronary syndrome (ACS) with the qualifying event being at least one episode of ischemic symptoms at rest. Subjects were randomized to either ranolazine or placebo and followed for at least 8 months.

The primary efficacy endpoint was a composite of cardiovascular (CV) death, MI, and recurrent ischemia. The primary efficacy analysis was time from randomization to first occurrence of CV death, myocardial infarction (MI), or recurrent ischemia. The null hypothesis was that there is no difference between the study treatments with respect to the time to first occurrence of any element of the primary efficacy endpoint.

Key results: There were 1448 subjects who experience a primary efficacy event. The null hypothesis was not rejected. There was no statistical difference between the treatment groups for the composite endpoint (p=0.11).

The incidence of death from any cause was approximately 5.3% for both treatment groups. The relative risk of mortality (ranolazine: placebo) was 0.988 (95% CI 0.80, 1.21). Therefore, a 21% or greater increase in mortality resulting from ranolazine use can be excluded with 95% confidence. The percents of those deaths deemed to be sudden were also similar for the two treatment groups (2% for placebo and 1.7% for ranolazine).

Based on the findings of this medium sized study, ranolazine, compared to placebo and within certain limits, does not increase mortality, the occurrence of MIs, or recurrent ischemia in subjects with non-ST elevation ACS. It is reasonable to allow the promotion of ranolazine as a first-line treatment for chronic stable angina.

Conclusions from the 6 additional trials are:
-The addition of diltiazem 180 mg bid increases ranolazine AUC_{0-12} by more than 2 fold (CVT 301-19);
-many subjects are unable to tolerate doses 1500 mg bid and above. Dose limiting adverse events include syncope, nausea, dizziness, and vomiting (CVT 3023);
-no unexpected adverse events were reported in the uncontrolled safety trials (CVT 3024, 3032, 3034).

Study CVT 3036, the clinical outcome trial, is discussed in detail in this review. The other studies are briefly presented.

Background

A total of seven studies were submitted to support the efficacy supplement. These are briefly outlined below.

Study ID	Design	No. of subjects dosed	Doses used	Duration of rx	Major objective
CVT 3036 (MERLIN)	Double blind, randomized	6541	RAN IV infusion RAN 375/500 mg ER bid	8 months	Clinical outcome trial (including survival)
CVT 301-19	Open label, cross over	31	RAN 500 and 1000 mg Diltiazem 90 mg	2 weeks	Diltiazem interaction
CVT-3023	Double blind, randomized	37	RAN 375 mg ER	2 weeks	Tolerability of extended release
CVT 3024	Open label follow up to CVT 3023	9	RAN 500 mg ER bid	14 months	Safety
CVT 3032	Open label follow up to CVT 3031	143	RAN ER 375, 500,750 mg bid	Mean exposure 3.8 years	Safety
CVT 3034	Open label follow up to CVT 3033 and 3037	1108	RAN 500,750, 1000 mg ER bid	Mean exposure 2.25 years	Safety

Study CVT 3036
Title: Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes (MERLIN)-TIMI 36

The study was conducted by 457 investigators at 442 sites in 17 countries.

Study Period: October 8, 2004 (first patient enrolled) to February 14, 2007 (last patient completed)

Objectives: The primary efficacy objective was to determine if ranolazine compared to placebo is effective in reducing the rate of cardiovascular (CV) death, myocardial infarction (MI), or recurrent ischemia during long-term treatment of patients with non-ST elevation acute coronary syndrome (ACS) receiving standard therapy.

Secondary efficacy objectives were to determine whether ranolazine was superior to placebo:
(1) for reducing the rate of major cardiovascular events (CV death, MI, or severe recurrent ischemia) during long-term treatment;

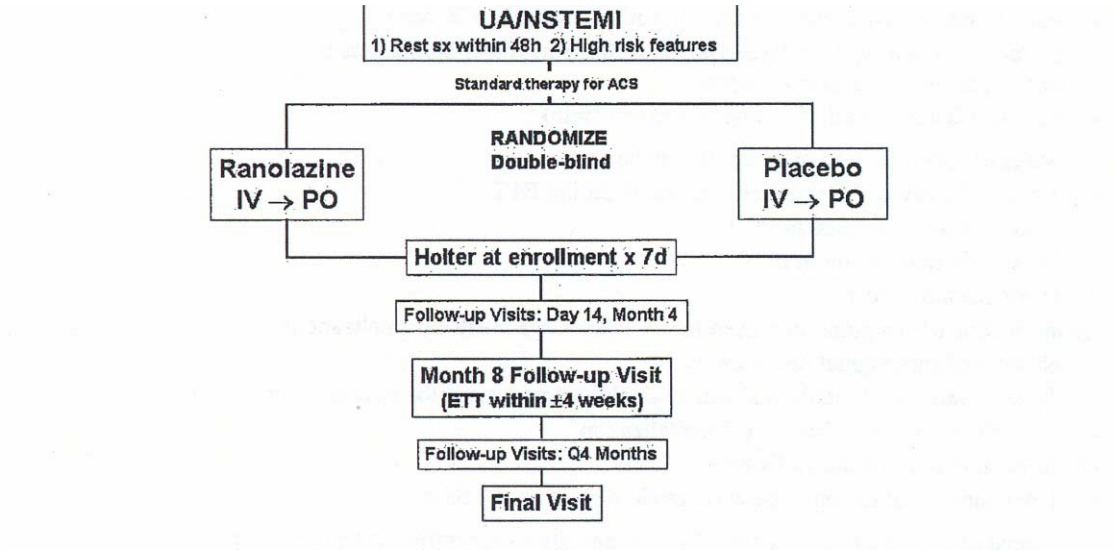
(2) for reducing the rate of failure of therapy (CV death, MI, recurrent ischemia, positive Holter for ischemia, hospitalization for new/worsening heart failure, or early positive exercise tolerance test [ETT]) during long-term treatment;
(3) for reducing the rate of CV death, MI, severe recurrent ischemia, or positive Holter for ischemia during acute treatment (30 days);
(4) for improving quality of life (QOL) as assessed using the anginal frequency scale and the physical limitation scale of the Seattle Angina Questionnaire (SAQ) at 4 months;
(5) with respect to the duration of exercise on ETT at 8 months (or Final Visit if earlier); and
(6) with respect to the total duration of ischemia on Holter monitoring early after presentation with ACS (between randomization and 72 hours).

Methodology: This was a randomized, double-blind, parallel-group, placebo-controlled, multinational clinical trial. Eligible patients were randomized no later than 48 hours after the most recent rest symptoms in a 1:1 ratio to receive either ranolazine or placebo, stratified by the physicians intended initial management strategy (early invasive vs. conservative) as declared at the time of randomization.

Ranolazine (or matched placebo) was administered initially as a 200 mg intravenous (iv) infusion over 1 hour, followed by an 80 mg/h infusion (or 40 mg/h for patients with severe renal insufficiency), adjusted downward for patients experiencing adverse events deemed treatment related. The infusion was to be continued for a minimum of 12 hours and up to a maximum of 96 hours.

Patients to be managed with an early invasive evaluation were to have received iv ranolazine/placebo for at least 6 hours prior to angiography, and for a minimum of 6 hours after percutaneous coronary intervention. Following infusion, patients were transitioned to oral ranolazine (or matched placebo) at a dose of 1000, 750, 500, or 375 mg bid, based upon the final infusion rate. Oral dose adjustments were to be made for patients with renal insufficiency, and those experiencing adverse events deemed to be treatment related. Patients were to be treated with ranolazine or placebo until the end of follow-up. However, patients who discontinued therapy continued to be followed for efficacy endpoints and survival until the end of the study.

Patients were to receive other therapies that were commensurate with contemporary local treatment guidelines and practices. A digital continuous ECG (Holter) monitor for ischemia was applied at the time of randomization and remained in place for 7 days. After discharge, patients returned for study visits at Day 14, Month 4, and every 4 months thereafter, until the end of the study, at which time a final visit occurred. Fourteen days after the final study visit, a follow-up telephone call was conducted to assess adverse events for the purpose of safety reporting. The trial was designed to continue until at least 730 major CV events (CV death, MI, severe recurrent ischemia) and 310 deaths from any cause were recorded. When both of these minimums were met, sites scheduled final visits for all patients.



Assignment to Treatment Groups
Subjects were randomized centrally in a 1: 1 ratio to receive either ranolazine or placebo; randomization was stratified by the physician's intent to manage the patient with an early invasive strategy (angiography within 48 hours and revascularization if appropriate).

Diagnosis and Main Criteria for Inclusion:
(1) > 18 years;
(2) hospitalized with non-ST elevation ACS defined as chest discomfort or anginal equivalent occurring at rest, lasting ≥ 10 minutes, and consistent with myocardial ischemia;
(3) at least one episode of ischemic symptoms (≥ 5 minutes) at rest within 48 hours of enrollment (may include the index episode);
(4) at least one of the following indicators of moderate to high risk:
-elevated cardiac troponin or CK-MB (> the upper limit of normal);
-ST depression (horizontal or down-sloping) ≥ 0.1 mV;
-diabetes mellitus (requiring insulin or oral therapy);
-TIMI Risk Score for unstable angina/non-ST elevation MI ≥ 3;
(5) willing and able to provide written informed consent.

Exclusion Criteria
1) Persistent (>20 min) acute ST -segment elevation > 0.1 mV in 2 or more contiguous leads
2) Successful revascularization of the culprit stenosis during the qualifying hospitalization, prior to randomization
3) Acute pulmonary edema requiring endotracheal intubation, sustained systolic blood pressure < 90 mm Hg, or evidence of cardiogenic shock
4) Left bundle branch block, electronic pacemaker, or left ventricular hypertrophy (LVH) with severe repolarization abnormality (baseline> 0.1 mV ST depression) that would interfere with interpretation of the Holter
5) Pregnant or lactating women, or women of child bearing potential not using an acceptable

form of birth control (negative pregnancy test also required)
6) Use at randomization of agents that are strong inhibitors of the cytochrome P450 pathway isoform 3A4
7) Need for ongoing or anticipated need for chronic treatment during the study period with any of the following agents which might interfere with the evaluation of the therapeutic response or safety of the study drug:
-Agents known to prolong the QT interval
-Any digitalis preparation (e.g. digoxin)
8) Clinically significant hepatic disease
9) End stage renal disease requiring dialysis
10) Participation in another trial of an investigational drug or device within 30 days (or longer as per local requirements), or treatment with ranolazine, (concomitantly or within 14 days of enrollment), or previous participation in MERLIN
11) Inability to comply with the protocol and follow-up visits
12) Any serious medical co-morbidity such that the patient's life expectancy is less than 12 months
13) Any condition which might increase the risk to the patient or decrease the chance of obtaining satisfactory data to achieve the objectives of the study.

Recommended Concomitant Therapy
All study subjects were to be treated with standard therapy consistent with local guidelines for the acute management of unstable angina and non-ST elevation MI, as well as secondary prevention.

It was recommended that concomitant antianginal medication (beta-blockers, calcium channel blockers, long-acting nitrates, and/or drugs in other classes indicated for the treatment of chronic angina outside the United States (e.g., nicorandil) were to be instituted or titrated upwards for angina (ischemia) only for clear evidence of recurrent ischemia. Similarly, to the extent possible, hypertension was to be treated with alternatives to adding or increasing the doses of calcium channel blockers, nitrates, or beta blockers.

Prohibited Concomitant Therapy
Any agent known to prolong the QT interval was prohibited during treatment with study medication. Study medication was to be temporarily withheld if treatment of limited duration with such an agent was required.

Subjects receiving or anticipated to require chronic treatment with preparations of digitalis at the time of randomization were excluded from participation in the trial. Digoxin (or other preparations of digitalis) could have been initiated after enrollment, if clinically necessary; however, alternative medications were to be administered whenever possible.

Number of Patients: A total of 6,560 patients (3,281 placebo; 3,279 ranolazine) were randomized into the study and included in the intent-to-treat (ITT) analysis population; of these, 6,541 (> 99%) patients (3,273 placebo; 3,268 ranolazine) received at least one dose of study drug and were included in the safety analysis population. The goal was to enroll

subjects until at least 730 major cardiovascular events (CV death, MI, severe recurrent ischemia) and 310 deaths occurred.

Study drug:
1) iv infusion of study drug (ranolazine/placebo) started within 30 minutes after randomization. Patients received an iv loading dose of ranolazine/placebo at a rate of 200 mg over 1 hour, followed immediately by a maintenance infusion at a rate of 80 mg/h between 12 and 96 hours, inclusive. (Patients with severe renal insufficiency (creatinine clearance < 30 mL/min) had a starting maintenance infusion rate limited to 40 mg/h.) During administration of the maintenance infusion, the infusion rate was to be titrated downward or temporarily discontinued in the event of profound and persistent QTc prolongation or other specific adverse events. Subjects who were stratified to the early invasive evaluation were to receive IV study drug for at least 6 hours prior to angiography, and for a minimum of 6 hours after PCI.

2) Approximately one hour prior to completion of the maintenance infusion, patients were to receive their first oral dose of ranolazine extended release (ER)/placebo at a dose that was based on the infusion dose at the time of transition; patients receiving an infusion rate of 80, 60, 40, or 30 mg/h were to receive ranolazine ER at a dose of 1000, 750, 500, or 375 mg bid, respectively.

The oral dose administered following the maintenance infusion was to be maintained through the end of the study unless the patient had newly developed severe renal insufficiency, profound or persistent QTc prolongation or other specific adverse events, in which case, the oral dose was to be down-titrated.

Table 1 Schedule of Procedures

Procedures	Screening	Day 1	Day 2 – Hospital D/C	Day 14[a]	M4[b]	M8[b]	4 Month Visits[b] (M12, M16, etc)	Final Visit[c]
Informed consent	X							
Medical history	X							
Full Physical exam[d]	X							X
Targeted Physical exam (w/orthostatic vital signs)			X	X	X	X	X	
12-lead ECG	X[e]		X[f]	X		X	Q8 months	X
Serum Chemistries, Hematology (Local)	X		X[k]	X[l]	X	X	Q8 months	X
CK-MB and/or cardiac troponin (Local)[j]	X	X[f]	X[f]					
Pregnancy test (women of child-bearing potential)	X			X	X	X	X	
Blood for Cardiac Biomarkers (Central Lab)	X	X[h]	X[h]	X				X
Blood for Genetic Analysis	X							
HgbA1c, Lipids (Local)	X				X	X	Q8 months	X
Blood sample for ranolazine levels		X[m]	X[m]	X[m]	X[m]			
Oral glucose tolerance test (OGTT)								X[f]
Randomization		X						
Dispense Study Drug		X	X		X	X	X	
Holter Monitor[g]		X	X					
Transthoracic echo (selected sites only)	X[n]	X[n]			X			
Exercise Tolerance Testing						X		X[f]
Assess for Adverse Events		X	X	X	X	X	X	X
Assess for Endpoints		X	X	X	X	X	X	X
QOL Questionnaires	X				X	X	X (M12)	X
Monitor Concomitant Medications		X	X	X	X	X	X	X
Monitor Compliance with Study Drug				X	X	X	X	X
Study Status/Discharge								X

[a] The Day 14 visit was to occur between day 10 and day 21 following randomization (inclusive).
[b] The Month 4 visit was to occur at 4 months after randomization (± 14 days), Month 8 at 8 months after randomization (± 14 days), etc.
[c] The Final Visit procedures were to be conducted upon completion of the study or permanent cessation of study medication.
[d] Including orthostatic vital signs and waist circumference.
[e] Retain ECG from qualifying event, as well as immediately prior to randomization.
[f] Local serial CK-MB and/or cardiac troponin for evaluation of qualifying event was to be performed; this testing was to be repeated for any episodes of chest symptoms consistent with ischemia lasting ≥ 10 min (During 24 hours post-PCI or CABG, serial local measurement of CK-MB x 2 were also to be repeated).
[g] Holter monitor for ischemia was to be placed within 15 min of starting study drug and worn by patient for 7 days after enrollment.
[h] Blood samples for central laboratory cardiac biomarkers were to be drawn pre-randomization, at 12–16 h and 24–36 h post-randomization (North America and selected centers in Europe).
[i] 12-lead ECG was to be obtained on Day 3 or discharge (whichever was sooner), and after any adjustment of study drug for prolonged QTc interval.
[j] Only serum creatinine was to be analyzed.
[k] Measurement of platelet density was to be recorded from local CBC pre-randomization and then QD x 5 days or until discharge (Selected centers).
[l] If not already performed. The OGTT was to be performed upon notification by the Operations Committee that this end-of-study procedure could occur.
[m] Selected centers only: A blood sample for ranolazine levels was to be drawn at 12–16 h, 24–36 h, and at the end of the iv infusion, Day 14, Month 4 and at the time of specific adverse events, or profound and persistent QTc prolongation (whenever possible).
[n] Patients enrolled in echo substudy: echo at 1–3 h after start of study drug. Baseline echo performed in selected patients.

Criteria for Efficacy: Efficacy was measured through evaluation of the time from randomization to CV death, MI, or recurrent ischemia (primary endpoint), time to severe recurrent ischemia, time to CV re-hospitalization, SAQ scores, duration of exercise on ETT, cardiac biomarkers, and antianginal medications.

Efficacy Endpoints
All elements of the primary composite and major secondary endpoint were to be reviewed by members of a Clinical Events Committee blinded to treatment allocation, or a central laboratory (Holter and ETT) blinded to treatment allocation and clinical outcomes.

Primary Endpoint
The primary efficacy endpoint was the time to first occurrence of any element of the composite of CV death, MI, or recurrent ischemia. The definitions of the elements of the composite primary endpoint are as follows:

1) CV Death: Any death for which there was no clearly documented noncardiovascular cause. Cardiovascular death was to be sub-categorized into sudden vs. nonsudden cardiac death as described in the separate Clinical Events Committee Charter.

2) Myocardial infarction must be distinct from the index event, and was defined by symptoms suggestive of ischemia/infarction in association with either electrocardiographic, cardiac biomarker or pathologic evidence of infarction.

Recurrent ischemia was defined by ischemia meeting any of the criteria below:
1) Recurrent ischemia with ECG changes: Recurrent ischemic discomfort or equivalent at rest lasting > 10 minutes associated with new ST or T -wave changes consistent with ischemia or
2) Recurrent ischemia leading to hospitalization: Recurrent ischemic discomfort or equivalent at rest lasting >10 minutes, repeated episodes at rest lasting >5 minutes, or an accelerating pattern of ischemic discomfort (episodes that are more frequent, severe, longer in duration and/or precipitated by less exertion) prompting re-hospitalization and considered to be myocardial ischemia upon final diagnosis (not meeting criteria for recurrent ischemia with ECG changes) or
3) Recurrent ischemia prompting revascularization, defined as:
a) During the index hospitalization: PCI or CABG prompted by recurrent ischemia with ECG changes (In countries where waiting lists exist, the revascularization must be scheduled during the hospitalization and carried out within 30 days) or
b) After hospital discharge from index hospitalization: PCI or CABG prompted by
1. Increase in angina to a higher Canadian Cardiovascular Society Class, or
2. Evidence for ischemia on provocative testing* or
4) Worsening angina/ischemia requiring additional therapy occurring after the Day 14 visit**, defined as:
a) An increase in angina to a higher Canadian Cardiovascular Society Class and

b) Requiring intensification of anti-anginal therapy with new or increasing doses of anti-anginal medications

*Evidence for ischemia on provocative testing must be manifest by ischemic symptoms and/or ECG criteria, or ischemic symptoms in conjunction with reversible perfusion defects or wall motion abnormalities on nuclear or echocardiographic imaging. Reversible perfusion deficits in the absence of symptoms or diagnostic ST changes are not sufficient to meet this criterion. Moreover, this criterion may not be met by adenosine or persantine stress imaging.

**This definition of recurrent ischemia may be applied only after baseline Canadian Cardiovascular Society Class is established at the Day 14 Visit.

Statistical Methods: All efficacy analyses were based on the analysis set of all patients randomized with intention to treat. Patients were assigned to treatment groups based on randomized treatment, regardless of treatment actually received. Hypotheses of no treatment difference were tested for the primary and secondary efficacy endpoints in the following pre-specified order using a closed testing procedure in order to control the family-wise error rate at 0.05:

1. Primary efficacy endpoint (CV death, MI, or recurrent ischemia).

2. Major secondary composite endpoint (CV death, MI, or severe recurrent ischemia).
3. Failure of therapy (CV death, MI, recurrent ischemia, positive Holter for ischemia, hospitalization for new/worsening heart failure, or early positive ETT).
4. CV death, MI, severe recurrent ischemia, or positive Holter for ischemia at or before 30 days.
5. The angina frequency scale of the Seattle Angina Questionnaire.
6. The physical limitation scale of the Seattle Angina Questionnaire.
7. Duration of exercise on ETT at 8 months (or Final Visit, if earlier).
8. Total duration of ischemia on Holter between randomization and 72 hours.

Time to event variables were analyzed using a Cox proportional hazards model with effect for treatment, stratifying by the intention for early invasive management. Relative risk estimates were calculated along with 95% confidence intervals and times to event were described using Kaplan-Meier curves and Nelson-Aalen cumulative hazard curves. Safety analyses were performed using the analysis set of all patients who received study medication. The relative risk of all-cause mortality was estimated along with a 95% confidence interval using a Cox proportional hazards model with effect for treatment, stratifying by intention for early invasive management. The composite of death from any cause or cardiovascular hospitalization was analyzed using the same methods. The incidence of symptomatic documented arrhythmia, based on the events adjudicated by the clinical events committee, was compared between treatment groups using the Cochran-Mantel-Haenszel test, stratifying by intention for early invasive management. The incidence of clinically significant arrhythmias observed during the 7-day Holter was compared between treatment groups using the same method.

All components of the primary and major secondary endpoints, as well as hospitalization for new or worsening heart failure and the safety endpoint of symptomatic documented arrhythmias were adjudicated by a blinded, independent Clinical Events Committee.

There was a planned efficacy interim analysis of the endpoint CV death conducted by an independent DSMB, with a significance level of 0.001. The reference significance level in the final analysis was adjusted to 0.0497 using the method of Fleming, Harrington and O'Brien.

The protocol required the study to continue until 730 major cardiovascular events and 310 deaths were observed. The projected power for the major secondary endpoint to detect a 20% reduction in relative risk was 90%, assuming a placebo incidence of 18% at one year. Assuming a 22% one-year incidence for the primary efficacy endpoint in the placebo group, the projected power to detect a 20% reduction in the primary efficacy analysis was 95%. A sample size of 5,500 patients was planned with a resizing calculation when 1,000 patients had 4 months of follow-up that permitted an increase up to 6,500 patients in order that the duration of the study not be unduly extended if the rates of major cardiovascular events and mortality differed substantially from pre-study predictions.

Results

Subject disposition.

The numbers of subjects enrolled and the numbers dropping out or completing the study are shown below.

Table 2 Patient Disposition: ITT Analysis Set

	Treatment		
	Placebo (n=3281)	Ranolazine (n=3279)	All (n=6560)
Number of patients taking at least one dose of study drug	3273 (>99%)	3268 (>99%)	6541 (>99%)
Total Follow-up (Days)			
n	3281	3279	6560
Mean (SEM)	347 (2.6)	346 (2.6)	346 (1.9)
Median	348	347	348
25th Percentile - 75th Percentile	238 - 458	234 - 460	236 - 460
Min - Max	1 - 759	1 - 784	1 - 784
Number of patients who prematurely and permanently ceased taking study drug	745 (23%)	925 (28%)	1670 (25%)
Primary reason for prematurely and permanently ceasing to take study drug			
Adverse event	154 (5%)	286 (9%)	440 (7%)
Protocol violation	13 (<1%)	8 (<1%)	21 (<1%)
Lost to follow-up	18 (<1%)	21 (<1%)	39 (<1%)
Does not meet entrance criteria	6 (<1%)	3 (<1%)	9 (<1%)
Patient withdrew consent to treatment	408 (12%)	455 (14%)	863 (13%)
Non-compliance	44 (1%)	44 (1%)	88 (1%)
Other	94 (3%)	96 (3%)	190 (3%)
Missing	8 (<1%)	12 (<1%)	20 (<1%)
All Reasons reported for prematurely and permanently ceasing to take study drug			
Adverse event	267 (8%)	449 (14%)	716 (11%)
Protocol violation	14 (<1%)	12 (<1%)	26 (<1%)
Lost to follow-up	22 (<1%)	24 (<1%)	46 (<1%)
Does not meet entrance criteria	7 (<1%)	7 (<1%)	14 (<1%)
Patient withdrew consent to treatment	462 (14%)	532 (16%)	994 (15%)
Non-compliance	82 (2%)	76 (2%)	158 (2%)
Other	124 (4%)	130 (4%)	254 (4%)
End of study status			
Alive	2940 (90%)	2931 (89%)	5871 (89%)
Withdrew consent to follow-up in writing	165 (5%)	170 (5%)	335 (5%)
Lost to follow-up	2 (<1%)	7 (<1%)	9 (<1%)
Dead	174 (5%)	171 (5%)	345 (5%)

Note: Patients may have more than 1 reason for permanently ceasing taking drug although only one is considered the primary reason. The end of study status is collected at the final visit for all patients.

A total of 6560 subjects were randomized: 3281 to placebo and 3279 to ranolazine. Nearly all randomized subjects took at least one dose of study drug. The numbers of subjects who prematurely discontinued study drug for any reason were greater in the ranolazine group (925, 28%) compared to placebo (745, (23%). Mean follow up days were similar for both treatment groups (placebo: 347 days, ranolazine: 346 days).

There were more ranolazine subjects who withdrew primarily because of adverse event (s) (286, 9%) compared to placebo subjects 154 (5%).

At the end of study, there were slightly more placebo subjects known to be alive (2940, 90%) compared to ranolazine subjects (2931, 89%). The percents of subjects who either withdrew consent to follow up or were lost to follow up were the same (5%) for both treatment groups. The percents of subjects who were known to have died were also the same (5%) for both treatment groups.

The primary reason for the largest number of subjects who prematurely discontinued was "patient withdrew consent to treatment." As of February 29, 2008[4], status unknown or no response from study site includes 39 ranolazine subjects and 27 placebo subjects. Therefore, follow up on vital status was unobtainable for 1% of the study population.

Baseline demographics

Baseline characteristics of the study population by treatment groups are shown below.

[4] Email sent 2-29-2008 from Carol Karp

Table 5 Demographics and Baseline Characteristics

	Treatment			
	Placebo (n=3281)	Ranolazine (n=3279)	P-value	All (n=6560)
Age (yrs)				
n	3281	3279	.32 (ANOVA)	6560
Mean (SD)	63.6 (11.0)	63.3 (11.0)		63.5 (11.0)
Median	64	64		64
25th - 75th Percentile	56 - 72	55 - 72		55 - 72
Min - Max	24 - 97	26 - 99		24 - 99
< 65	1647 (50%)	1703 (52%)	.35 (CMH)	3350 (51%)
65 - 74	1042 (32%)	1014 (31%)		2056 (31%)
>= 75	592 (18%)	562 (17%)		1154 (18%)
Sex				
Male	2096 (64%)	2173 (66%)	.042 (CMH)	4269 (65%)
Female	1185 (36%)	1106 (34%)		2291 (35%)
Race				
Asian	39 (1%)	49 (1%)	.73 (CMH)	88 (1%)
Black	53 (2%)	50 (2%)		103 (2%)
Caucasian	3129 (95%)	3112 (95%)		6241 (95%)
Hispanic	23 (<1%)	23 (<1%)		46 (<1%)
Other	37 (1%)	45 (1%)		82 (1%)
Body mass index (kg/m^2)				
n	3235	3235	.45 (ANOVA)	6470
Mean (SD)	28.9 (5.3)	28.8 (4.9)		28.8 (5.1)
Median	28.3	28.2		28.3
25th - 75th Percentile	25.5 - 31.6	25.4 - 31.4		25.5 - 31.5
Min - Max	15.4 - 145.5	15.0 - 68.9		15.0 - 145.5

Note: ANOVA = Analysis of variance model with effects for treatment and intention for early invasive management; CMH = Cochran-Mantel-Haenszel general association test stratifying by the intention for early invasive management.

Source: 14.1.2

The average subject was 63 years old, male (65%) and white (95%). Elderly subjects comprised 18% of the population. The treatment groups were well balanced.

Renal function

The majority of subjects (77%) had creatinine clearance above 60 mL/min; 2% had a rate of $\leq$ 30 mL/min. The percent of subjects per creatinine clearance rates were similar between the two treatment groups.

Region of origin

Patients were enrolled at 442 study centers in 17 countries; 1,102 patients (17%) enrolled in North America; 2,485 (38%) enrolled in Eastern Europe; and 2,973 (45%) enrolled in Western Europe, Israel, and South Africa.

Stratification

At randomization, patients were stratified by whether early invasive management (angiography within 48 hours and revascularization, if appropriate) was the intended therapeutic strategy or not. Approximately 41 % of patients in each group (1334/3281 placebo, 1333/3279 ranolazine) had a management plan that included an early invasive strategy.

Medical history and risk factors by treatment group are shown below.

Table 6 Medical History and Risk Factors (ITT Analysis Set)

Parameter	Treatment		p value	All
	Placebo (n = 3281)	Ranolazine (n = 3279)		(n = 6560)
Cardiovascular History[a]				
Previous MI	1095 (33%)	1119 (34%)	0.52	2214 (34%)
Angina pectoris	1776 (54%)	1789 (55%)	0.72	3565 (54%)
Hypertension	2409 (73%)	2395 (73%)	0.73	4804 (73%)
Previous PCI	636 (19%)	684 (21%)	0.13	1320 (20%)
Previous CABG	380 (12%)	389 (12%)	0.72	769 (12%)
CHF	557 (17%)	538 (16%)	0.52	1095 (17%)
TIMI risk score				
0–2	884 (27%)	882 (27%)	0.99	1766 (27%)
3–4	1730 (53%)	1727 (53%)		3457 (53%)
5–7	667 (20%)	670 (20%)		1337 (20%)
Risk Factors[b]				
Dyslipidemia	2022 (62%)	2028 (62%)	0.85	4050 (62%)
Diabetes mellitus	1116 (34%)	1104 (34%)	0.77	2220 (34%)
Current or former smoker	1862 (57%)	1911 (58%)		3773 (58%)
ST Depression (Qualifying Event)[d]				
0.5–0.9 mm	585 (18%)	599 (18%)		1184 (18%)
≥ 1 mm	1162 (35%)	1142 (35%)		2304 (35%)
Non-cardiac History[c]				
Asthma	132 (4%)	153 (5%)	0.20	285 (4%)
COPD	266 (8%)	280 (9%)	0.53	546 (8%)

The majority of subjects had either one or more of the following medical conditions: hypertension, angina, or dyslipidemia. Regarding cardiovascular status, about 33% had had a previous MI, more than half complained of angina, about 20% had had PCI, 12% a previous CABG and 17% had CHF. The majority of subjects were TIMI risk score 3-4 and ST depression for the qualifying event was $\geq$ 1 mm for the majority of subjects. The treatment groups were well balanced.

The qualifying event was non-STEMI for 51% of subjects and unstable angina in 47%. There were no differences between groups regarding time from onset of qualifying event to randomization, time from hospitalization for qualifying event to randomization, and duration of qualifying episode. The groups were well balanced (14.1.7).

There were 51 subjects randomized to ranolazine who had severe renal impairment (defined as creatinine clearance rate of < 30 mL/min). Of these, 18 received the initial maintenance infusion rate of 80 mg/h, 32 received 40 mg/h and 1 received <40 mg/h (14.3.1.1.1).

Subjects whose dose of study drug was down titrated at least once included 22 (9 placebo and 13 ranolazine) because of impaired creatinine clearance and 44 (13 placebo and 31 ranolazine) for QT prolongation (14.3.1.1.1, 16.2.7.4).

Concomitant medications
The most commonly used medications included ACE inhibitors, anticoagulants, beta-blockers, calcium channel blockers, diuretics, lipid lowering agents, nitrates/coronary vasodilators, and platelet inhibitors.

The percentages of subjects using one or more of concomitant medications either before admission, during hospitalization, and/or after hospitalization were similar for the treatment groups.

Table 8 Summary of Commonly Used Concomitant Medications

Medication Type	Placebo			Ranolazine		
	2 Weeks Before Admission[a] n = 3273	During Hospitalization[a] n = 3273	After Hospitalization[b] n = 3273	2 Weeks Before Admission[a] n = 3268	During Hospitalization[a] n = 3268	After Hospitalization[b] n = 3268
ACE Inhibitors	1403 (43%)	2164 (66%)	2367 (72%)	1343 (41%)	2119 (65%)	2331 (71%)
Anticoagulants	247 (8%)	2977 (91%)	427 (13%)	254 (8%)	3015 (92%)	392 (12%)
Beta-blockers	1505 (46%)	2747 (84%)	2887 (88%)	1495 (46%)	2712 (83%)	2862 (88%)
Calcium Channel Blockers	755 (23%)	998 (30%)	1200 (37%)	780 (24%)	971 (30%)	1119 (34%)
Diuretics	797 (24%)	1236 (38%)	1547 (47%)	812 (25%)	1148 (35%)	1411 (43%)
Lipid Lowering Agents	1354 (41%)	2462 (75%)	2828 (86%)	1348 (41%)	2474 (76%)	2863 (88%)
Nitrates/Coronary Vasodilators	1540 (47%)	2772 (85%)	2032 (62%)	1522 (47%)	2749 (84%)	2020 (62%)
Platelet Inhibitors	2011 (61%)	3094 (95%)	3170 (97%)	2001 (61%)	3093 (95%)	3181 (97%)

Source: [a]Section 14.1.10.1, [b]Section 14.1.10.2

Despite the exclusion criterion[5] prohibiting the use of these agents during the trial, 8 percent of subjects per treatment group were receiving a CYP3A4 inhibitor (diltiazem being the most frequent). Table 118.adhoc

Efficacy
The primary endpoint was a composite of CV death, MI, and recurrent ischemia.

[5] Any agent known to prolong the QT interval was prohibited during treatment with study medication. Study medication was to be temporarily withheld if treatment of limited duration with such an agent was required.

Table 10 **Primary Efficacy Analysis: Time from Randomization to First Occurrence of CV Death, MI, or Recurrent Ischemia**

	Placebo (n=3281)	Ranolazine (n=3279)
Number of Patients with Events	753	695
Endpoint-defining events		
CV Death	78 (10.4%)	87 (12.5%)
MI	210 (27.9%)	208 (29.9%)
Recurrent Ischemia	465 (61.8%)	400 (57.6%)
Severe Recurrent Ischemia	332 (44.1%)	302 (43.5%)
Worsening angina/ischemia requiring additional therapy	133 (17.7%)	98 (14.1%)
Relative Risk Ranolazine:Placebo	0.919	
95% Confidence Interval	(0.83, 1.02)	
P-value	.11	
Proportion of patients experiencing an event (KM estimates)		
30 days	8.3%	7.7%
60 days	10.9%	9.9%
90 days	12.5%	11.8%
180 days	17.0%	16.2%
270 days	20.5%	19.7%
360 days	23.5%	21.8%
450 days	25.7%	23.6%
540 days	30.1%	26.3%

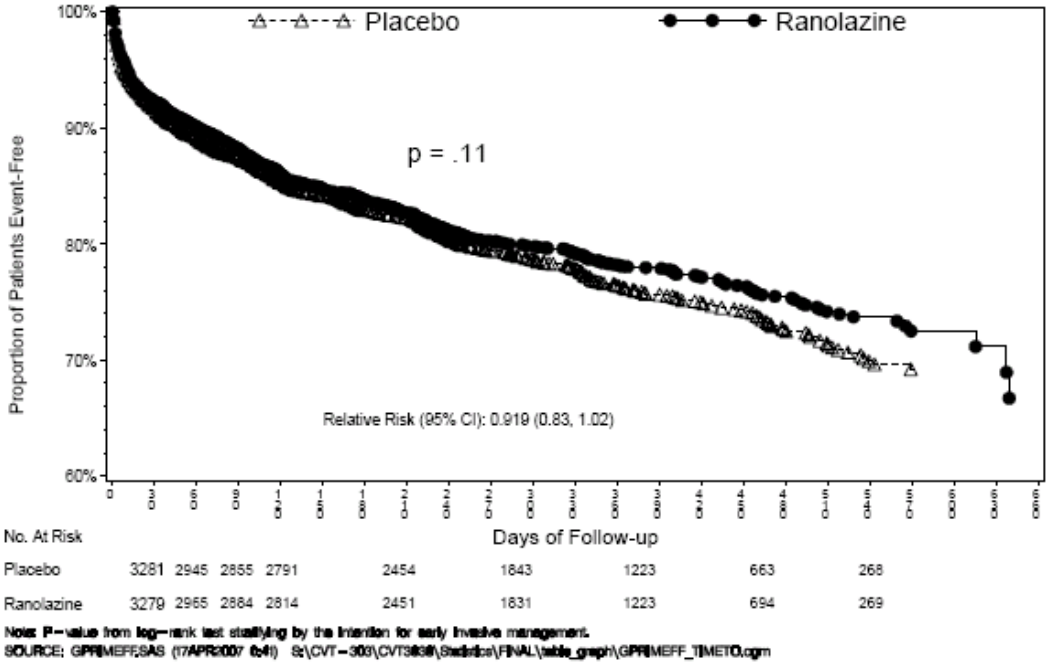
Note: P-value from log-rank test stratifying by the intention for early invasive management. Relative risk estimates from Cox regression model stratifying by the intention for early invasive management. KM = Kaplan Meier.

There were 753 (23%) placebo subjects who experienced a primary efficacy event compared to 695 (21.2%) ranolazine subjects. There was no statistical difference between the treatment groups (p=0.11). Relative risk (ranolazine: placebo) was 0.919 with 95% CI=(0.83,1.02).

There were slightly higher percentages of CV deaths and MI in the ranolazine group (12.5% and 29.9%) compared to the placebo group (10.4% and 27.9%). As expected, there were slightly higher percentages of recurrent ischemia in the placebo group (61.8%) compared to the ranolazine group (57.6%).

The composite endpoint evaluated $\leq$ 30 days and $\geq$ 30 days after randomization were similar for the 2 treatment groups.

Figure 2 **Time from Randomization to First Occurrence of CV Death, MI, or Recurrent Ischemia**



Secondary endpoints

The primary analysis was not met, therefore the review of the secondary endpoints is only exploratory.

1. There was no difference between treatment groups regarding the time to first occurrence of CV death, MI, or severe recurrent ischemia during long term treatment. The relative risk (ranolazine to placebo) was 0.962 (95% CI =(0.86, 1.08); p=0.50).

2. Time to Failure of Therapy During Long-term Treatment (failure of therapy was defined as CV death, MI, recurrent ischemia, positive Holter for ischemia, hospitalization for new or worsening heart failure, or early positive ETT). The relative risk (ranolazine to placebo) was 0.943 (95% CI =(0.87, 1.02); p= 0.15).

3. Incidence of CV Death, MI, Severe Recurrent Ischemia, or Positive Holter for Ischemia During Acute Treatment (at 30 Days). The relative risk (ranolazine to placebo) was 0.92 (95% CI = (0.84, 1.00)).

4. Quality of Life at 4 Months after Randomization. At 4 months following randomization, Seattle Angina Questionnaire results showed that subjects randomized to ranolazine had less perceived angina compared to subjects randomized to placebo ($p < 0.001$). However, there was no difference in the physical limitation scale between the two treatment groups ($p = 0.91$).

5. Duration of Exercise on ETT at 8 Months or Final Visit (combining treadmill with bicycle data) was not significantly different between the two treatment groups (542.8 ± 5.5 seconds for the placebo group vs. 550.0 ±5.5 seconds for the ranolazine group, $p = 0.35$).

6. Total Duration of Ischemia on Holter between Randomization and 72 Hours. The mean duration of ischemia showed no significant difference between the two treatment groups: 28.1 ± 2.3 minutes for placebo patients and 31.8± 2.5 minutes for ranolazine patients (p = 0.26).

Safety

The safety data base includes a total of 6541 subjects (3273 received placebo and 3268 received ranolazine. This represents a total of 99.7% of the randomized population.

The majority of subjects received iv infusion of study drug at 80 mg/h for the entire infusion period. There were 51 subjects in the ranolazine group with creatinine clearance rate < 30 mL/min and, therefore, received a lower infusion rate. There were 4% of placebo subjects and 5% of ranolazine subjects who were down titrated because of adverse events, QTc prolongation, and/or decreased creatinine clearance.

Most subjects began the oral doses of 1000 mg bid. The last oral dose being 1000 mg bid was true for 89% of placebo subjects and 83% of ranolazine subjects. There were 6% of placebo subjects and 11% of ranolazine subjects who had their dose down titrated. The mean duration for oral placebo treatment was 302 days and 284 days for oral ranolazine treatment.

Serious safety

Percent of death from any cause was 5.3% for both treatment groups. The relative risk of mortality (ranolazine: placebo) was 0.988 (95% CI=(0.80, 1.22)). The percents of those deaths deemed to be sudden were also similar (2% for placebo and 1.7% for ranolazine[6]).

Combined deaths from any cause or cardiovascular hospitalization were similar for the treatment groups. Estimated relative risk (ranolazine:placebo) was 0.975 (95% CI=(0.90, 1.06)).

The incidences of symptomatic documented arrhythmias leading to or prolonging hospitalization or deemed to be medically important were similar for the two treatment groups (3.1% and 3.0% for placebo and ranolazine, respectively).

The number of reported different types of arrhythmias are shown below.

[6] 14.3.1.8.1

Table 23 Incidence and Frequency of Symptomatic Documented Arrhythmias

	Placebo (n=3273)	Ranolazine (n=3268)	P-value
Incidence of Symptomatic Documented Arrhythmias	102 (3.1%)	99 (3.0%)	.84 (CMH)
Incidence of Symptomatic Documented Arrhythmia by Category			
Ventricular arrhythmia	29 (0.9%)	22 (0.7%)	
Supraventricular arrhythmia	41 (1.3%)	38 (1.2%)	
Bradyarrhythmia	29 (0.9%)	34 (1.0%)	
Cardiac arrest NOS	9 (0.3%)	10 (0.3%)	
Frequency of Symptomatic Documented Arrhythmias per Patient by Category			
Ventricular arrhythmia			
1	29	20	
2	0	1	
5	0	1	
Supraventricular arrhythmia			
1	39	34	
2	1	4	
3	1	0	
Bradyarrhythmia			
1	29	32	
2	0	2	
Cardiac arrest NOS			
1	9	10	

Note: P-value from Cochran-Mantel-Haenszel general association (CMH) test stratifying by the intention for early invasive management.

The results for the two treatment groups are similar.

Subjects underwent 7-day Holter monitoring starting a 0-15 minutes after initiation of study drug. The data card was sent to the (b) (4)
The significant arrhythmias and their occurrence by treatment group are shown below.

Table 24 **Incidence and Frequency of Clinically Significant Arrhythmias During the 7-Day Continuous ECG (Holter) Monitoring**

	Placebo (n=3273)	Ranolazine (n=3268)	P-value
Number of Patients with Holter Data	3189	3162	
Incidence of Clinically Significant Arrhythmias	2650 (83.1%)	2330 (73.7%)	<.001 (CMH)
Incidence of Any Clinically Significant Arrhythmias			
Any VT>=100 bpm >= 3 beats	1211 (38.0%)	948 (30.0%)	
Any SVT>=120 bpm	1752 (54.9%)	1413 (44.7%)	
New-onset Atrial fibrillation	75 (2.4%)	55 (1.7%)	
Any Bradycardic episode	1485 (46.6%)	1257 (39.8%)	
Frequency of Triplets			
0	1502 (47.1%)	1737 (54.9%)	
1 to 5	912 (28.6%)	765 (24.2%)	
6 to 10	174 (5.5%)	174 (5.5%)	
11 to 25	212 (6.6%)	183 (5.8%)	
26 to 50	105 (3.3%)	92 (2.9%)	
51 to 100	106 (3.3%)	80 (2.5%)	
> 100	172 (5.4%)	127 (4.0%)	
Frequency of VT >= 100 bpm lasting >= 4 beats			
0	2242 (70.3%)	2496 (78.9%)	
1 to 5	834 (26.2%)	595 (18.8%)	
6 to 10	58 (1.8%)	34 (1.1%)	
11 to 25	31 (1.0%)	21 (0.7%)	
26 to 50	12 (0.4%)	9 (0.3%)	
51 to 100	3 (<0.1%)	0 (0.0%)	
> 100	3 (<0.1%)	3 (<0.1%)	
Frequency of bradycardia			
0	1813 (56.9%)	2033 (64.3%)	
1 to 5	376 (11.8%)	335 (10.6%)	
6 to 10	107 (3.4%)	92 (2.9%)	
11 to 25	150 (4.7%)	127 (4.0%)	
26 to 50	104 (3.3%)	85 (2.7%)	
51 to 100	114 (3.6%)	92 (2.9%)	
> 100	519 (16.3%)	394 (12.5%)	
Frequency of ventricular pauses >= 2.5sec			
0	2806 (88.0%)	2839 (89.8%)	
1 to 5	254 (8.0%)	220 (7.0%)	
6 to 10	32 (1.0%)	35 (1.4%)	
11 to 25	36 (1.1%)	30 (0.9%)	
26 to 50	31 (1.0%)	18 (0.6%)	
51 to 100	7 (0.2%)	12 (0.4%)	
> 100	17 (0.5%)	4 (0.1%)	

Note: P-value from Cochran-Mantel-Haenszel general association (CMH) test stratifying by the intention for early invasive management. Frequencies are based on actual number of events reported for each patient. No adjustment has been made for patients who wore Holter device longer or shorter than the protocol specified 7 days.

Nearly all subjects (97%) had Holter monitoring data. A somewhat higher percentage of placebo subjects (83%) had clinically significant arrhythmias compared to ranolazine subjects (74%). A post hoc examination of the data by the sponsor revealed more subjects with ventricular tachycardia (>100 bmp) $\geq$ 8 bpm in the placebo group (8.3%) compared to ranolazine subjects (5.2%). The differences between groups could be the result of chance.

Renal impairment

There were similar reported adverse renal events in the 2 treatment groups (5% placebo and 7% ranolazine). The incidence rates for renal failure (acute, chronic and not otherwise specified), and renal impairment were 1% or less for both treatment groups.

There were 102 subjects (50 placebo and 52 ranolazine) with creatinine clearance $\leq$ 30 ml/min at enrollment. The blood pressure measurements for these 2 groups at baseline and endpoint are shown below.

SBP/DBP mmHg

	supine		standing	
	placebo	ranolazine	placebo	ranolazine
baseline	133/69 (50)+	135/72 (52)	126/66 (34)	130/70 (32)
final visit	132/72 (24)	143/73 (24)	127/75 (21)	136/74 (24)

+numbers in parentheses are sample sizes.

Compared to placebo, there appears to be negligible effect of ranolazine on the renal impaired subgroup (with possible exception of supine systolic blood pressure). However, half the subject did not have final visit blood pressure measurements. This result does not override the finding of elevated diastolic blood pressure in subjects with severe renal impairment (CVT 3016).

Concomitant diltiazem[7]
Of the 234 patients in the ranolazine treatment group who received diltiazem at any time during the course of the study, 12 patients died while receiving ranolazine, and an additional 7 patients died after having discontinued ranolazine treatment for a period ranging from 10 to 450 days. Of the 219 patients in the placebo group who received diltiazem at any time during the course of the study, 11 died.

A total of 69 of the 234 patients in the ranolazine treatment group who received diltiazem at any time during the course of the study discontinued ranolazine treatment, and 63 out of the 219 placebo patients who received diltiazem discontinued placebo treatment at any time during the study. A total of 41 out of the 234 patients in the ranolazine treatment group who received diltiazem and 18 out of the 219 patients who received placebo and diltiazem had their oral dose down titrated.

QTc prolongation
The trial did not have an exclusion criterion for subjects with prolonged QTc at baseline.

There were 615 subjects randomized to ranolazine and 618 subjects randomized to placebo group with a baseline QTc value $\geq$ 450 msec. There were 68 subjects randomized to ranolazine and 79 subjects randomized to placebo with a baseline QTc value $\geq$ 500 msec[4].

Of the 62 subjects needing reduction of the dose of study drug because of prolonged QTc, 40 had been randomized to ranolazine and 22 to placebo. 16.2.7.4

All adverse events
The overall adverse event reporting rates were similar for the treatment groups (73% placebo and 76% ranolazine). Events reported more frequently by at least 3% of subjects in either treatment group and reported more often in the ranolazine group compared to placebo are shown below.

Percents

Adverse event	Placebo N=3273	Ranolazine N=3268	Placebo subtracted
Dizziness	7	13	6
Constipation	3	9	6
Nausea	6	9	3
Asthenia	3	5	2
Hypotension	3	5	2

14.3.1.4

This is consistent with the safety summary supporting the original NDA.

[7]Data received in email sent from sponsor dated 2-25-08

Laboratory abnormalities
Differences between ranolazine and placebo at final visit compared to baseline for selected laboratory values were largest for hemoglobin, creatinine, and total bilirubin (see table below).

Change from baseline

Lab value	Month 4		Month 8		Last visit	
	Pla	Ran	Pla	Ran	Pla	Ran
Creatinine mcmol/L	1.6	6.4	2.3	8.4	2.7	6.5
Hemoglobin G/L	0.5	-2.2	1.2	-0.8	1.3	-1.0
Total bilirubin mcmol/L	-0.9	-0.5	-0.2	-0.2	-0.1	3.3

14.3.5.1

There was a greater persistent rise in creatinine in the ranolazine group compared to placebo. A total of 50 subjects (2%) reported increased blood creatinine in the ranolazine group compared to 34 subjects (1%) in the placebo group. The percents of subjects reporting renal dysfunction (defined as renal failure, renal failure acute, renal impairment, renal failure chronic) were slightly higher in the ranolazine group (3.0%) compared to placebo (2.0%).

Compared to placebo, there was a small decline in hemoglobin throughout the study in the ranolazine group and there was a small and inconsistent increase in total bilirubin.

CVT 301-19

Conclusion
The addition of diltiazem 180 mg bid increases ranolazine AUC_{0-12} by more than 2 fold.

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

Primary Objective
To evaluate the effect of diltiazem hydrochloride (DILT) 180 mg bid at steady state on the pharmacokinetic parameters of ranolazine (RAN) extended-release (ER) at the 500 mg bid dose level at steady state in subjects with PM and EM genotypes for CYP2D6.

Methodology
This study was an open-label, multiple dose, cross-over study in healthy volunteers in which dosing was to last for 15 days. Subjects were to receive oral ranolazine ER at the following doses and times: 500 mg bid starting on Day 1 until the morning of Day 4; 1000 mg bid starting the evening of Day 4 through the morning of Day 8; and 500 mg bid starting the evening of Day 8 through the morning of Day 15. Subjects were also to receive an oral dose of diltiazem at the following doses and times: 90 mg the evening of Day 8 and the morning of Day 9; 180 mg bid the evening of Day 9 through the morning of Day 15. The study included an additional treatment period lasting from the evening of Day 15 to the

morning of Day 22, during which subjects received RAN 1000 mg bid concomitantly with DILT 180 mg bid.

Number of subjects
52 healthy male and female volunteers were planned, 33 subjects were enrolled, and 31 subjects were dosed in the study.

Study design
Plasma samples for the measurement of ranolazine and metabolite concentrations were to be obtained on Days 1, 2, and 3 at 0 h and 12 h (predose); on Days 4, 8, and 15 at 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 h (full PK profile); and on Days 5, 6, 7, 9, 10, 11, 12, 13, and 14 (trough sample taken prior to evening dose at 12 h). For subjects enrolled in the original protocol, blood was also to be drawn for a full ranolazine PK profile on Day 22 and for analysis of trough samples on Days 16-21.

Pharmacokinetic Results
Ranolazine AUC0-12 at steady state increased by around 2.11-fold in poor metabolizers (PM) and 2.42-fold in extensive metabolizers (EM) when diltiazem 180 mg bid was added. The corresponding increases for Cmax were 1.86-fold in PMs and 2.20-fold in EMs.

Safety Results
Reported adverse events included dizziness, postural dizziness, application site erythema (at Holter electrode sites), chest pain, nausea, and paresthesia. There were 9 subjects (2 PMs and 7 EMs) who discontinued the study because of an adverse event and eight others (3 PMs and 5 EMs) were withdrawn because of the protocol-specified ECG interval stopping rule (PR interval exceeding 0.22 sec or QTc interval exceeding 500 msec). There were no serious safety events reported in this study.

Two subjects (1 PM and 1 EM) had an asymptomatic episode of ventricular tachycardia (up to 6 beats) captured on Holter recording during treatment with RAN 500 mg bid + diltiazem180 mg bid.

<u>CVT 3023</u>

Conclusions
This high dose tolerability study showed that many subjects were unable to tolerate doses 1500 mg bid and above. Dose limiting adverse events included syncope, nausea, dizziness, and vomiting (25%). The ten subjects who withdrew because of QTc prolongation or adverse events had been taking the 1500 mg bid dose.

Three patients reported at least one serious adverse event including one report of involuntary muscle contractions by subject 12122309 who had been receiving the 750 mg dose. There was a positive rechallenge with the 1500 mg dose. The episode resolved when he was discontinued from study drug. Blood concentration of ranolazine 9.5 hours after the last dose taken by this subject was 14,000 ng/mL[8].

Title of Study
A Double-Blind, Randomized, Parallel-Group Dose Escalation Tolerability Study of Ranolazine ER in Patients with Chronic Angina.

[8] Mean steady state Cmax with the 1000 mg dose bid is less than 2600 ng/mL.

Objectives
The primary objective of this study was to determine the tolerability of ranolazine ER at oral doses up to 3000 mg bid in subjects with chronic angina, as assessed by specific adverse events. The secondary objective was to characterize the adverse events and the changes in vital signs and laboratory parameters associated with ranolazine ER at oral doses up to 3000 mg bid in these subjects.

Study design
This was a double-blind, randomized, parallel-group, dose escalation study of ranolazine ER at oral doses ranging from 750 mg bid up to a maximum of 3000 mg bid in patients with chronic angina.

The maximum dose of ranolazine given was 2250 mg bid. Subjects were in the clinic for 14 days and started with 750 mg bid. They were titrated to the highest level. The plan to titrate to the 3000 mg bid dose was dropped.

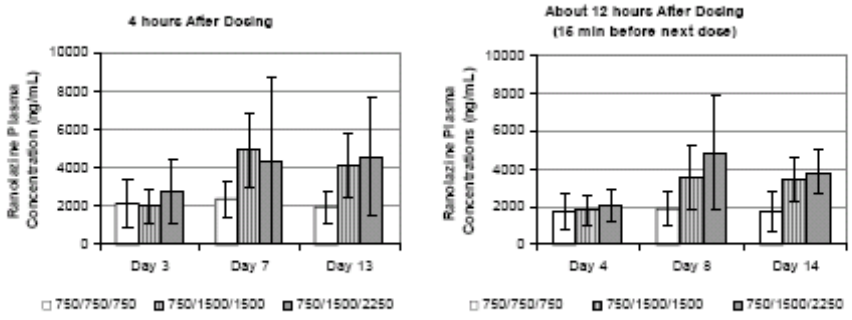
Number of Patients
A total of 37 patients were enrolled and dosed. Of these, 12 received the highest dose (2250 mg). There were 14 subjects who prematurely discontinued from the study (5 were withdrawn for an adverse event and 1 for a QTc interval prolongation, 4 withdrew consent, 2 were withdrawn by the sponsor, and 2 were withdrawn for evacuation of the study site).

Main inclusion criteria
Subjects had to have at least a 3-month history of chronic angina pectoris that was triggered by physical effort and was relieved by rest and/or sublingual nitroglycerin; had a diagnosis of coronary artery disease (as documented by angiographic evidence of > 60% stenosis of one or more major arteries; or had a history of myocardial infarction with positive MB-CPK enzymes, troponin, or EGG changes; or had a cardiac imaging scan indicating coronary artery disease); had or will have a minimum of 2 weeks treatment with daily chronic anti-anginal medications prior to admission.

Intolerability was defined as the number of subjects who (1) experienced syncope, diplopia, somnolence, depressed level/loss of consciousness, confusion/disorientation, symptomatic hypotension, dizziness, nausea, vomiting, or (2) had any severe adverse event, or (3) terminated from the study due to an adverse event.

PK results

Figure 1 Ranolazine Plasma Concentrations at Scheduled Timepoints



Note: The figures show mean ranolazine plasma concentration on each of the days; the error bars reflect the standard deviation.

The number and percent of patients who experienced one or more of the tolerability endpoint events were as follows: 1 (8%) patient in the 750 mg bid regimen, 6 (46%) patients in the 750 mg bid followed by 1500 mg bid regimen, and 9 (75%) patients in the 750 mg bid followed by 1500 mg bid followed by 2250 mg bid regimen.

Table 6 Primary Endpoint Analysis: Tolerability

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

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

Safety
There were no deaths. Subjects in highest dose group reported the highest incidence of nausea (50%), dizziness (42%), and vomiting (25%).

The most frequently reported adverse events included orthostatic hypotension (51%), headache (41%), constipation (32%), nausea (24%), and dizziness (22%). Dose dependent adverse events included nausea, vomiting, and dizziness. Three patients reported at least one serious adverse event including one report of involuntary muscle contractions by a subject randomized to the 750/1500/2250 regimen. Subjects receiving the higher ranolazine dose reported more laboratory abnormalities (increased creatinine or creatinine phosphokinase).

There were 6 subjects who withdrew from the study for either an adverse event (5 patients) or QTc interval prolongation (1 patient). Most of the adverse events that led to withdrawal occurred while the

patients were taking the 1500-mg dose of ranolazine; at the time of withdrawal, 4 of 6 patients had ranolazine plasma concentrations that were high relative to their cohorts.

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

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

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

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

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

BQL = below the quantitation limit of the assay

CVT 3024

Conclusions
The data from this is truncated, open label safety study are difficult to interpret. Of a total of 150 subjects planned only 9 were enrolled. There was 1 death (pancreatic cancer) and 1 discontinuation for adverse events (hospitalized for unstable angina).

Title of Study
An open-label, long-term safety and tolerability study of ranolazine ER at doses up to 1000 mg twice daily in patients with chronic angina.

Investigators and Study Centers
The study was conducted at 2 sites in the United States:
Study Period: August 29, 2005 (first patient enrolled) to November 29, 2006 (last patient completed)

Objectives

The objective of this study was to determine the safety and tolerability of ranolazine extended- release (ER) at oral doses up to 1000 mg twice daily (bid) in patients with chronic angina who had previously completed study 3023.

Study design
This study was a 1-year open-label, uncontrolled follow up to base study 3023. All subjects started on a ranolazine ER dose of 500 mg bid. If this dose was not tolerated, the patient was discontinued from the study. If it was well-tolerated, the dose was escalated to 1000 mg bid. If the 1000 mg bid dose was not tolerated, the dose was reduced back to 500 mg bid, where the subject was maintained for the duration of the study. If the 1000 mg bid dose was well-tolerated, the subject remained at this higher dose for the duration of the study.

Number of Patients
The study planned to enroll up to 150 subjects. However, since study 3023 was terminated early, enrollment in CVT 3024 was only 9.

Serious Safety
Of the 9 subjects studied, 5 were prematurely discontinued (3 withdrew consent, 1 was hospitalized because of chest pain, and 1 died from metastatic pancreatic cancer).

CVT 3032

Conclusions
The results of this small, open label, uncontrolled, long term study with doses up to 1000 mg bid are difficult to interpret. There were numerous reports of death (12%), reports of serious adverse events and withdrawals for adverse events (37%, mostly for angina). However, nothing unexpected was reported during the study.

Title of Study
A Phase 3, Open-label, Long-term, Safety Study of Ranolazine SR for Chronic Stable Angina Pectoris at Doses of 750 mg and 1000 mg bid

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

Study design
Long-term open-label safety study of ranolazine ER administered with or without other antianginal therapy in patients with chronic stable angina who had completed Study CVT 3031. Subjects received open-label treatment with ranolazine ER at an initial dose of 750 mg bid which may have been titrated to 1000 mg bid based on clinical response. If at a ranolazine ER dose of 1000 mg bid symptoms were not controlled, subjects may also have taken additional antianginal therapy (calcium channel blockers or beta-blockers) as necessary.

Number of Patients

A total of 143 patients enrolled in this follow-on study to CVT 3031.

Main Criteria for Inclusion
The study population consisted of patients with stable angina pectoris who completed Study CVT 3031. Subjects were not eligible to enter Study CVT 3032 if they had NYHA Class IV congestive heart failure, second or third degree atrioventricular block or uncontrolled clinically significant cardiac arrhythmias, QTc > 500 msec, required medications known to prolong the QTc interval, required medications significantly affecting cytochrome P450 3A4, active acute myocarditis or pericarditis, hypertrophic cardiomyopathy, uncontrolled hypertension, any chronic illness likely to hinder or confuse the follow-up evaluation, or were unwilling to refrain from consumption of grapefruit/grapefruit juice.

Continued eligibility criteria
If a patient developed any of the following criteria during this study they were not eligible to continue: clinically significant hepatic disease, end-stage renal disease requiring dialysis or a calculated creatinine clearance (CLcr) < 30 mLlmin.

Duration of Treatment
This study was intended to last up to approximately 10 years. The actual duration of the study was approximately 8 years.

Results
The mean duration of exposure was 3.8 years (range: 12 days to 8 years).

There were 17 deaths and 87 serious adverse events: 53 subjects withdrew for an adverse event (most common were for angina (5), MI (4), dizziness (3), coronary artery surgery(3)).

The causes of death included myocardial infarction (4%), cancer (3%), sudden death (1%). Other rarely reported events included cerebrovascular event, ventricular fibrillation/tachycardia, acute respiratory failure, multi-system failure, congestive heart failure, and cardiovascular insufficiency.

The serious adverse events included angina, MI, unstable angina, CHF, and CAD. Cerebrovascular accident and syncope were reported by 4% and 2% of the study population, respectively. Torsade de Pointes was not reported.

The most frequently reported adverse events were angina pectoris (29%), dizziness (22%), constipation (16%), chest pain (15%) peripheral edema (14%), and fatigue (13%).

There was one report of "a prolonged QTc" in a subject who had been started on amiodarone 7 days previously for atrial fibrillation and the second was an "arrhythmia" in a subject with a history of atrial fibrillation and supraventricular tachycardia.

CVT 3034

Conclusions
There were no unusual findings in this large open label, uncontrolled study.

Title of Study

A Phase 3, Open-label, Long-term, Safety Study of Ranolazine SR for Chronic Stable Angina Pectoris at Doses of 500, 750 mg and 1000 mg bid Administered in Combination with Background Antianginal Therapy

Objectives
The primary objective of this study was to determine the long-term safety and tolerability of ranolazine ER 500 mg bid, 750 mg bid and 1000 mg bid in patients with chronic stable angina during an open-label treatment period of up to 8 years.

Study design
Long-term open-label safety study of ranolazine ER administered with or without other antianginal therapy in patients with chronic stable angina who had completed Study CVT 3033 or CVT 3037. Subjects received open-label treatment with ranolazine ER at an initial dose of 750 mg bid which may have been titrated to 1000 mg bid based on clinical response. If at a ranolazine ER dose of 1000 mg bid symptoms were not controlled, subjects may also have taken additional antianginal therapy (calcium channel blockers or beta-blockers) as necessary.

Number of Patients
A total of 1108 subjects were enrolled for up to 6 years.

Results
A total of 814 (74%) subjects completed the trial. The mean duration of exposure was 2.25 years (range: 6 days to 6.27 years).

There were 74 deaths and 87 serious adverse events: 90 subjects (8%) withdrew for an adverse event (most common were cardiac disorders including MI, and one subject was discontinued because of abnormal BUN, serum creatinine and serum uric acid). Torsade de Pointes was not reported.

The causes of death included myocardial infarction (3%), sudden death (1%), and cancer (1%). Other reported events in 3 or few subjects included accident/trauma, ventricular fibrillation/ tachycardia, and pulmonary embolism. There were 2 subjects who died of unknown causes.

There were 290 (26%) subjects who reported a serious adverse event.

The most commonly reported adverse events included constipation (9%), angina (7%), dizziness (7%), peripheral edema (6%), unstable angina (5%), and hypertension (4%).

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/s/

Maryann Gordon
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MEDICAL OFFICER