MEDICAL REVIEW OF SAFETY

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

Table of Contents

Summary of safety

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

QT interval prolongation and T wave morphology changes

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

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

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

Table N-1.3.2.1vol 1.0376

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

No. and (percent) of patients

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

Table N-15.3.1 vol 1.0377

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

% of subjects with notched T waves

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

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

[1] From fax dated 6-27-03

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

% of subjects with notched T waves (at peak)

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

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

Drug interactions

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

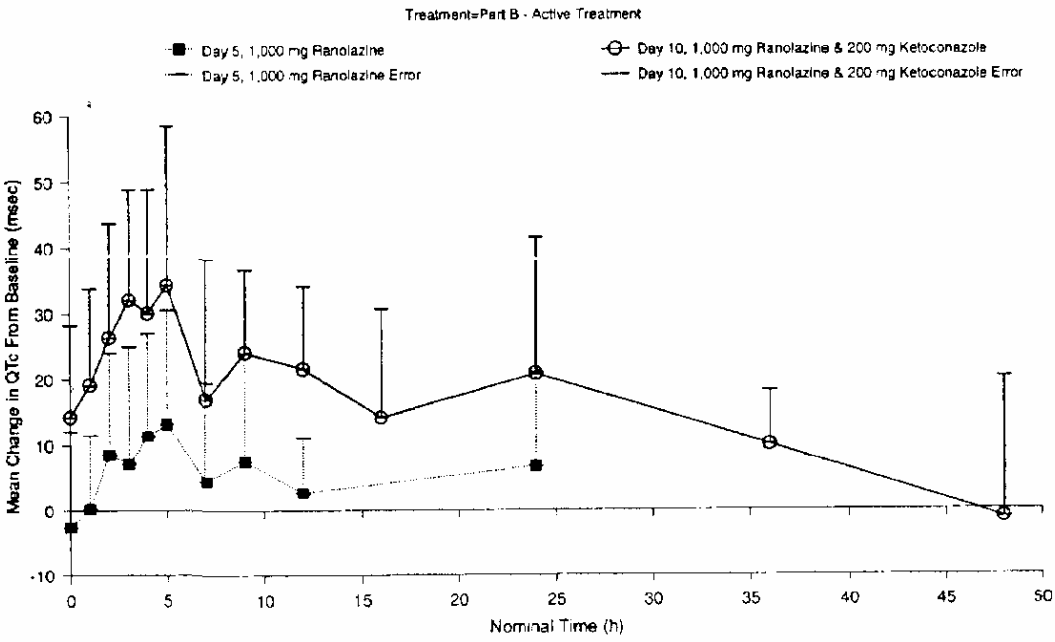
[2] Roden DM, Spooner PM. Inherited long QT syndromes: a paradigm for understanding arrhythmogenesis. J Cardiovasc Electrophysiol. 1999;
10: 1664-1683.

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

[4] Malfatto G, Beria B, Sala S, et al. Quantitative analysis of T wave abnormalities and their prognostic implications in the idiopathic long QT syndrome. J Am Coll Cardiol. 1994; 23: 296-30l.

[5] Study CVT 301-10

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



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

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

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

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

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

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

1.0 Overall clinical program

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

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

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

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

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

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

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

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

Table 4 Overview of the Ranolazine Development Program by Treatment Group

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

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

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

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

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

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

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

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

"All" subjects (ISS data base)

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

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

[9] Correspondence with sponsor

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

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

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

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

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

Controlled trials

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

RANOLAZINE ISS
PHASE II/III CONTROLLED STUDIES

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

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

RANOLAZINE ISS
PHASE II/III CONTROLLED STUDIES

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

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

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

Controlled SR angina trials

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

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

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

Table 7 Patient Disposition and Reason for Discontinuation—Phase 2/3 SR Controlled Angina Studies Population

	Number of Subjects/Patients					
	Ranolazine SR b.i.d.					
Category	**Total SR N = 749**	**500 mg N = 181**	**750 mg N = 279**	**1,000 mg N = 459**	**1,500 mg N = 187**	**Placebo N = 455**
Mean Duration of Exposure [Days]	66	8	82	50	8	53
Discontinuation [n (%)]	91 (12.1)	4 (2.2)	29 (10.4)	44 (9.6)	14 (7.5)	35 (7.7)
Reason for Discontinuation						
Unacceptable AE	59 (7.9)	1 (0.6)	20 (7.2)	27 (5.9)	11 (5.9)	15 (3.3)
Inappropriate Enrollment	1 (0.1)	0	0	1 (0.2)	0	0
Non-compliance (Drug/Protocol)	2 (0.3)	0	2 (0.7)	0	0	2 (0.4)
Lost to Followup	1 (0.1)	0	0	1 (0.2)	0	0
Elective Withdrawal	10 (1.3)	1 (0.6)	1 (0.4)	5 (1.1)	3 (1.6)	4 (0.9)
Death	4 (0.5)	1 (0.6)	2 (0.7)	1 (0.2)	0	2 (0.4)
Study Termination by Sponsor	0	0	0	0	0	1 (0.2)
Other	14 (1.9)	1 (0.6)	4 (1.4)	9 (2.0)	0	11 (2.4)

Abstracted from **Appendix V A Table D-3.3** and **Appendix V B Table E-1.3**.

The mean durations of exposure were 66 days for the total SR population (n=749) and 53 days for placebo (n=455). The dose of ranolazine with the largest number of patients is 1000 mg bid (459 patients). Discontinuation rates for any reason was 12.1% for any dose of ranolazine compared to 7.7% for placebo. The reason with the largest percent of discontinuations in the total SR group was for an adverse event (7.9%). There is no obvious dose response for noncompleters but sample sizes and length of exposure are unequal.

Long term, open label trials

CVT 3032 and CVT 3034

Of the 550 patients enrolled in these studies[11], 440 are still ongoing and 110 (20%) were discontinued. Of the patients who discontinued, 58 did so because of an adverse event. In addition, there were 262 subjects who received the IR formulation during one of 5 uncontrolled IR studies.

The disposition of these subjects (and IR patients from earlier trials) is shown in the table below.

[11] cut off date 10-15-01

TABLE D-2.3 (PAGE 1 OF 1)
Patient Disposition

Disposition	IR (Immediate Release)	SR (Sustained Release)
Total Number of Patients in Summary	262	550
Normal Completion	97(37.0)	0
Ongoing	0	440(80.0)
Early Termination	165(63.0)	110(20.0)
Unacceptable Adverse Event	34(13.0)	58(10.5)
Inappropriate Enrollment	2(0.8)	0
Non-compliance (drug/protocol)	3(1.1)	4(0.7)
Lost to Follow up	0	3(0.5)
Elective Withdrawal	0	16(2.9)
Death	6(2.3)	16(2.9)
Study Termination by Sponsor	66(25.2)	0
Other	54(20.6)	13(2.4)

Twenty percent of long term subjects withdrew early from ranolazine treatment. More than half of these withdrew for unacceptable adverse events.

Other populations
There were 6 studies with patient populations with diseases other than angina. These include CHF (2 studies, 96 patients), intermittent claudication (2 studies, 48 patients), renal impairment (1 study, 29 subjects), hepatic impairment (1 study, 32 subjects). Data from these populations were integrated into the ISS database.

Extent of exposure

"All" subjects (ISS data base)
The numbers of subjects who received treatment (ranolazine, placebo, or both) for a specified amount of time are shown below.

Table 8 Extent of Exposure for All Treated Subjects/Patients—ISS Database

Exposure	Number (%) of Subjects/Patients[a]	
	Total Ranolazine N = 2,682	Total Placebo N = 1,529
≤ 1 Day	196 (7.3)	213 (13.9)
2–6 Days	371 (13.8)	137 (9.0)
7–13 Days	295 (11.0)	560 (36.6)
14–27 Days	187 (7.0)	152 (9.9)
28–41 Days	477 (17.8)	205 (13.4)
42–55 Days	26 (1.0)	10 (0.7)
56–83 Days	172 (6.4)	21 (1.4)
≥ 84 Days	958 (35.7)	231 (15.1)
Average Duration (Days)	160	25

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

Abstracted from **Appendix III B Table E-1.1**.

The mean duration of exposure was 160 days for ranolazine compared to 25 days for placebo.

Phase 2/3 SR controlled angina studies

Extent of exposure for this subpopulation is shown below.

Table 9 Extent of Exposure for All Treated Subjects/Patients—Phase 2/3 SR Controlled Angina Studies Population

Category	Number (%) of Subjects/Patients[a]					
	Ranolazine SR (b.i.d.)					
	500 mg N = 181	750 mg N = 279	1,000 mg N = 459	1,500 mg N = 187	Total SR N = 749	Placebo N = 455
≤ 1 day	0	0	0	0	0	1 (0.2)
2–6 days	8 (4.4)	4 (1.4)	14 (3.1)	19 (10.2)	12 (1.6)	18 (4.0)
7–13 days	170 (93.9)	1 (0.4)	186 (40.5)	165 (88.2)	26 (3.5)	168 (36.9)
14–27 days	3 (1.7)	8 (2.9)	10 (2.2)	3 (1.6)	179 (23.9)	14 (3.1)
28–41 days	0	4 (1.4)	3 (0.7)	0	24 (3.2)	1 (0.2)
42–55 days	0	3 (1.1)	4 (0.9)	0	7 (0.9)	2 (0.4)
56–83 days	0	37 (13.3)	48 (10.5)	0	85 (11.3)	20 (4.4)
≥ 84 days[b]	0	222 (79.6)	194 (42.3)	0	416 (55.5)	231 (50.8)
Average Duration (Days)	8	82	50	8	66	53

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

[b] Maximum period of exposure for any patient in Studies CVT 3033 and RAN2240 was 103 days, see CSR **Item 8, Section 8. 16**

Abstracted from **Appendix V B Table E-1.3**.

The average duration of exposure for all ranolazine was 66 days compared to 53 days for placebo. The 750 mg dose had the longest average duration of exposure (82 days).

Long term, open label studies

CVT 3032 and CVT 3034

The mean duration of exposure to ranolazine SR in uncontrolled studies was 448 days. A total of 276 patients received the drug for at least one year and 101 received it for at least 2 years.

Adequacy of clinical experience

The development program was excessively large in number but had only a limited number of clinical trials that were helpful in assessing safety. That said, there are enough patients studied under controlled conditions to comfortably determine the major safety effects of ranolazine.

Case report forms were submitted and spot checked for subjects who died or were withdrawn for adverse event.

2.0 Demographics

The table below shows demographic and baseline characteristics for the ISS database population and the Phase 2/3 SR controlled studies.

Table 10 Demographic and Baseline Characteristics—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations

	Number (%) of Patients					
	ISS Database Population			Phase 2/3 SR Controlled Studies		
Category	Ranolazine N = 2,682	Placebo N = 1,529	Total N = 2,985	Ranolazine N = 749	Placebo N = 455	Total N = 1,025
Gender						
Male	2,170 (80.9)	1,207 (78.9)	2,400 (80.4)	580 (77.4)	341 (74.9)	788 (76.9)
Female	512 (19.1)	322 (21.1)	585 (19.6)	169 (22.6)	114 (25.1)	237 (23.1)
Age						
< 65 years	1,753 (65.4)	965 (63.1)	1,935 (64.8)	370 (49.4)	220 (48.4)	504 (49.2)
65 to < 75 years	751 (28.0)	465 (30.4)	847 (28.4)	287 (38.3)	189 (41.5)	405 (39.5)
≥ 75 years	178 (6.6)	99 (6.5)	203 (6.8)	92 (12.3)	46 (10.1)	116 (11.3)
Race						
Caucasian	2,306 (86.0)	1,347 (88.1)	2,569 (86.1)	715 (95.5)	434 (95.4)	986 (96.2)
Non-Caucasian	376 (14.0)	182 (11.9)	416 (13.9)	34 (4.5)	21 (4.6)	39 (3.8)
Underlying Disease						
Diabetes Mellitus	383 (14.3)	217 (14.2)	436 (14.6)	179 (23.9)	102 (22.4)	238 (23.2)
CHF	331 (12.3)	150 (9.8)	407 (13.6)	197 (26.3)	107 (23.5)	274 (26.7)
CAD	1,869 (69.7)	1,217 (79.6)	2,106 (70.6)	749 (100)	455 (100)	1,025 (100)
Prior Unstable Angina	223 (8.3)	104 (6.8)	241 (8.1)	160 (21.4)	89 (19.6)	215 (21.0)
Previous MI	990 (36.9)	634 (41.5)	1,133 (38.0)	427 (57.0)	247 (54.3)	580 (56.6)

Table 10 Demographic and Baseline Characteristics—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations (Cont'd)

Category	Number (%) of Patients					
	ISS Database Population			Phase 2/3 SR Controlled Studies		
	Ranolazine N = 2,682	Placebo N = 1,529	Total N = 2,985	Ranolazine N = 749	Placebo N = 455	Total N = 1,025
Ventricular Arrhythmias	254 (9.5)	173 (11.3)	289 (9.7)	78 (10.4)	44 (9.7)	97 (9.5)
Valvular Heart Disease	111 (4.1)	59 (3.9)	132 (4.4)	40 (5.3)	23 (5.1)	60 (5.9)
Prior Cardiac Arrest	15 (0.6)	14 (0.9)	22 (0.7)	10 (1.3)	9 (2.0)	16 (1.6)
Hypertension	1,039 (38.7)	627 (41.0)	1,218 (40.8)	479 (64.0)	291 (64.0)	657 (64.1)
Prior Stroke	80 (3.0)	43 (2.8)	95 (3.2)	39 (5.2)	19 (4.2)	50 (4.9)
Angioplasty (including PTCA)	371 (13.8)	243 (15.9)	4021 (13.5)	164 (21.9)	115 (25.3)	220 (21.5)
Cardiac Revascularization	431 (16.1)	261 (17.1)	471 (15.8)	162 (21.6)	88 (19.3)	199 (19.4)
Concomitant Medications						
ACE Inhibitors	501 (18.7)	264 (17.3)	—	279 (37.2)	172 (37.8)	—
Alpha and Beta Blockers	704 (26.2)	325 (21.3)	—	265 (35.4)	135 (29.7)	—
AT1 Angiotensin II Antagonists	59 (2.2)	21 (1.4)	—	26 (3.5)	19 (4.2)	—
Calcium Channel Blockers	771 (28.7)	385 (25.2)	—	324 (43.3)	159 (34.9)	—

Table 10 Demographic and Baseline Characteristics—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations (Cont'd)

Category	Number (%) of Patients					
	ISS Database Population			Phase 2/3 SR Controlled Studies		
	Ranolazine N = 2,682	Placebo N = 1,529	Total N = 2,985	Ranolazine N = 749	Placebo N = 455	Total N = 1,025
Fibrates	141 (5.3)	88 (5.8)	—	38 (5.1)	25 (5.5)	—
HMG CoA Reductase Inhibitors	670 (25.0)	349 (22.8)	—	348 (46.5)	218 (47.9)	—
Platelet Aggregation Inhibitors	162 (6.0)	96 (6.3)	—	50 (6.7)	34 (7.5)	—

AT = angiotensin; ACE = angiotensin-converting enzyme; CHF = congestive heart failure; CAD = coronary artery disease; HMG CoA = hydroxymethyl glutaryl coenzyme A; PTCA = percutaneous transluminal coronary angioplasty; MI = myocardial infarction; NA = not available.

Abstracted from **Appendix III A Table D-4.1, Appendix III A Table D-4.1.1, Appendix III A Table D-5.1, Appendix V A Table D-4.3,** and **Appendix V A Table D-5.3**.

<u>"All" subjects (ISS data base)</u>

The 2 treatment groups were well balanced. The majority of subjects were male, less than 65 years of age, and white. Less than 7% of subjects were 75 years of age or older.

Overall, around 14% of subjects had diabetes mellitus and about 14% had congestive heart failure. The majority had coronary artery disease, around 8% had prior unstable angina, and around 40% had had a previous myocardial infarction. About 10% had ventricular arrhythmias, about 4% had valvular heart disease, less than 1% had had a prior cardiac arrest, about 40% had hypertension, about 3% had had a prior stroke, about 14% had had angioplasty and about 16% had had cardiac revascularization.

Commonly used concomitant medication includes ACE inhibitors, alpha/beta blockers, calcium channel blockers, and HMG CoA reductase inhibitors.

<u>Phase 2/3 SR controlled angina studies</u>

The majority of subjects was male, less than 75 years of age, and mostly white.
About 11% of subjects were at least 75 years of age. The 2 treatment groups were well balanced.

Around 23% of subjects had diabetes mellitus and about 25% had congestive heart failure. All had coronary artery disease, around 20% had prior unstable angina, and around 55% had had a previous myocardial infarction. About 10% had ventricular arrhythmias, about 5% had valvular heart disease, around 2% had had a prior cardiac arrest, 64% had hypertension, about 5% had had a prior stroke, less than 25% had had angioplasty and about 20% had had cardiac revascularization. The 2 treatment groups were well balanced.

Commonly used concomitant medication includes ACE inhibitors, alpha/beta blockers, calcium channel blockers, and HMG CoA reductase inhibitors. The 2 treatment groups were well balanced.

Exclusion criteria
The list below outlines the patients who were excluded from the 2 of the largest placebo controlled efficacy trials (CVT 3033 and 3031).

-presence of electrocardiographic or other factors that might interfere with ECG interpretation or may cause a false positive stress test
- New York Heart Association Class III-IV CHF;
-Clinically significant valvular heart disease or congenital cardiac defects;
-Unstable angina pectoris within the 2 months prior to study entry;
-Second or third degree atrio-ventricular block or uncontrolled clinically significant cardiac arrhythmias or a history of life-threatening ventricular arrhythmias unassociated with acute MI;
-Corrected QT interval (QTc) > 0.50 sec at Visit 1;
-Required medications known to prolong the QT interval;
-Required medications that inhibit or induce cytochrome P450 3A4,
-Unwillingness to refrain from grapefruit/grapefruit juice consumption for the duration of the study
-Requirement for digoxin;
-MI, CABG, PTCA, or other catheter-based rcvascularization procedures within 2 months before study entry;
-Active acute myocarditis or pericarditis;
-Hypertrophic cardiomyopathy;
-Uncontrolled hypertension;
-Systolic BP< 100 mmHg;

3.0 All adverse events
Methodology
According to the sponsor, adverse event data were collected by routine monitoring and reporting while the patient was on-study. An adverse event was defined as any unfavorable or unintended sign (including laboratory values), symptom, or disease that appeared or worsened during the clinical trial, whether or not deemed causally associated with the study drug. Investigators identified and graded adverse events by direct observation, questioning, and spontaneous reports from patients. Investigators identified the action taken regarding the adverse event, and they assigned a causality descriptor. An adverse event could result in the patient's premature discontinuation from the study. Adverse events were reported as verbatim terms in the case report forms (CRFs); these terms were subsequently mapped (using a COSTART thesaurus) to a preferred term and body system.

The table below shows the reporting of all adverse events in the ISS database and the Phase 2/3 SR controlled angina studies.

Table 11 Incidence of Treatment-Emergent Adverse Events by Category and by Treatment—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations

Category	Number (%) of Subjects/Patients			
	ISS Database		Phase 2/3 SR Controlled Studies	
	Total Ranolazine (N = 2,682)	All Placebo (N = 1,529)	Total Ranolazine (N = 749)	Placebo (N = 455)
Mean Duration of Exposure (Days)	160	25	66	53
Any AE	1,465 (54.6)	418 (27.3)	275 (36.7)	101 (22.2)
Any SAE	255 (9.5)	30 (2.0)	51 (6.8)	16 (3.5)
Any Severe AE	286 (10.7)	47 (3.1)	46 (6.1)	14 (3.1)
Any Possibly/Probably Drug-Related AE	852 (31.8)	182 (11.9)	140 (18.7)	26 (5.7)
Any AE Leading to Death	23 (0.9)	3 (0.2)	4 (0.5)	3 (0.7)
Any AE Leading to Dose Reduction	48 (1.8)	1 (0.1)	0	0
Any AE Leading to Dose Interruption	70 (2.6)	8 (0.5)	23 (3.1)	3 (0.7)
Any AE Leading to Study Drug Discontinuation	210 (7.8)	28 (1.8)	60 (8.0)	17 (3.7)
Any AE Leading to Adding Concomitant Medication	646 (24.1)	136 (8.9)	112 (15.0)	45 (9.9)

AE = adverse event; SAE = serious adverse event

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

"All" subjects (ISS data base)

The mean duration of exposure is more than 4 times for the ranolazine treatment group than the placebo group (25 days vs. 160 days, respectively). Therefore, it is not unusual that the group with the longer exposure (ranolazine, in this case) would have a higher reporting rate. The usefulness of conclusions drawn from these data is questionable.

Phase 2/3 SR controlled angina studies

The mean duration of exposure was similar for the 2 treatment groups (66 days and 53 days for ranolazine and placebo, respectively). There were more reports of any adverse event for the ranolazine group (36.7%) compared to placebo (22.2%), and the ranolazine group reported more serious events (6.8% vs. 3.5%), and more events resulting in treatment interruption (3.1% vs. 0.7%)/discontinuation (8.0% vs. 3.7%).

Individual adverse events

The table below shows the reporting of adverse events that were reported by at least 2% of the subjects in the ISS database on any treatment.

Table 12 Treatment-Emergent Adverse Events Reported for ≥ 2% of Subjects/Patients—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations

Body System Preferred Term	Number (%) of Patients[a]			
	ISS Database		Phase 2/3 SR Controlled Studies	
	Total Ranolazine (N = 2,682)	Total Placebo (N = 1,529)	Total Ranolazine (N = 749)	Placebo (N = 455)
Mean Duration of Exposure (Days)	160	25	66	53
Total Patients with Any AEs	1,465 (54.6)	418 (27.3)	275 (36.7)	101 (22.2)
Body as a Whole				
Abdominal Pain	101 (3.8)	18 (1.2)	13 (1.7)	3 (0.7)
Asthenia	265 (9.9)	51 (3.3)	31 (4.1)	10 (2.2)
Back Pain	56 (2.1)	14 (0.9)	1 (0.1)	3 (0.7)
Chest Pain	87 (3.2)	17 (1.1)	2 (0.3)	2 (0.4)
Headache	359 (13.3)	90 (5.9)	22 (2.9)	9 (2.0)
Infection	56 (2.1)	6 (0.4)	9 (1.2)	4 (0.9)
Pain	83 (3.1)	23 (1.5)	11 (1.5)	3 (0.7)
Cardiovascular System				
Angina Pectoris	177 (6.6)	32 (2.1)	34 (4.5)	21 (4.6)
Palpitation	65 (2.4)	16 (1.0)	7 (0.9)	5 (1.1)
Peripheral Edema	59 (2.2)	8 (0.5)	4 (0.5)	3 (0.7)

Table 12 Treatment-Emergent Adverse Events Reported for ≥ 2% of Subjects/Patients—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations (Cont'd)

Body System Preferred Term	Number (%) of Patients[a]			
	ISS Database		Phase 2/3 SR Controlled Studies	
	Total Ranolazine (N = 2,682)	Total Placebo (N = 1,529)	Total Ranolazine (N = 749)	Placebo (N = 455)
Digestive System				
Constipation	149 (5.6)	4 (0.3)	49 (6.5)	2 (0.4)
Diarrhea	61 (2.3)	16 (1.0)	5 (0.7)	7 (1.5)
Dyspepsia	132 (4.9)	28 (1.8)	16 (2.1)	4 (0.9)
Nausea	200 (7.5)	16 (1.0)	43 (5.7)	3 (0.7)
Nervous System				
Dizziness	354 (13.2)	44 (2.9)	61 (8.1)	6 (1.3)
Respiratory System				
Cough Increased	53 (2.0)	13 (0.9)	8 (1.1)	1 (0.2)
Dyspnea	76 (2.8)	20 (1.3)	14 (1.9)	6 (1.3)
Pharyngitis	64 (2.4)	17 (1.1)	3 (0.4)	2 (0.4)
Rhinitis	71 (2.6)	11 (0.7)	1 (0.1)	0
Skin and Appendages				
Rash	72 (2.7)	13 (0.9)	3 (0.4)	3 (0.7)

[a] Some patients may have been treated at more than one dose level.
AE = adverse event
Abstracted from **Appendix III B Table E-1.1, Appendix V B Table E-1.3, Appendix III D Table G-2.1,** and **Appendix V D Table G-2.3.**

"All" subjects (ISS data base)
Since the duration of use was more than 6 times longer in the ranolazine group compared to the placebo group, the usefulness of examining the individual events in the ISS data base is questionable.

Phase 2/3 SR controlled angina studies
The numbers and percents of patients in the Phase 2/3 controlled angina studies who reported an adverse event (limited to those events reported by more than 1% of the total ranolazine group and reported more in the ranolazine group than the placebo group) are shown in the table below, by treatment group. The placebo subtracted rate is also shown.

No. and (percent) of patients

event	Total ranolazine N=749	Total placebo N=455	Placebo subtracted %
Any event	275 (36.7)	101 (22.2)	14.5
Dizziness	61 (8.1)	6 (1.3)	6.8
Constipation	49 (6.5)	2 (0.4)	6.1
Nausea	43 (5.7)	3 (0.7)	5.0
Asthenia	31 (4.1)	10 (2.2)	1.9
Dyspepsia	16 (2.1)	4 (0.9)	1.2
Abdominal pain	13 (1.7)	3 (0.7)	1.0
Cough increased	8 (1.1)	1 (0.2)	0.9
Headache	22 (2.9)	9 (2.0)	0.9
Pain	11 (1.5)	3 (0.7)	0.8
Dyspnea	14 (1.9)	6 (1.3)	0.6
Infection	9 (1.2)	4 (0.9)	0.3
Rhinitis	1 (0.1)	0	0.1

Table 12 vol 1.0340 pg 62

The placebo subtracted rate for reporting any adverse event was 14.5%. Those events with placebo subtracted rates greater than 2% includes dizziness (6.8%), constipation (6.1%), and nausea (5.0%).

Dose response
Events possibly associated with dose are shown in the table below for the SR formulation, by dose.

No. and (percent) of patients reporting events

	Ranol 500 mg N=181	Ranol 750 mg N=279	Ranol 1000 mg N=459	Ranol 1500 mg N=187
Any event	28 (15.5)	87 (31.2)	134 (29.2)	63 (33.7)
Dizziness	2 (1.1)	10 (3.6)	29 (6.3)	22 (11.8)
Asthenia	0	5 (1.8)	16 (3.5)	11 (5.9)
Nausea	1 (0.6)	9 (3.2)	17 (3.7)	16 (8.6)
Syncope	0	0	5 (1.1)	3 (1.6)
Sweating	0	3 (1.1)	5 (1.1)	5 (2.7)
Vomiting	0	2 (0.7)	5 (1.1)	4 (2.1)

Table G2.2 vol 1.0364

Unfortunately, the sample sizes for the SR formulation are small. However, the most convincing dose related adverse events are shown above. For example, syncope was only reported with doses 1000 mg and above.

4.0 Serious safety

Methodology

According to the sponsor, a serious adverse event (SAE) was characterized by one of the following criteria: resulted in death, was life threatening, required hospitalization or prolongation of an existing hospitalization, resulted in persistent or significant disability or incapacity, caused congenital anomaly or birth defect, and/or was considered medically significant by the investigator. Prior to 1997, the criteria for an SAE also included cancer and drug overdose. For some older (Syntex) studies, SAEs were not identified on the case report forms. Consequently, for those studies, SAEs were identified by medical monitors after review of the safety database. Summary tables regarding SAEs included: the type of SAE, concomitant medications received, action taken, outcome, and treatment assignment. All treatment-emergent SAEs were included in the summary tables, regardless of their severity or relationship to the study drug. SAEs occurring in the run-in period were excluded.

Deaths

There were 37 reported deaths (33 ranolazine and 4 placebo) in all 81 ranolazine studies[12]. For the total ranolazine group (including IR, SR, and IV formulations), the mortality rate was 1.2% (33/2682). The controlled trials randomized 749 subjects to ranolazine with a mortality rate of 0.7% (5/749) and 455 subjects to placebo also with a mortality rate of 0.7% (3/455).

Subject ID	Dose SR bid and IR tid/duration (days)	Cause of death
Controlled studies		
3031/133-1017	Dosing schedule: Ranol SR 1000 mg for 9 days, placebo for 7 days, ranol 500 mg for 3 days	V fib/collapsed at home
3033/177-9027	Ranol SR 750 mg/33	Acute MI
3033/704-7600	Ranol SR 750 mg/18	Sudden death
3033/706-9575	Ranol SR 1000 mg/13	Sudden death
3033/710-7631	Placebo/18	Sudden death (elevated ethanol level)

[12] as of 10-15-01

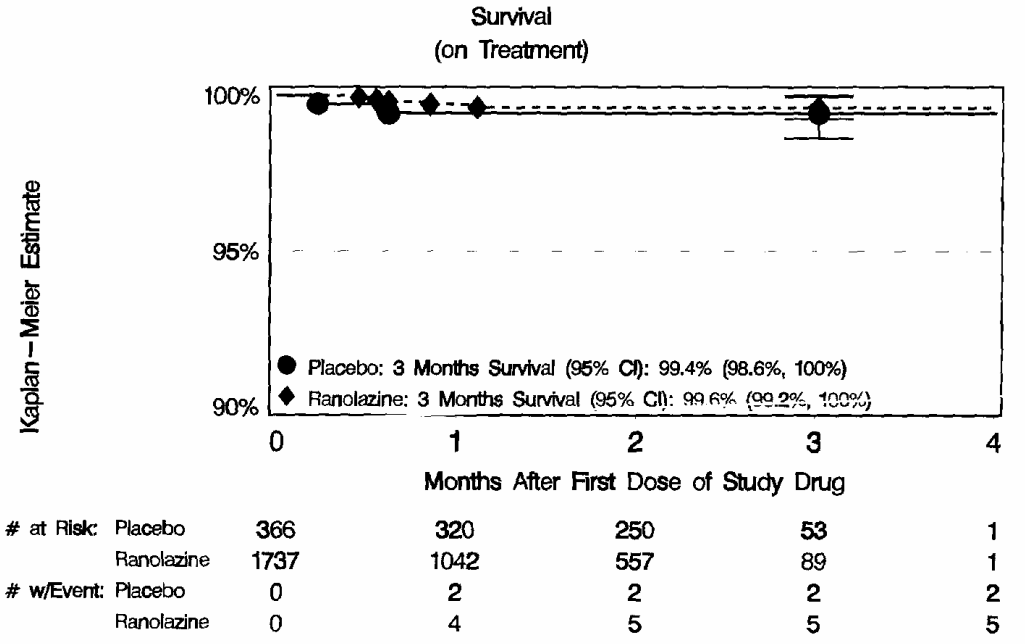
3033/717-8668	Placebo/6	Sudden death while driving
3033/751-9386	Placebo/95	Dissection of coronary arteries followed by cardiac arrest during elective PTCA
054/6858-414	Ranol IR 120 mg/41	MI
Uncontrolled studies		
054/6858/415+	Dosing schedule: ranol IR 240 mg for 28 days, placebo for 28 days, ranol IR 120 mg for 28 days.	Sudden death (died 2 days after last dose)
1513/3073-4609	Ranol IR 30 mg/died 45 days after last dose	Pulmonary embolism
3032/133-1018	Ranol SR 1000 mg/26	Malignant melanoma
3032/133-1019	Ranol SR 1000 mg/24	Lung carcinoma
3032/149-1193	Dosing schedule: Ranol SR 750 mg for 70 days, 1000 mg for 261 days	Sudden death. Developed a fib/flutter earlier, QTc was increased to 525 msec on day 173. QTc was 386 msec about 6 weeks prior to death
3032/153-1249	Ranol SR 750 mg/86	Esophageal carcinoma
3032/162-1281	Ranol SR 1000 mg/19	Sudden death. QTc interval up to 533 msec. Had complaints of dyspnea and chest pain immediately prior to death
3032/180-1462	Ranol SR 750 mg/366	CVA
3032/182-1458	Ranol SR 750 mg/210	Sudden death
3032/501-1441	Ranol SR 750 mg/167	CHF
3032/512-1366	Ranol SR 750 mg/256	AMI
3032/515-1392	Ranol SR 750 mg/342	Cardiovascular insufficiency S/P revascularization
3034-181-8445	Ranol SR 1000 mg/84	AMI with arrhythmia
3034/182-9269	Ranol SR 500 mg/428	Sudden death
3034/185-8374	Ranol SR 1000 mg/176	Sudden death
3034/190-8007	Ranol SR 1000 mg/298	Sudden death proceeded by complaints of angina and dyspnea
3034/195-8051	Ranol SR 750 mg/315	Sudden death (heart arrest)
3034/204-9024	Ranol SR 1000 mg/224	Sudden death (VF)
3034/236-8480	Ranol SR 750 mg/8	MI
3034/510-8353	Ranol SR 1000 mg/53	Pulmonary embolism proceeded by nausea and vomiting
3034/562-9186	Ranol SR 750 mg/332	unknown
081/6810/181	Ranol IR 400 mg/325	MI
1515/3838/2210	Ranol IR 120 mg/1319	MI
1515/3435/3702	Ranol IR 60 mg/187	Smoke inhalation
2074/3953/7001	Ranol IR 400 mg/526	Sudden death
2074/3971/15008	Ranol IR 400 mg/168	Died while undergoing CABG with balloon pump support
2074/1807/28002	Ranol IR 400 mg/364	Ruptured aortic aneurysm
1789/3645/2302^	Placebo IV/13	Complication of PTCA

+not included in clinical data base
^not included in ISS

Many causes of death were reported as sudden or other cardiovascular related; such deaths are not unexpected in this patient population.

Survival curve: all patients from Phase 2/3 controlled angina studies

Figure 1 **Survival of Chronic Angina Patients on Ranolazine: All Patients from Phase 2/3 Controlle Angina Studies**



# at Risk:	Placebo	366	320	250	53	1
	Ranolazine	1737	1042	557	89	1
# w/Event:	Placebo	0	2	2	2	2
	Ranolazine	0	4	5	5	5

Patient RAN054_6858415 death was captured in safety report, not in database.
SOURCE: GSURV_RAN_VS_PLA (07AUG2002 16:53) GSURV_RAN_VS_PLA_TRT_ALL.CGM

There was no difference in the survival curves between the placebo and ranolazine groups. Also, there was no difference between the groups when patients who received <120 mg ranolazine were removed from the analysis.

The survival data were analyzed using a Cox proportional hazards regression model[13] with a single effect for treatment. The hazard ratio and the 95% two sided confidence interval are shown in the table below.

Table 1 **Ranolazine ISS Phase 2/3 Controlled Studies – Cox Regression Analysis of Survival Time**

Hazard Ratio	*95% Confidence Interval*	*p-Value*
0.633	(0.122, 3.27)	0.58

Source: GSURV RAN_VS_PLA (30JUN2003 18:30)

[13] from fax sent 7-1-03

The estimated hazard ratio of 0.633 corresponds to a 36.7% reduction in the risk of death in the ranolazine treatment group. However, this estimate is highly variable because of the small number of events in the dataset. Therefore, the confidence interval for the hazard ratio is very wide. The analysis rules out that ranolazine is more than 3.27 times worse than placebo, or more than 8.2 times better than placebo, with regard to patient survival.

Long term, open label trials

CVT 3032 and CVT 3034

Of the 550 patients enrolled in these studies[14], 440 are still ongoing and 110 (20%) were discontinued. Of the patients who discontinued, 58 did so because of an adverse event. In addition, there were 262 subjects who received the IR formulation during one of 5 uncontrolled IR studies.

There were 25 deaths (table F-1.3 vol. 1.0378). Causes of death are shown below.

Cause of death	Number of subjects
Cancer	2
AMI	5
Sudden death	7
CVA	1
Congestive heart failure	2
V fib/tach	1
Cardiac arrest	2
Pul embolism	1
Unknown	2
House fire	1
AAA rupture	1
total	25

Table F-1.3 vol 1.0378

Causes of death included 7 sudden deaths, 1 ventricular fibrillation, and 5 acute myocardial infarctions.

Withdrawals for adverse events

The table below shows the numbers and percents of subjects who withdrew from a study because of an adverse event.

[14] cut off date 10-15-01

Table 24 Number (%) of Subjects/Patients Who Discontinued Study Medication Due to Treatment-Emergent Adverse Events by Category and Treatment—All Treated Subjects/Patients

Category	Ranolazine		Placebo	
	Total N	Number (%) of Subjects/Patients[a]	Total N	Number (%) of Subjects/Patients[a]
All Treated Subjects/Patients	2,955	240 (8.1)	1,688	38 (2.3)
ISS Database	2,682	237 (8.8)	1,529	35 (2.3)
Phase 2/3 SR Controlled Angina Studies	749	63 (8.4)	455	18 (4.0)
16 Early Studies not in the ISS Database	237	3 (1.3)	159	3 (1.9)
Bioequivalence Study (CVT 301-15)[b]	36	0	0	0

[a] Number of subjects/patients reflects number of subjects/patients who received at least one dose of study drug. See **Table 4**.

[b] See **ISS Section 23** for a summary of safety data.

Abstracted from **End-of-Text Table-1, Appendix III A, Table D-4.1, Appendix III F Table I-1.1, Appendix IV A Table D-4.2, Appendix V A Table D-4.3, Appendix V F Table I-1.3, Appendix VI A Table D-4.4, Appendix III G Table J-1.1, Appendix V G Table J-1.3, Study Report CVT 301-15**, and **Item 8, Section 8.15**.

The percents of dropouts for adverse events in all but the smallest categories were at least twice as high in the ranolazine group compared to placebo. One explanation is that the mean duration of exposure is much higher for the treated compared to the placebo groups (in the ISS database the ranolazine and placebo groups mean duration of exposure were 160 days and 25 days, respectively). However, in the Phase 2/3 controlled angina trials where the mean duration were similar (ranolazine 66 days and placebo 53 days), the dropout rate was more than 2 times higher in the ranolazine group (8.4%) compared to placebo (4.0%).

ISS database

The table below shows the adverse events leading to discontinuation in at least 0.5% of subjects in the ranolazine group and reported more often in the ranolazine group than the placebo group.

No. and (percent) of patients

Event	Placebo N=1529	Ranolazine N=2682	Placebo subtracted
Any event	31 (2.0)	226 (8.4)	6.4
Dizziness	1 (0.1)	30 (1.1)	1.0
Nausea	1 (0.1)	26 (1.0)	0.9
Angina	11 (0.7)	36 (1.3)	0.6
Asthenia	0	13 (0.5)	0.5
Headache	1 (0.1)	17 (0.6)	0.5
Myocardial infarct	0	14 (0.5)	0.5
Constipation	0	14 (0.5)	0.5

Table G-6.1

The adverse events leading most often to discontinuation in the ranolazine group compared to placebo included dizziness, nausea, and angina.

Phase 2/3 controlled trials
The table below shows the adverse events leading to discontinuation in at least 0.5% of subjects in the ranolazine group and reported more often in the ranolazine group than the placebo group.

No. and (percent) of patients

Event	Placebo N=455	Ranolazine N=749	Placebo subtracted
Any event	18 (4.0)	62 (8.3)	4.3
Dizziness	1 (0.2)	13 (1.7)	1.5
Nausea	0	10 (1.3)	1.3
Headache	0	6 (0.8)	0.8
Constipation	0	6 (0.8)	0.8
Asthenia	0	5 (0.7)	0.7
Myocardial infarct	0	4 (0.5)	0.5
Syncope	0	4 (0.5)	0.5
Vomiting	0	4 (0.5)	0.5

Table G-6.3

A total of 62 (8.3%) subjects discontinued ranolazine compared to 18 (4.0%) placebo subjects. The adverse events leading most often to discontinuation in the ranolazine group compared to placebo included dizziness, nausea, headache, and constipation.

By dose
Specific adverse events that led to discontinuation and are suggestive of a dose response are shown in the table below.

No. and (percent) of patients

	Ranol 500 mg N=181	Ranol 750 mg N=279	Ranol 1000 mg N=459	Ranol 1500 mg N=187
Any event	2 (1.1)	22 (7.9)	28 (6.1)	10 (5.3)
Dizziness	0	2 (0.7)	8 (1.7)	3 (1.6)
Nausea	0	1 (0.4)	5 (1.1)	4 (2.1)
Headache	0	1 (0.4)	2 (0.4)	3 (1.6)
Constipation	0	2 (0.7)	2 (0.4)	2 (1.1)
Vomiting	0	1 (0.4)	1 (0.2)	2 (1.1)
Syncope	0	0	3 (0.7)	1 (0.5)
Asthenia	0	1 (0.4)	3 (0.7)	1 (0.5)

Table J-1.3 vol 1.0366

Although the sample sizes are relatively small, the highest ranolazine group (1500 mg) had the highest reporting rates for these events.

Serious adverse events
The numbers and percents of patients reporting serious events in the 81 ranolazine studies are shown below.

Table 18 Incidence of Serious Adverse Events by Category and Treatment—All Treated Subjects/Patients

Category	Ranolazine		Placebo	
	Total N	Number (%) of Subjects/ Patients with Any SAEs	Total N	Number (%) of Subjects/ Patients with Any SAEs
All Treated Subjects/Patients (all studies)	2,955	268 (9.1)	1,688	36 (2.1)
ISS Database (64 studies)	2,682	255 (9.5)	1,529	30 (2.0)
Phase 2/3 SR Controlled Angina Studies	749	51 (6.8)	455	16 (3.5)
16 Early Studies not in the ISS Database	237	13(5.5)	159	6 (3.8)
Bioequivalence Study CVT 301-15	36	0	0	0

Abstracted from **Appendix III A Table D-4.1, Appendix III F Table I-1.1, Appendix IV A Table D-4.2, Appendix V A Table D-4.3, Appendix V F Table I-1.3, Appendix VI A Table D-4.4,** Final Study Reports of 16 Early Studies not in the ISS database (**Item 8, Section 8.15**), and Study CVT 301-15 (**Item 8, Section 8.15**).

In all cases except the 16 early studies, the percents of ranolazine patients reporting serious events were at least twice as high compared to placebo patients.

Phase 2/3 SR controlled angina studies

Only angina was identified as a serious adverse event that was reported by at least 1% of subjects in any treatment group. Out of 749 ranolazine subjects in the controlled angina studies, 1.7% reported angina compared to 1.8% in the placebo group.

Syncope

The number and percent of subjects reporting adverse events of syncope or suggestive of syncope or pre syncope are shown below from the ISS data base.

S Database

TABLE K-1 (PAGE 1 OF 1)
Summary of Potential Syncope Related Adverse Events*

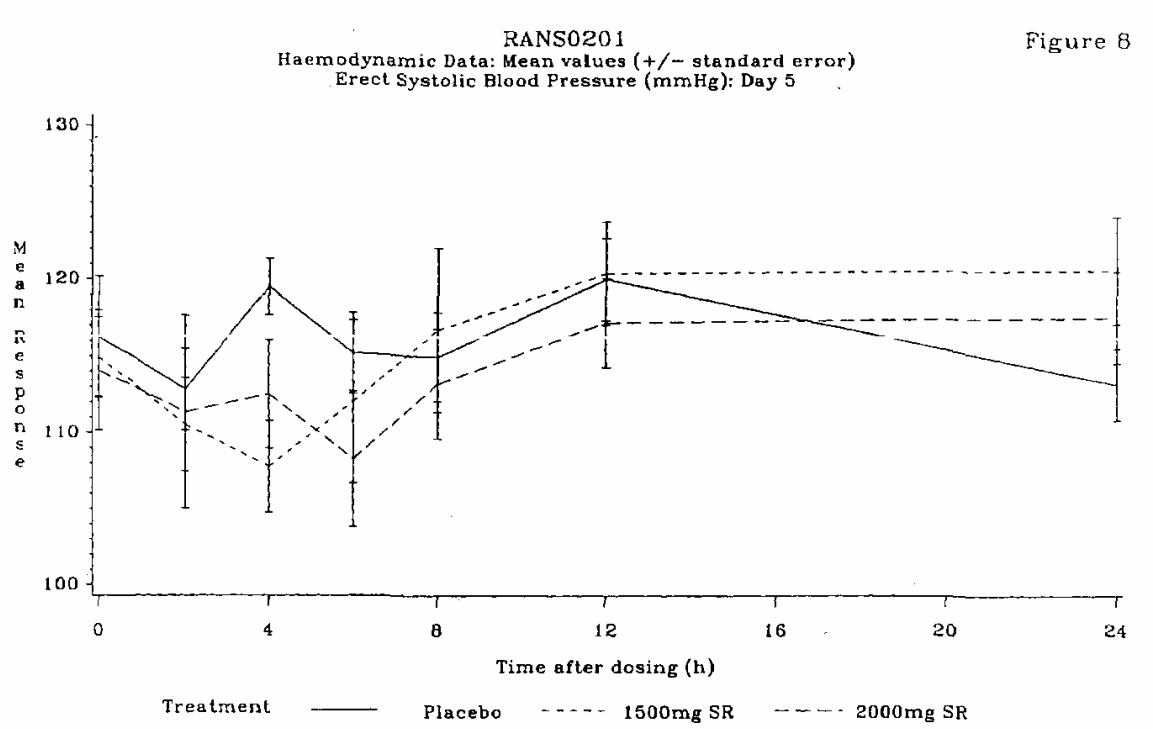
Preferred Term	Placebo IR N (%)	Ranolazine IR N (%)	Placebo IV N (%)	Ranolazine IV N (%)	Placebo SR N (%)	Ranolazine SR N (%)	Total Placebo N (%)	Total Ranolazine N (%)
tal Number of Patients in Summary	947	1299	13	77	569	1359	1529	2682
tal Patients With Any AEs	35(3.7)	201(15.5)	2(15.4)	33(42.9)	31(5.4)	284(20.9)	68(4.4)	516(19.2)
DY AS A WHOLE	35(3.7)	201(15.5)	2(15.4)	33(42.9)	31(5.4)	284(20.9)	68(4.4)	516(19.2)
ABNORMAL VISION	0	4(0.3)	0	2(2.6)	0	12(0.9)	0	18(0.7)
BLACKOUT	0	2(0.2)	0	0	0	0	0	2(0.1)
COLLAPSE	1(0.1)	1(0.1)	0	0	0	1(0.1)	1(0.1)	2(0.1)
DIPLOPIA**	0	1(0.1)	0	5(6.5)	0	4(0.3)	0	10(0.4)
DIZZINESS**	11(1.2)	75(5.8)	2(15.4)	24(31.2)	12(2.1)	123(9.1)	25(1.6)	220(8.2)
FAINT	3(0.3)	9(0.7)	1(7.7)	1(1.3)	2(0.4)	6(0.4)	6(0.4)	16(0.6)
HYPOTENSION	0	8(0.6)	0	1(1.3)	3(0.5)	25(1.8)	3(0.2)	34(1.3)
LIGHT HEADED	9(1.0)	45(3.5)	0	5(6.5)	7(1.2)	58(4.3)	16(1.0)	108(4.0)
LOSS OF CONSCIOUSNESS	0	0	0	0	0	1(0.1)	0	1(0.0)
NAUSEA AND VOMITING**	0	3(0.2)	0	0	0	3(0.2)	0	6(0.2)
NAUSEA**	11(1.2)	71(5.5)	0	19(24.7)	5(0.9)	119(8.1)	16(1.0)	200(7.5)
PRE/NEAR SYNCOPE/SYNCOPAL	0	0	0	0	0	3(0.2)	0	3(0.1)
SYNCOPE/SYNCOPAL	0	4(0.3)	0	2(2.6)	1(0.2)	13(1.0)	1(0.1)	19(0.7)
VASOVAGAL	0	4(0.3)	0	2(2.6)	0	2(0.1)	0	8(0.3)
VERTIGO**	1(0.1)	5(0.4)	0	0	1(0.2)	16(1.2)	2(0.1)	21(0.8)
VOMITING**	6(0.6)	11(0.8)	0	3(3.9)	3(0.5)	31(2.3)	9(0.6)	45(1.7)

Verbatim and Preferred Terms are used in this Table
Preferred Terms also Appear in G, H, I, J Series Tables
URCE: TAE_S1 (25OCT2002 17:14) CVT-303\ISS\STATISTICS\MODULE0\TABLE_GRAPH\TAE_S1.RTF

The percent of total ranolazine subjects reporting one or more of these events was 19.2%, this is more than 4 times the percent of placebo patients reporting the same events (4.4%). The percents of subjects reporting syncope and/or near syncope were 0.1% (1) for placebo and 0.8% (21) for ranolazine. Reports of dizziness and light headed were also more common with ranolazine.

Doses associated with syncope (orthostatic changes)

There were 10 reports of syncope (called syncopal episode, vasovagal episode, loss of consciousness, collapse) in the Phase 2/3 controlled trials. The doses being used at the time the event was reported were 1500 mg SR (3), 5 at 1000 mg SR (5), 120 tid IR (1), and placebo (1). In study RANSO201, doses of 1500 and 2000 mg bid produced significant mean orthostatic changes (-9.8 mmHg and -8.4 mmHg, respectively, compared to placebo) at 4-6 hours after dosing. Some of the subjects could not have their erect blood pressures recorded because of these changes. The figure below shows the mean erect systolic blood pressures profiles by dose.



Erect systolic blood pressure decreased from baseline at around 4 hours after dose intake, the time of peak drug concentration. The drop was greater for the 2000 mg dose. Three subjects could not undergo erect blood pressure recordings because of symptoms of lightheadedness.

5.0 ECG

Methodology

All ECGs from CVT-conducted multiple dose studies were read by a central Core ECG Laboratory (St. Louis University Core ECG Laboratory). The parameters summarized are the ECG intervals as measured in msec: PR, QRS, QT, and the corrected QT (QTc).

Each QT value from CVT-conducted multiple dose studies is the maximum QT value among the 12 leads in that ECG, corrected as indicated for heart rate.

ECG intervals

ISS database

Mean changes from baseline at endpoint for ECG intervals are shown below. The ECG recordings were not necessarily obtained at peak effect.

Table 36 Summary of Mean Overall Change From Baseline by Treatment Group in ECG Intervals—ISS Database

	Ranolazine SR	Placebo SR	Total Ranolazine	Total Placebo
PR Interval				
N	1,277	550	2,276	1,316
Mean Change from Baseline (msec)[a]	1.1	-1.1	0.2	-1.5
SD	14.0	13.8	23.8	28.6
QRS Interval				
N	1,287	553	2,342	1,322
Mean Change from Baseline (msec)[a]	0.2	-0.2	0.5	-0.1
SD	8.5	8.1	14.1	13.4
QT Interval				
N	1,276	552	2,327	1,317
Mean Change from Baseline (msec)[a]	3.6	-3.8	2.7	-1.5
SD	22.6	20.6	25.3	26.9
QT_cB Interval				
N	1,276	552	2,333	1,320
Mean Change from Baseline (msec)[a]	2.0	-1.6	1.5	-1.2
SD	16.3	18.3	24.5	28.7

[a] Mean changes were calculated over the duration of treatment and were not correlated to peak/trough measurements.

Abstracted from **Appendix III J Table N-1.1.**

Compared to placebo, there were larger changes from baseline for all of the ECG intervals listed above. The changes from baseline for the QT and QTc intervals for the ranolazine SR group were 3.6 msec and 2.0 msec, respectively, and 2.7 msec and 1.5 msec, respectively, for total ranolazine. Comparative changes for the placebo groups were negative. These measurements are independent of time of last dose so results are underestimates of the true effect.

Shift tables

The following table shows the number and percent of subjects who received either placebo or ranolazine SR only (in the ISS database) and had a normal QT/QTc interval at baseline that became abnormal at endpoint.

No. and (percent) of subjects

	Placebo SR N=569	Ranolazine SR N=1359
Normal QT at baseline abnormal QT at endpoint	49 (8.6)	210 (15.5)+
Normal QTc at baseline abnormal QTc at endpoint	28 (4.9)	70 (5.2)^

+includes 2 subjects whose abnormal QT interval was judged not to be clinically significant
^includes 65 subjects whose abnormal QTc interval was judged not to be clinically significant
Table N 8.1 vol1.0363 pg 379-380

Phase 2/3 SR controlled angina studies

The table below shows the mean changes from baseline for ECG intervals by dose.

Table 37 Summary of the Mean Changes From Baseline by Dose in ECG Parameters for the Phase 2/3 SR Controlled Angina Studies Population

		Ranolazine (mg)				
	Placebo	500 b.i.d.	750 b.i.d.	1,000 b.i.d.	1,500 b.i.d.	Total Ranolazine SR
PR Interval						
N	438	177	269	434	172	706
Mean Change from Baseline (msec)[a]	-0.5	0.6	1.6	2.1	5.7	1.7
SD	14.1	14.0	13.8	14.5	14.5	13.9
QRS Interval						
N	440	177	271	438	172	712
Mean Change from Baseline (msec)[a]	-0.1	0.4	0.7	1.2	1.8	1.0
SD	8.6	9.9	8.6	9.4	10.5	8.8
QT Interval						
N	439	177	269	434	173	706
Mean Change from Baseline (msec)[a]	-3.1	1.3	7.0	6.6	10.5	6.7
SD	21.0	23.1	23.7	22.2	24.9	22.3
QT_cB Interval						
N	439	177	269	434	173	706
Mean Change from Baseline (msec)[a]	-2.0	2.1	3.7	4.6	8.7	4.6
SD	19.1	24.7	13.6	17.2	25.9	15.7

[a] Mean changes were calculated over the duration of treatment and were not correlated with peak/trough measurements.

There were dose related increases in all of the ECG intervals and these changes were greater than those for placebo. Mean increases from baseline for QT/QTc were 1.3/2.1 msec for the 500 mg dose and 10.5/8.7 msec for the 1500 mg dose.

Maximum mean QT changes were 11.4, 9.9, 25.7, 20.5, and 18.4 msec for placebo, ranolazine 500 mg, 750 mg, 1000 mg, and 1500 mg, respectively (table N-1.3.1 vol 1.0376).

The measurements discussed above are independent of time of last dose (and peak effect is greater than trough effect) so they are underestimates of the true effect.

Peak effect
Mean change from baseline in QTc interval (msec) at peak

	Placebo 455	Ranol 500 N=177	Ranol 750 N=269	Ranol 1000 N=428	Ranol 1500 N=170
Mean change from baseline	-2.0	3.3	3.5	5.0	11.0
Max mean change from baseline	1.1	3.3	8.9	8.1	11.0

Table N-1.3.2.1vol 1.0376

Effects of ranolazine on QTc interval are greater when measured at peak drug concentration than effects measured at trough (or at random).

The shift table below shows the number and percent of patients, by dose, who had a normal QTc interval at baseline and an abnormal one at endpoint. ECG measurements were made at peak drug concentration.

No. and (percent) of patients

	Placebo N=455	Ranol 500 N=181	Ranol 750 N=279	Ranol 1000 N=459	Ranol 1500 N=187
Normal at baseline and abnormal+ at endpoint	24 (5.3)	18 (9.9)	10 (3.6)	28 (6.1)	40 (21.4)

+includes those that the sponsor identified as not clinically significant.
Table N-8.3.2.1 vol 1.0377

A total of 40 subjects (21.4%) of subjects who received the 1500 mg dose of ranolazine developed an abnormal QTc interval that was “normal” at baseline.

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

No. and (percent) of patients

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

Table N-15.3.1 vol 1.0377

Major placebo controlled trials and their follow up studies
A total of 980 patients were randomized into Studies CVT 3031 or CVT 3033 and had baseline and at least one post-randomization ECG. Of these patients, 550 also elected to continue ranolazine treatment in the respective open-label studies, Studies CVT 3032 or CVT 3034 as of the NDA cut-off date (October 15, 2001). Of this selected group, those with either an increase from baseline ≥ 60 msec in the QTc interval or a QTc value > 500 msec using Bazett’s correction are summarized by treatment in the table below.

Table 39 Summary of Bazett QT_c Outliers by Treatment in Studies CVT 3031, CVT 3032, CVT 3033, and CVT 3034

Treatment	Number of Patients Treated	Number (%) of Patients with a QT_c Increase ≥ 60 msec from Baseline	Number (%) of Patients with a QT_c > 500 msec	Either	Both
Placebo	436	7 (1.6%)	7 (1.6%)	11 (2.5%)	3 (0.7%)
Placebo (Rebound Phase)	245	0 (0%)	1 (0.4%)	1 (0.4%)	0 (0%)
Ranolazine 500 mg b.i.d.	500	12 (2.4%)	11 (2.2%)	17 (3.4%)	6 (1.2%)
Ranolazine 750 mg b.i.d.	611	9 (1.5%)	2 (0.3%)	10 (1.6%)	1 (0.2%)
Ranolazine 1,000 mg b.i.d.	528	9 (1.7%)	15 (3.0%)	22 (4.2%)	3 (0.6%)
Ranolazine 1,500 mg b.i.d.	173	11 (6.9%)	13 (7.5%)	21 (12.1%)	4 (2.3%)
Off-Treatment	112	0	1 (0.9%)	1 (0.9%)	0

Abstracted from Appendix VII F Table N-23, and Appendix VII F Table N-28.1.

Overall, the effect of ranolazine on the QTc interval was worse compared to placebo. For patients receiving the highest dose, 2.3% had both an increase in QTc of at least 60 msec over baseline and had QTc >500 msec compared to 0.7% of placebo patients. Again, this is probably an underestimate because the effect of ranolazine is worse at peak concentration.

The sponsor states that the Fridericia correction is "better [because it] eliminates the relationship between QT and heart rate as well as reduces variability." The table below shows the number and percent of QT outliers using Fridericia's correction.

Table 41 Summary of Fridericia QT_c Outliers by Treatment in Studies CVT 3031, CVT 3032, CVT 3033, and CVT 3034

Treatment	Number of Patients Treated	Number (%) of Patients with a QT_c Increase ≥ 60 msec from Baseline	Number (%) of Patients with a QT_c > 500 msec	Either	Both
Placebo	436	1 (0.2%)	2 (0.5%)	3 (0.7%)	0 (0%)
Placebo (Rebound Phase)	245	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ranolazine 500 mg b.i.d.	500	7 (1.2%)	4 (0.8%)	9 (1.6%)	2 (0.4%)
Ranolazine 750 mg b.i.d.	611	6 (1.0%)	1 (0.2%)	7 (1.2%)	0 (0%)
Ranolazine 1,000 mg b.i.d.	528	9 (1.7%)	5 (0.9%)	13 (2.5%)	1 (0.2%)
Ranolazine 1,500 mg b.i.d.	173	7 (4.6%)	7 (4.1%)	10 (6.4%)	4 (2.3%)
Off-Treatment	112	0	1 (0.9%)	1 (0.9%)	0

Abstracted from **Appendix VII F Table N-28.3**, and **Appendix VII F Table N-28.2**.

Regardless of the correction used, ranolazine has been shown to prolong the QT interval.

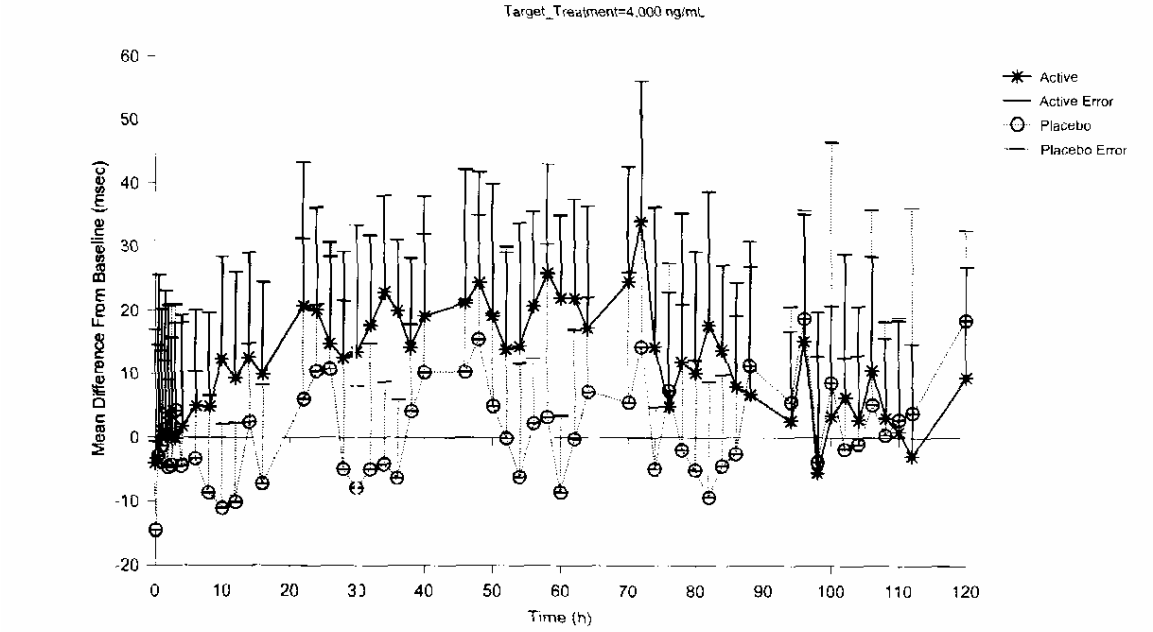
Plasma concentration and QT effect

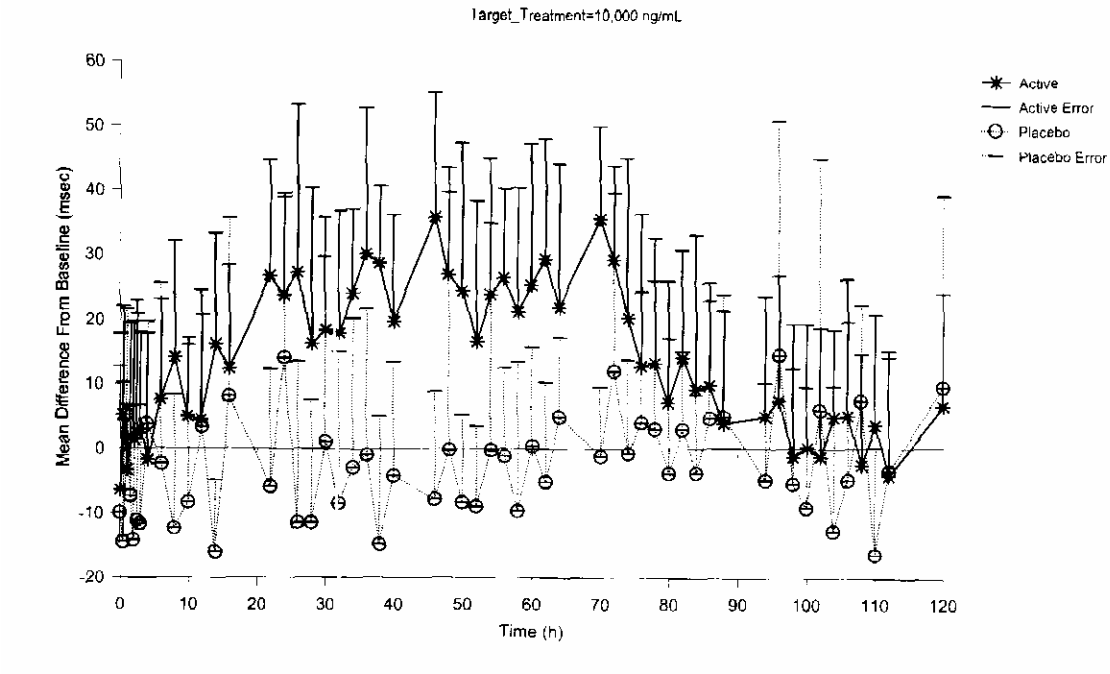
Study CVT 3111 was designed to characterize the relationship between the plasma ranolazine concentration and the effect of ranolazine (and its major metabolites) on the QTc interval by achieving plasma ranolazine concentrations higher than those typically generated.

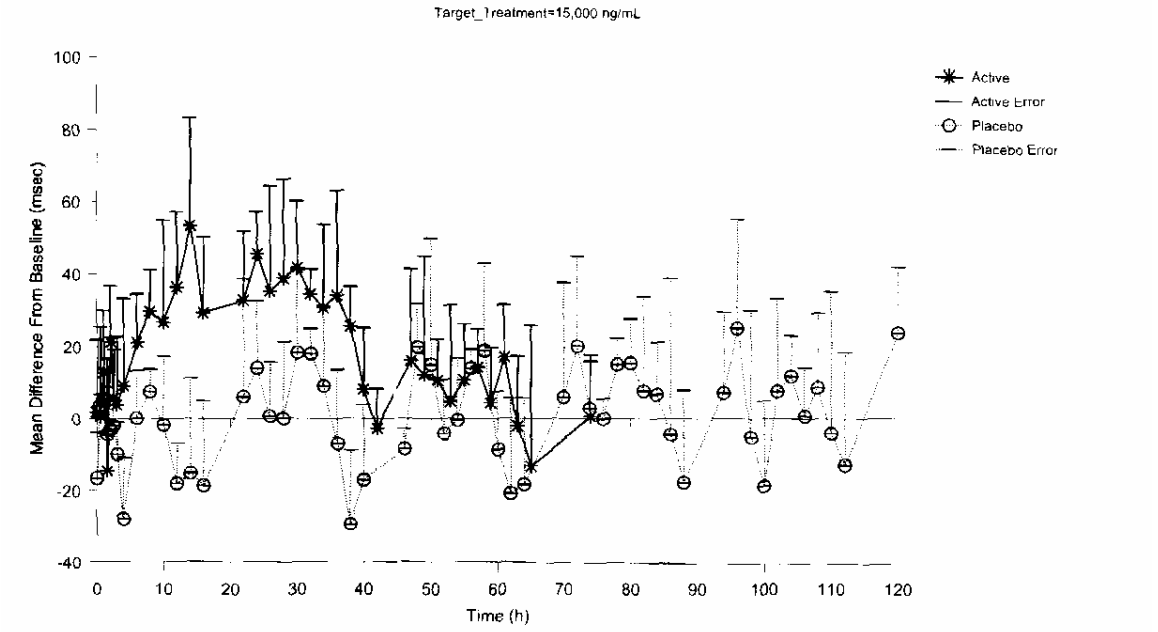
This was a randomized, placebo-controlled, single IV infusion, dose escalation, 4 period study involving 30 female and male healthy subjects. Period I consisted of a 2 hour IV infusion of ranolazine aiming for a target peak plasma ranolazine concentration of 2,000 ng/mL. Period 2 consisted of a 72 hour IV infusion of ranolazine/placebo aiming for a target peak plasma ranolazine concentration of 4,000 ng/mL. Period 3 consisted of a 72 hour IV infusion of ranolazine/placebo aiming for a target peak plasma ranolazine concentration of 10,000 ng/mL. Period 4 consisted of a 72 hour IV infusion of ranolazine/placebo aiming for a target peak plasma ranolazine concentration of 15,000 ng/mL. In each period the infusion of ranolazine/placebo was preceded by a 24 hour placebo infusion.

The figures below show the mean difference from baseline in QTc versus time for each target plasma concentration.

Figure 12.3.3 Mean (+SD) Difference From Baseline in QTc Interval of Subjects Receiving Ranolazine or Placebo for Each Target Treatment (Bazett)







Only 1 subject completed the ranolazine infusion in period 4.

A linear relationship between ranolazine plasma concentration and change in QTc interval from baseline was estimated to have an average slope of 2.29 msec per 1000 ng/mL. Three subjects were discontinued prematurely because of the attainment of protocol specified stopping rule of a greater than 30% increase in QTc from baseline or a value >500 msec.

There was no delay between QTc interval change and the achievement of steady-state ranolazine concentration. Therefore, it is likely that QTc changes are related to ranolazine and not its metabolites.

Higher oral dose
Subjects in Study RAN0201 received the highest single dose of oral ranolazine administered (ranolazine SR 2,000 mg b.i.d.). These doses resulted in significant orthostatic changes in systolic blood pressure compared to placebo 4 to 6 hours post-dosing (about 10 mmHg drop in standing systolic blood pressure). The mean plasma ranolazine concentration at the same time points ranged from 7,223 to 6,328 ng/mL in those receiving 2,000 mg bid. Three of eight volunteers administered ranolazine SR developed severe symptoms of lightheadedness upon standing.

PR Interval: the mean value was higher with ranolazine with a statistically significant increase over placebo of 8.8 msec at 2 hr post-dose on Day 5 with the 2000 mg dose ($p = 0.024$). This difference disappeared by 24 h after the final dose.

QT Interval: by Day 5 QT interval tended to be prolonged with both doses of ranolazine compared to placebo at all time points. The statistically significant increases seen with the 2000 mg dose were at 2 h post-dose (+ 14.2 msec), 4 h post-dose (+ 19.2 msec), and 6 h post-dose (+ 18.2 msec) on Day 5.

The mean QTc/QT intervals and mean differences from baseline profiles at steady state are shown below.

RANS0201
Table 49
ECG DATA
QT Interval (msec)
Mean Values and Treatment Comparisons : Day 5

Treatment		Time						
		Pre-dose	2 h	4 h	6 h	8 h	12 h	24 h
1500 mg SR	mean	407.6	409.1	412.1	386.1	405.1	388.1	404.6
	se	8.8	8.8	8.8	8.8	8.8	8.8	8.8
	n	8	8	8	8	8	8	8
2000 mg SR	mean	417.0	416.0	419.0	396.0	406.0	383.5	405.0
	se	8.8	8.8	8.8	8.8	8.8	8.8	8.8
	n	8	8	8	8	8	8	8
Placebo	mean	409.9	401.9	399.9	377.9	397.9	377.4	397.4
	se	8.7	8.7	8.7	8.7	8.7	8.7	8.7
	n	8	8	8	8	8	8	8
1500 mg SR - Placebo	mean difference	-2.3	7.2	12.2	8.2	7.2	10.7	7.2
	sed	6.3	6.3	6.3	6.3	6.3	6.3	6.3
	P	0.713	0.261	0.058	0.201	0.261	0.095	0.261
	95% CI	(-14.9,10.2)	(-5.4,19.7)	(-0.4,24.7)	(-4.4,20.7)	(-5.4,19.7)	(-1.9,23.2)	(-5.4,19.7)
2000 mg SR - Placebo	mean difference	7.2	14.2*	19.2**	18.2**	8.2	6.2	7.7
	sed	6.2	6.2	6.2	6.2	6.2	6.2	6.2
	P	0.253	0.025	0.003	0.004	0.193	0.325	0.221
	95% CI	(-5.2,19.5)	(1.8,26.5)	(6.8,31.5)	(5.8,30.5)	(-4.2,20.5)	(-6.2,18.5)	(-4.7,20.0)

Key:
mean = least square mean
se = standard error of least square mean
n = number of subjects
mean difference = least square mean difference
sed = standard error of least square mean difference
p = probability - * = p<0.05, ** = p<0.01, *** = p<0.001
95% C.I. = 95% Confidence Interval for mean difference

Changes in QT were large (up to 19.2 msec) and statistically different from placebo at hours 2, 4, and 6 (for the 2000 mg dose), the time of peak drug concentrations.

RANS0201
Table 52
ECG DATA
QT_c Interval (msec)
Mean Values and Treatment Comparisons : Day 5

Treatment		Time						
		Pre-dose	2 h	4 h	6 h	8 h	12 h	24 h
1500 mg SR	mean	412.6	410.2	408.8	418.1	410.9	415.8	406.6
	se	6.3	6.3	6.3	6.3	6.3	6.3	6.3
	n	8	8	8	8	8	8	8
2000 mg SR	mean	415.0	415.0	416.4	414.4	411.5	415.4	402.1
	se	6.3	6.3	6.3	6.3	6.3	6.3	6.3
	n	8	8	8	8	8	8	8
Placebo	mean	396.4	393.6	388.2	400.2	390.4	402.4	395.4
	se	6.2	6.2	6.2	6.2	6.2	6.2	6.2
	n	8	8	8	8	8	8	8
1500 mg SR - Placebo	mean difference	16.1**	16.6**	20.6***	17.9**	20.5***	13.4*	11.1*
	sed	5.4	5.4	5.4	5.4	5.4	5.4	5.4
	P	0.004	0.003	<0.001	0.001	<0.001	0.015	0.043
	95% CI	(5.4,26.9)	(5.9,27.4)	(9.9,31.4)	(7.1,28.6)	(9.7,31.2)	(2.6,24.1)	(0.4,21.9)
2000 mg SR - Placebo	mean difference	18.6***	21.4***	28.2***	14.2**	21.1***	12.9*	6.7
	sed	5.2	5.2	5.2	5.2	5.2	5.2	5.2
	P	<0.001	<0.001	<0.001	0.007	<0.001	0.014	0.201
	95% CI	(8.3,28.9)	(11.1,31.8)	(17.9,38.5)	(3.9,24.5)	(10.8,31.4)	(2.6,23.3)	(-3.6,17.0)

Key:
mean = least square mean
se = standard error of least square mean
n = number of subjects
mean difference = least square mean difference
sed = standard error of least square mean difference
p = probability · * = p<0.05, ** = p<0.01, *** = p<0.001
95% C.I. = 95% Confidence Interval for mean difference

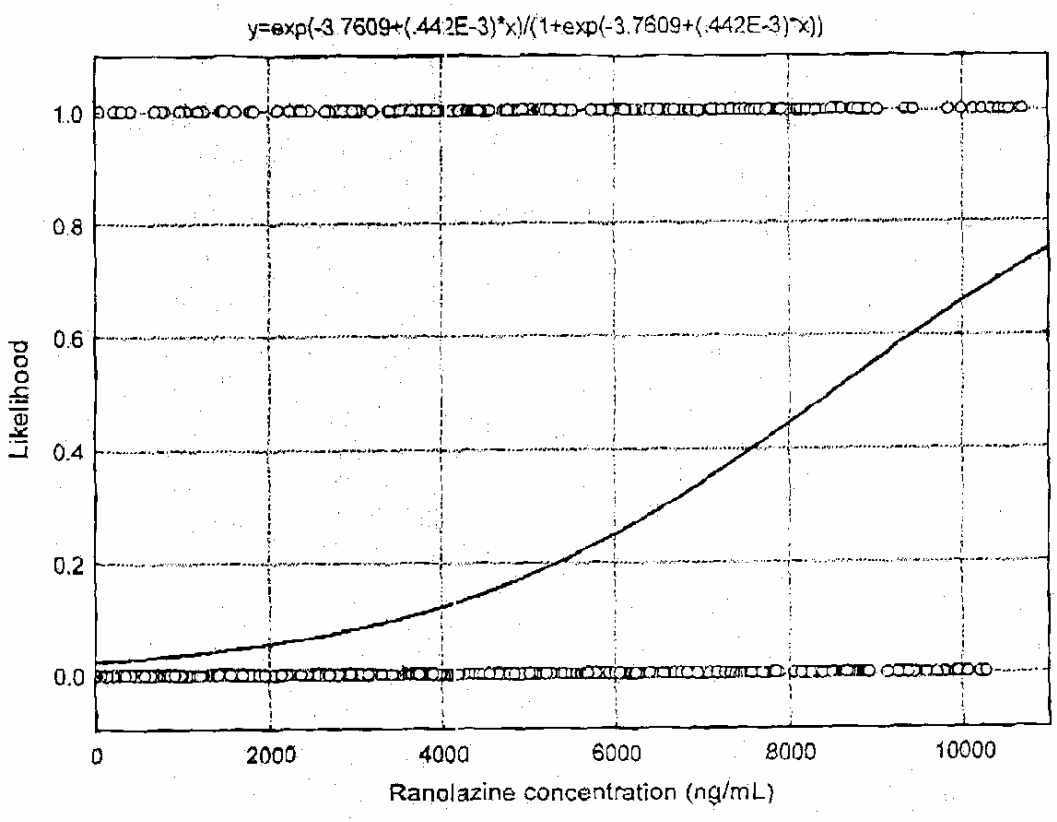
Substantial differences between active and placebo treatment n the mean QTc intervals were evident on Day 5, with statistical significant differences from placebo at every time point with both doses of ranolazine, except at 24 h after the final dose of 2000 mg. The maximum mean differences seen were at 4 h post-dose, when the mean value for the 1500 mg treatment was 20.6 msec greater than for placebo and the mean value for the 2000 mg treatment was 28.2 msec greater than for placebo.

T wave Morphology: repolarization abnormalities, represented by blunting or notching of the T wave, were detected in 1/8 subjects during placebo treatment, 5/8 subjects during treatment with 1500 mg ranolazine and 7/8 subjects during treatment with 2000 mg ranolazine SR. The only subject without any observed changes in T wave morphology also had the lowest plasma ranolazine concentrations.

T wave morphology
Along with QT interval changes, there were changes in T-wave morphology. These changes include both a reduction in amplitude as well as change in its configuration. The T-waves were classified by the Core EGG Laboratory according to the following system: amplitude (positive, negative, flat) and configuration (biphasic +/-, biphasic -/+, and notched).

The figure below shows the logistic regression function fitted to all data from active treatment to determine the likelihood of a notched T-wave at various ranolazine concentrations.

Figure 8.6-18 Likelihood of Observing a Notched T-wave in Study CVT 3111 at Different Ranolazine Plasma Concentrations



A decrease in amplitude was seen up to a concentration of approximately 3,000 ng/mL. Of the 109 ECGs with reported T wave notching, the average ranolazine concentration was 3,020 ng/mL (SD 2,310). The remaining ECGs (about 5700) with no T wave notching reported, the average ranolazine concentration was 1,360 ng/mL (SD 1583).

There were 3 episodes of syncope, one was considered to be serious and 2 that occurred during standing for blood pressure measurements. These episodes tended to be preceded by nausea, dizziness, sinus bradycardia (despite hypotension), blurring of vision, diplopia.

There were 3 withdrawals for QTc greater than 500 msec.

In total, 10 out of the 15 subjects who reached plasma ranolazine concentrations higher than 8,000 ng/mL in any of the dosing periods had their dosing interrupted because of CNS-related AEs, including visual disturbances and altered sensation. One additional subject also had dosing interrupted because of adverse event at a plasma ranolazine concentration of 5,510 ng/mL. None of the subjects' ECGs showed signs of cardiac arrhythmia.

In study CVT 3031, there were changes in the morphology of the T-wave during ranolazine use. These changes include both a reduction in amplitude (positive, negative, flat) as well as changes in its configuration (biphasic +/-, biphasic -/+, and notched).

The frequency of notched T waves is shown below by treatment group at peak and trough concentrations.

% of subjects with notched T waves

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

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

Genetic studies have shown that long-QT syndrome (LQTS) is a primary electrical disease caused by mutations in specific ion channels.[15] LQTS patients exhibit QT prolongation on the ECG and are at risk of arrhythmogenic syncope and sudden death. In addition to duration, T-wave morphology is often abnormal, and notched T waves have been included in diagnostic criteria.[16] This pattern has been associated with a poor prognosis.[17]

6.0 Vital signs

The tables below show the mean change from baseline for vital signs at trough and peak drug concentration. The data are grouped into ISS database, Phase 2/3 SR controlled trials, and open labeled studies.

Table 33 Summary of Mean Change from Baseline to Endpoint in Vital Sign Parameters in the ISS Database or Phase 2/3 SR Controlled Angina Studies Populations

	ISS Database		Phase 2/3 SR Controlled Studies		Open-Label Studies	
					Ranolazine	
Parameter	Total Ranolazine	Total Placebo	Total Ranolazine	Placebo	12-24 months	>24 months
	At Trough					
Systolic BP (mm Hg)						
N	2,044	944	716	442	220	93
Change from Baseline [n (%)]	-0.3 (0.6)	0.6 (1.1)	-0.2 (0.8)	0.3 (0.9)	-1.7	-3.0
SD[a]	16.0	14.6	16.9	14.8	16.7	17.2
Diastolic BP (mm Hg)						
N	2,044	944	716	442	220	93
Change from Baseline [n (%)]	-0.8 (0.0)	-0.3 (0.1)	0.1 (0.8)	0.8 (1.6)	-1.8	-3.5
SD[a]	9.5	9.1	9.1	9.0	9.0	10.2
Heart Rate (bpm)						
N	1,886	794	717	444	220	93
Change from Baseline [n (%)]	-0.2 (1.7)	1.2 (3.5)	-1.6 (-0.4)	-0.4 (1.2)	-6.3	-10.6
SD[a]	13.7	13.6	11.8	12.8	14.0	14.4

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

[17] Malfatto G, Beria B, Sala S, et al. Quantitative analysis of T wave abnormalities and their prognostic implications in the idiopathic long QT syndrome. J Am Coll Cardiol. 1994; 23: 296-30l.

Table 33 Summary of Mean Change from Baseline to Endpoint in Vital Sign Parameters by Dose in the ISS Database or Phase 2/3 SR Controlled Angina Studies Population (Cont'd)

Parameter	ISS Database		Phase 2/3 SR Controlled Studies		Open-Label Studies	
					Ranolazine	
	Total Ranolazine	Total Placebo	Total Ranolazine	Placebo	12-24 months	>24 months
At Peak						
Systolic BP (mm Hg)						
N	1,382	908	707	432	NA	NA
Change from Baseline [n (%)]	-4.2 (-2.5)	-3.3 (-1.8)	-6.1 (-3.8)	-4.1 (-2.3)	NA	NA
SD[a]	15.6	14.6	16.1	15.9	NA	NA
Diastolic BP (mm Hg)						
N	1,382	908	707	432	NA	NA
Change from Baseline [n (%)]	-2.1 (-2.1)	-0.5 (-0.1)	-3.2 (-3.5)	-0.8 (-0.4)	NA	NA
SD[a]	9.1	8.2	9.3	8.5	NA	NA
Heart Rate (bpm)						
N	1,223	756	707	432	NA	NA
Change from Baseline [n (%)]	-1.0 (-0.1)	0.5 (1.8)	-0.6 (0.6)	1.1 (2.9)	NA	NA
SD[a]	11.5	11.0	11.6	11.9	NA	NA

[a] The standard deviation presented is associated with the mean change from baseline data.

BP = blood pressure; bpm = beats per minute; mm Hg = millimeters of mercury; NA = not available; SD = standard deviation.

Abstracted from **Appendix III I Table M-1.1**, **Appendix V I Table M-1.3.1**, and **Appendix VI I M-7.1**.

Phase 2/3 SR controlled angina studies

The tables below shows mean changes in pre-exercise standing vital signs at peak and trough drug concentrations, by dose.

Table 34 Summary of Mean Change from Baseline to Endpoint in Pre-Exercise Standing Vital Sign Parameters by Dose—Phase 2/3 SR Controlled Angina Studies Population

Parameter	Placebo	Ranolazine SR (mg)				Total Ranolazine
		500 b.i.d	750 b.i.d.	1,000 b.i.d.	1,500 b.i.d.	
At Trough						
Systolic BP (mm Hg)						
N[a]	437	177	272	438	172	713
Change from Baseline [n (%)]	1.0 (1.5)	-3.1 (-1.7)	3.2 (3.1)	-0.2 (0.7)	-2.9 (-1.4)	0.9 (1.5)
SD[b]	13.1	14.8	12.3	14.8	17.3	13.2
Diastolic BP (mm Hg)						
N[a]	437	177	272	438	172	713
Change from Baseline [n (%)]	1.1 (2.0)	-0.4 (0.3)	1.4 (2.5)	0.4 (1.2)	-0.2 (0.2)	0.7 (1.6)
SD[b]	7.9	8.7	6.8	8.1	8.2	7.2
Heart Rate (bpm)						
N[a]	437	177	272	438	172	713
Change from Baseline [n (%)]	0.1 (1.8)	-0.8 (0.1)	-0.8 (0.7)	-1.6 (-0.5)	-3.6 (-3.1)	-1.2 (0.1)
SD[b]	11.7	11.1	10.5	10.9	11.4	10.4

7.0 Laboratory values

Methodology

Laboratory assessments collected at baseline and the end visit of each study phase were used. Laboratory parameters were in three panels:

- Hematology: white cell count, red cell count, hemoglobin, hematocrit, platelets, granulocytes, lymphocytes, and monocytes;

- Chemistry: BUN, creatinine, sodium chloride, total carbon dioxide, potassium, glucose, SGOT, SGPT, alkaline phosphatase, total bilirubin, creatinine kinase (OK), CK-MB isoenzymes;

- Urinalysis: color, pH, protein, glucose, ketones, bilirubin, urobilinogen, and nitrates.

- Adrenocorticotropic hormone (ACTH) stimulation testing was performed in some studies.

Laboratory parameters were evaluated for abnormalities in the 64 studies in the ISS data base as well as in the Phase 2/3 SR controlled angina studies plus their long term follow up studies. Only data from the controlled angina are presented in this review, although the results in the ISS data base were examined.

Hematology

The table below shows the mean changes from baseline for selected hematology parameters for the Phase 2/3 SR formulation, by dose (numbers of patients are approximates). The parameters were selected for the table if they appeared to be consistently different from placebo.

Mean change from baseline

	Placebo N=260	Ranol 500 mg N=41	Ranol 750 mg N=237	Ranol 1000 mg n=264	Ranol 1500 mg n=52
Eosinophils %	0	1.1	0	0.2	1.1
Hematocrit %	-0.1	-1.5	-0.9	-1.2	-1.0
Hemoglobin g/dL	-0.1	-0.5	-0.5	-0.6	-0.4
Lymphocytes %	0.3	-1.7	-1.5	-1.4	-1.1
RBC 10^6/ul	-0.1	-0.2	-0.2	-0.3	-0.1

Appendix V B table L-1.3 vol 1.0367

Compared to placebo, there are small mean increases from baseline in eosinophils and small mean decreases in hematocrit/hemoglobin and lymphocytes. These changes were not dose related. The sponsor states that there was no evidence of occult blood loss. (vol 340 page 11).

Shift changes for these parameters are shown below.

Table 28 Shifts of Selected Parameters from Baseline to Endpoint by Dose—Phase 2/3 SR Controlled Angina Studies

		Total Placebo	500 mg b.i.d.	750 mg b.i.d.	1000 mg b.i.d.	1500 mg b.i.d.	Total RAN
Eosinophils N(%)							
	N	260	41	237	264	52	593
Normal	Normal	253 (97.3)	30 (73.2)	226 (95.4)	237 (89.8)	36 (69.2)	528 (89.0)
	High	3 (1.2)	10 (24.4)	4 (1.7)	14 (5.3)	8 (15.4)	36 (6.1)
Red Blood Cells N(%)							
	N	260	41	237	264	52	593
Normal	Normal	237 (91.2)	36 (87.8)	212 (89.5)	238 (90.2)	47 (90.4)	532 (89.7)
	Low	8 (3.1)	3 (7.3)	14 (5.9)	21 (8.0)	2 (3.8)	40 (6.7)
Low	Normal	5 (1.9)	1 (2.4)	3 (1.3)	0	0	4 (0.7)
	Low	10 (3.8)	1 (2.4)	7 (3.0)	5 (1.9)	3 (5.8)	16 (2.7)
Hematocrit N(%)							
	N	259	41	230	261	51	582
Normal	Normal	226 (87.3)	34 (82.9)	208 (90.4)	235 (90.0)	40 (78.4)	516 (88.7)
	Low	8 (3.1)	3 (7.3)	8 (3.5)	13 (5.0)	2 (3.9)	26 (4.5)
Low	Normal	7 (2.7)	0	4 (1.7)	2 (0.8)	4 (7.8)	10 (1.7)
	Low	12 (4.6)	4 (9.8)	5 (2.2)	9 (3.4)	5 (9.8)	23 (4.0)
Occult Blood N(%)							
	N	299	40	258	297	54	649
Normal	Normal	272 (91.0)	35 (87.5)	236 (91.5)	269 (90.6)	49 (90.7)	589 (90.8)
	Abnormal	10 (3.3)	1 (2.5)	9 (3.5)	7 (2.4)	1 (1.9)	18 (2.8)

RAN = Ranolazine

Abstracted from **Appendix V H Table L-8.3**.

These changes are small and seemingly unrelated to dose.

The summary of mean changes for selected hematology values for the ISS data base, the Phase 2/3 SR controlled studies (all doses combined), and the open label studies.

Table 27 Summary of Mean Changes From Baseline in Eosinophils, Red Blood Cells, and Hematocrit Values

	ISS Database		Phase 2/3 SR Controlled Angina Studies		Open-Label Studies				
			Total		Ranolazine SR				
Laboratory Parameter	**Ranolazine SR**	**Placebo**	**Ranolazine SR**	**Placebo**	**6–12 weeks**	**12 wks–6 months**	**6–12 months**	**12–24 months**	**>24 months**
Mean Duration of Exposure (days)	200	44	66	53			448		
Eosinophils (%) Normal range: 0 to 6%									
N[a]	1,251[a]	371[a]	651[a]	301[a]	278	492	426	221	98
Mean Value[b]	2.9[b]	2.7[b]	2.8[b]	2.7[b]	2.6	2.4	2.5	2.3	2.4
Mean Difference from Baseline	0.0	0.1	0.2	0.0	–0.2	–0.3	–0.2	–0.5	–0.8
Red Blood Cells ($10^6/\mu L$) Normal range: 3.8 to 6.4 x $10^6/\mu L$									
N[a]	1,271[a]	376[a]	651[a]	301[a]	278	492	426	221	98
Mean Value[b]	4.8[b]	4.8[b]	4.8[b]	4.7[b]	4.6	4.5	4.5	4.5	4.5
Mean Difference from Baseline	–0.2	–0.1	–0.3	–0.1	–0.2	–0.2	–0.2	–0.2	–0.2
Hematocrit (%) Normal range: 34 to 52%									
N[a]	1,233[a]	376[a]	643[a]	301[a]	278	491	426	221	98
Mean Value[b]	42.8[b]	42.4[b]	42.8[b]	42.3[b]	41.6	41.7	41.4	41.2	41.2
Mean Difference from Baseline	–1.0	–0.5	–1.1	–0.1	–1.1	–0.7	–1.2	–1.6	–2.1

[a] Number of patients at baseline **Appendix V H Table L-1.3**

[b] End point value for ISS database and Phase 2/3 SR controlled Angina Studies, Mean Value at each time point otherwise.

Mean difference from baseline = mean change from baseline to end of treatment

Abstracted from **Appendix III B Table E-1.1, Appendix V B Table E-1.3, Appendix III H Table L-1.1 and Appendix VI H Table L-7.**

In the ranolazine group[18], there was 1 withdrawal for anemia in the ranolazine group (IR formulation), 2 withdrawals for leukopenia (1 each IR and SR formulations). There were no placebo patients dropping out for these reasons.

Regarding serious adverse events, there were 3 reports of anemia (1 IR formulation and 2 SR formulation. There was 1 serious report of leukopenia (SR formulation). There were no placebo patients with these reports.

Blood chemistries

The table below shows the mean changes from baseline for selected blood chemistries parameters from the Phase 2/3 SR formulation, by dose (numbers of patients are approximates). The parameters were selected for the table if they appeared to be consistently different from placebo.

Mean change from baseline

	Placebo N=300	Ranol 500 mg N=41	Ranol 750 mg N=262	Ranol 1000 mg n=301	Ranol 1500 mg n=55
BUN mg/dl	-0.1	0.5	1.0	1.2	2.5
Creatinine mg/dl	0	0.1	0.1	0.1	0.2
Chloride mEq/l	0	0	-0.7	-0.6	-1.7
Glucose mg/dl	0.1	4.3	2.6	1.1	8.3
Sodium	-0.1	-0.7	-0.6	-0.8	-1.8

Appendix V B table L-1.3

Compared to placebo there were small increases in mean changes from baseline for both BUN and creatinine.

In the ranolazine groups from the ISS database, there was 1 withdrawal for increased BUN (IR formulation).[19]

8.0 Special populations

Age, race, gender

There were no clinical trials specifically designed to determine if there are age, gender, and/or race differences in safety.

The frequencies of reported adverse events, serious adverse events, and adverse events leading to discontinuation are shown below for the overall ISS database and Phase 2/3 SR controlled angina studies population.

[18] from Table G-6.1 vol 1.0349
[19] from Table G-6.1 vol 1.0349

Table 60 Incidence of Treatment-Emergent Adverse Events, Serious Adverse Events, and Adverse Events Leading to Discontinuation by Treatment, Age, Gender, Race—ISS Database and Phase 2/3 SR Controlled Angina Studies

Subgroup	Number (%) of Patients[a]											
	Ranolazine						Placebo					
	N	Total AEs	N	Total SAEs	N	Total DC	N	Total AEs	N	Total SAEs	N	Total DC
ISS Database												
Age [Years]												
< 65	1,753	950 (54.2)	1,753	116 (6.6)	1,753	97 (5.5)	965	278 (28.8)	965	17 (1.8)	965	15 (1.6)
65–<74	751	397 (52.9)	751	103 (13.7)	751	87 (11.6)	465	108 (23.2)	465	11 (2.4)	465	13 (2.8)
≥ 75	178	118 (66.3)	178	36 (20.2)	178	42 (23.6)	99	32 (32.3)	99	2 (2.0)	99	3 (3.0)
Gender												
Female	512	299 (58.4)	512	59 (11.5)	512	70 (13.7)	322	90 (28.0)	322	4 (1.2)	322	5 (1.6)
Male	2,170	1,166 (53.7)	2,170	196 (9.0)	2,170	156 (7.2)	1,207	328 (27.2)	1,207	26 (2.2)	1,207	26 (2.2)
Race												
Caucasian	2,306	1,250 (54.2)	2,306	236 (10.2)	2,306	201 (8.7)	1,347	353 (26.2)	1,347	28 (2.1)	1,347	31 (2.3)
Non-Caucasian	197	133 (67.5)	197	18 (9.1)	197	24 (12.2)	111	37 (33.3)	111	2 (1.8)	111	0

The placebo subtracted incidence rates are shown below.

Percent of patients

	age			gender		race	
	<65	65-<74	≥75	Female	Male	White	Non white
Total aes	25.4	29.7	34.0	30.4	26.5	28.0	34.2
Serious aes	4.8	11.3	18.2	10.3	6.8	8.1	7.3
Discontinued	3.9	8.8	20.6	12.1	5.0	6.4	12.2

Although there are differences in incidence rates, it's difficult to know if they are just the result of sample size discrepancies.

Table 60 Incidence of Treatment-Emergent Adverse Events, Serious Adverse Events, and Adverse Events Leading to Discontinuation by Treatment, Age, Gender, Race—ISS Database and Phase 2/3 SR Controlled Angina Studies (Cont'd)

Subgroup	Number (%) of Patients[a]											
	Ranolazine						Placebo					
	N	Total AEs	N	Total SAEs	N	Total DC	N	Total AEs	N	Total SAEs	N	Total DC
Phase 2/3 SR Controlled Angina Studies												
Age [Years]												
< 65	370	112 (30.3)	370	23 (6.2)	370	19 (5.1)	220	48 (21.8)	220	8 (3.6)	220	8 (3.6)
65–<74	287	110 (38.3)	287	19 (6.6)	287	26 (9.1)	189	41 (21.7)	189	6 (3.2)	189	7 (3.7)
≥ 75	92	53 (57.6)	92	9 (9.8)	92	17 (18.5)	46	12 (26.1)	46	2 (4.3)	46	3 (6.5)
Gender												
Female	169	63 (37.3)	169	9 (5.3)	169	18 (10.7)	114	26 (22.8)	114	3 (2.6)	114	4 (3.5)
Male	580	212 (36.6)	580	42 (7.2)	580	44 (7.6)	341	75 (22.0)	341	13 (3.8)	341	14 (4.1)
Race												
Caucasian	715	253 (35.4)	715	47 (6.6)	715	57 (8.0)	434	96 (22.1)	434	16 (3.7)	434	18 (4.1)
Non-Caucasian	34	22 (64.7)	34	4 (11.8)	34	5 (14.7)	21	5 (23.8)	21	0	21	0

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

AE = adverse event; DC = discontinuation due to an AE; SAE = serious adverse event.

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

Placebo subtracted incidence rates-Phase 2/3 SR controlled angina data base are shown below.

Percent of patients-placebo subtracted

	age			gender		race	
	<65	65-<74	≥75	Female	Male	White	Non white
Total aes	8.5	16.6	31.5	14.5	14.6	13.3	40.9
Serious aes	2.6	3.4	5.5	2.7	3.4	2.9	11.8
Discontinued	1.5	5.4	12.0	7.2	3.5	3.9	14.7

As with the ISS database, it's difficult to know if the differences in incidence rates are just the result of sample size discrepancies.

Hepatic impairment
Subjects with moderate hepatic impairment had an AUC and Cmax that were 76% and 51% higher, respectively, compared to healthy volunteers[20], when receiving ranolazine 875 mg followed by 500 mg bid. Subjects with mild impairment were similar to their healthy counterparts. The sponsor advises that this drug should not be used in patients with Child-Pugh category B or worse hepatic impairment. The table below shows the increase in QT with increasing hepatic impairment.

12.4.2.2 Mean Change from Baseline in QTc Interval

Day / Timepoint		Mean Change from Baseline (msec)		
		Healthy (n=16)	Hepatic Impairment	
			Mild (n=8)	Moderate (n=8)
Day 1	Predose	-6.9	-12.3	-11.6
	1 h	-14.3	-11.1	-14.8
	2 h	-6.9	-5.1	3.5
	3 h	-2.5	1.3	11.6
	4 h	0.9	11.6	13.1
	5 h	7.9	3.1	14.4
	7 h	-3.2	5.8	13.9
	9 h	-5.9	-5.5	3.8
	12 h	-4.9	3.4	4.4
Day 3	Predose	-3.6	-1.9	2.5
	1 h	-10.9	-14.8	-13.4
	2 h	-10.4	2.5	14.4
	3 h	-3.1	9.8	7.6
	4 h	-0.5	7.8	14.1
	5 h	12.5	18.1	12.3
	7 h	-6.4	12.3	20.8
	9 h	-4.0	3.5	4.4
	12 h	0.7	0.9	1.0

Note: Data presented in this table is located in Table 14.5.2.2.
Baseline is defined as the corresponding timepoint on Day -1.

The subjects had larger than expected prolongation of QTc. This could be the result of small sample sizes.

[20] Study CVT 3018

Renal impairment
With creatinine clearance decreasing from 100 mL/min to 30 mL/min, the average increase in ranolazine AUC and Cmax was approximately 80%[21].

Congestive heart failure
Study CVT 3031 enrolled 85 subjects with stable NYHA class III or IV heart failure and an ejection fraction <35%. Study design was double blind, placebo controlled, and randomized with patients receiving placebo or ranolazine SR 750 mg bid with or without digoxin. There were no deaths. Seven subjects reported a total of 8 serious events: cerebral ischemia, neuropathy, heart failure (2), myocardial ischemia, syncope, atrial flutter, and ventricular tachycardia. Half of these events were reported by subjects not receiving ranolazine. There were 2 discontinuations for adverse events: myocardial ischemia and heart transplant surgery.

Hypotension and/or postural hypotension were reported by 10 patients (all randomized to ranolazine). There was no evidence in this small study that ranolazine 750 mg bid worsens heart failure in patients with advanced CHF.

Regarding the entire ISS database, only 0.2% (5/2682) reported congestive heart failure or heart failure as an event that resulted in study drug discontinuation. There were 0/1529 placebo patients dropping out for this reason (table G-6.1).

Other concomitant diseases[22]
Adverse events, laboratory abnormalities, ECG changes, and vital signs were inspected in patients with concomitant reactive airway disease (N=153), or diabetes (383), or low BP, low HR and/or prolonged AV conduction (N=381). No studies were conducted to determine if there were effects of these concomitant diseases in patients taking ranolazine. There is no indication that patients with one or more of these concomitant diseases taking ranolazine are at increased risk compared to patients without additional disease.

9.0 Drug-drug interactions
CYP3A4 is a major determinant for ranolazine clearance. There was an average increase of plasma concentration of 3- to 4-fold in the presence of the potent CYP3A4 inhibitor ketoconazole (200 mg bid)[23]. Concomitant use with diltiazem resulted in increases in ranolazine plasma concentrations of 1.5- to 2.4-fold over the diltiazem total daily dose range (180-360 mg)[24]. Ranolazine 1,000 mg bid at steady-state caused a less than two-fold increase simvastatin exposure dosed at 80 mg qd[25]. Concomitant use of ranolazine and drugs that inhibit as well as those that are metabolized by CYP3A4 should be contraindicated.

In study CVT 3021, ranolazine SR 1000 mg bid was taken by healthy volunteers in conjunction with either placebo, or diltiazem 180, 240, or 360 mg qd for 8 days. There were statistically significant increases in ranolazine Cmax and AUC_{0-12}.

[21] Study CVT 3016
[22] Ns reflect number of ranolazine patients with concomitant disease in ISS database except for low BP/HR/increased PR interval (patient number from Phase 2/3 controlled angina studies)
[23] Study CVT 301-10
[24] Studies CVT 3012, RANO121, and RANO6S
[25] Study CVT 3017

Verapamil (120 mg t.i.d.) increased ranolazine average plasma concentrations 2.25-fold at steady-state[26]. The primary cause of this effect could be the inhibition of P-glycoprotein (P-gp) in the gut, increasing the bioavailability of ranolazine. Concomitant use of ranolazine and drugs that inhibit P glycoprotein in the gut should be contraindicated.

Digoxin concentrations increased by 1.2-1.6 fold when used with ranolazine.

10.0 Abrupt withdrawal
In study CVT 3033, a 2-day rebound assessment for possible increase in anginal events, as measured by exercise treadmill test duration, was included in the study design. Ranolazine patients were discontinued from doses of 750 mg twice a day or 1000 mg twice a day compared to patients who were maintained on placebo during a 12 week treatment period. Trough exercise testing was obtained in all patients.

No patients were withdrawn from the study during the 2-day assessment phase and there were no deaths. There were 2 serious adverse events (myocardial infarction and myocardial ischemia) in patients randomized to ranolazine SR 750 mg with diltiazem as the concomitant medication.

11.0 Safety update
The 4-month safety update summarizes data collected from CVT's two ongoing open-label studies (CVT 3032 and CVT 3034) during the period of 15 October 2001 to 31 October 2002. It includes data from 194 new patients enrolled in CVT 3034, and additional data from 440 patients whose participation was ongoing as of the 15 October 2001 NDA data cut-off date. This safety update does not include any new information from controlled clinical studies.

As agreed with the Agency, the data presented in this submission includes updated information on the following:
- deaths;
- serious adverse events (SAEs);
- withdrawals due to adverse events (AEs); and
- electrocardiogram (ECG) data.

With this update, the total exposure has increased from 1171 to 1714 subject/patient years. The ongoing studies used the ranolazine SR formulation in doses ranging from 500 mg bid to 1000 mg bid. Currently, 219 patients have been exposed to ranolazine for 6-12 months, 402 for 12-24 months, and 293 for more than 24 months. Mean duration of exposure for the ISS data base is now 321 days; for the phase 2/3 controlled angina studies, it is now 612 days.

[26] Study CVT 301-1 1

Table 4R Overview of the Ranolazine Development Program by Treatment Group

	Number of Subjects/Patients[a] in Original Submission					
	Ranolazine			Total Number Exposed		
Category	Immediate Release	Sustained Release	IV	Ranolazine[b]	Placebo	All Subjects/Patients[b]
ISS Database[c]	1,299	1,359	77	2,682	1,529	**2,985**
Bioequivalence Study CVT 301-15	0	36	0	36	0	**36**
16 Early Studies[d]	86	0	151	237	159	**304**
Overall Total	1,385	1,395	228	2,955	1,688	**3,325**
	Number of Subjects/Patients[a] in 4-month Update					
	Ranolazine			Total Number Exposed		
Category	Immediate Release	Sustained Release	IV	Ranolazine[b]	Placebo	All Subjects/Patients[b]
ISS Database[c]	1,299	1,460	77	2,783	1,529	**3,021**
Bioequivalence Study CVT 301-15	0	Included in ISS database number	0	Included in ISS database number	0	Included in ISS database number
16 Early Studies[d]	86	0	151	237	159	**304**
Overall Total	1,385	1,460	228	3,020	1,688	**3,325**

[a] Number of subjects/patients reflects number of subjects/patients who received at least one dose of study drug.
[b] For studies with a crossover design, subjects/patients were only counted once in the overall total number of subjects/patients columns but may appear in more than one treatment column.
[c] 64 studies in the original NDA, 65 in the 4-month safety update with addition of Study CVT 301-15 to the ISS database population.
[d] Includes Studies RAN001, RAN002, RAN003, RAN003B, RAN004, RAN005, RAN006A, RAN007, RAN008, RAN010, RAN011, RAN012, RAN014, RAN055, RAN070, and RAN1789.

Abstracted from **Appendix III A Table D-4.1, Appendix III A Table D-4.1.1, Appendix IV A Table D-4.2, Appendix IV A Table D-4.2.1, Appendix V A Table D-4.3, Appendix V A Table D-4.3.1, Appendix VI A Table D-4.4, Appendix VI A Table D-4.4.1, Appendix VIII A Table D-4.5**, and Study Reports for the 16 early studies.

Patient disposition

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

Category	Number of Subjects/Patients		
	Original Submission		4-Month Update
	Total Ranolazine N = 2,682	Total Placebo N = 1,529	Total Ranolazine N = 2,783
Mean Duration of Exposure [Days]	160	24	225
Discontinuation, n (%)	492 (18.3)	63 (4.2)	569 (20.4)
Reason for Discontinuation			
Unacceptable AE	212 (7.9)	28 (1.8)	233 (8.4)
Inappropriate Enrollment	7 (0.3)	0	7 (0.3)
Non-compliance (drug/protocol)	31 (1.2)	5 (0.3)	31 (1.1)
Need for Prohibited Medication	2 (< 0.1)	0	2 (<0.1)
Lost to Follow-up	7 (0.3)	0	9 (0.3)
Elective Withdrawal	31 (1.2)	5 (0.3)	64 (2.3)
Death	27 (1.0)	2 (0.1)	45 (1.6)
Study Termination by Sponsor	75 (2.8)	3 (0.2)	75 (2.7)
Other	100 (3.7)	20 (1.3)	103 (3.7)

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

Serious adverse events

There were 74 additional patients reporting a serious adverse event with submission of the safety update. The reports were mostly angina and myocardial infarction.

Table 19R Incidence of Treatment-Emergent Serious Adverse Events Reported for ≥ 1% of Subjects/Patients in Any Treatment Group by Body System—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations

	Number (%) of Subjects/Patients				
	ISS Database			Phase 2/3 SR Controlled Studies	
	Original Submission		4-Month Update	Original Submission	
Body System Preferred Term	Total Ranolazine N = 2,682	Total Placebo N = 1,529	Total Ranolazine N = 2,783	Total Ranolazine N = 749	Total Placebo N = 455
Mean Duration of Exposure (Days)	160	24	225	66	53
Total Patients With any SAEs	255 (9.5)	30 (2.0)	329 (11.8)	51 (6.8)	16 (3.5)
Cardiovascular System					
Angina Pectoris	77 (2.9)	15 (1.0)	99 (3.6)	13 (1.7)	8 (1.8)
Myocardial Infarct	23 (0.9)	1 (0.1)	40 (1.4)	6 (0.8)	0

SAE = serious adverse event.

Abstracted from **Appendix III B Table E-1.1, Appendix III F Table I-1.1, Appendix V B Table E-1.3, and Appendix V F Table I-1.3**.

Patient 3034/180/ 180 8213 was discontinued for elevated BUN (64 mg/dl), serum creatinine (2.0 mg/dl) , and serum uric acid (9.5 mg/dl). Drug was discontinued and the abnormalities started to resolve.

Deaths

There were reports of 21 additional deaths for this reporting period.

Table 22R Summary of Demographic Characteristics and Cause of Death—Phase 2/3 Controlled Angina Studies and Long-Term Open-Label Uncontrolled Studies Populations

	Frequency Count of Patients Who Died					
	Phase 2/3 Controlled Angina Studies[a]		Open-Label Angina Studies[a]			
	Original Submission		Original Submission		4-Month Update[c]	
	Ranolazine	Placebo[b]	Ranolazine	Off Treatment	Ranolazine	Off Treatment
Demographic Characteristics						
Mean Age (years)	62.6	56.0	71.3	65.6	68.4	65.0
Gender						
Male	6	3	14	9	25	16
Female	1	0	1	2	2	3
Cause of Death						
Sudden	2	1	6	1	8	4
VT/VF/CA	2	1	1	3	2	3
MI	2	0	3	4	7	7
Other CV	0	1	3	0	4	1
Other	1	0	1	3	5	4
Unknown	0	0	1	0	1	0

[a] Includes both ranolazine IR and ranolazine SR patients.

[b] Does not include 1 non-ISS population patient, a 70-year-old male patient (RAN 1789_2302) who died of multiple organ failure after treatment with placebo.

[c] Includes only patients exposed to ranolazine SR in Studies CVT 3032 and CVT 3034.

Abstracted from **Appendix II A, Appendix IV C Table F-1.1, and Appendix VI C Table F-1.3.**

Most of the causes of the newly reported deaths were cardiovascular in nature.

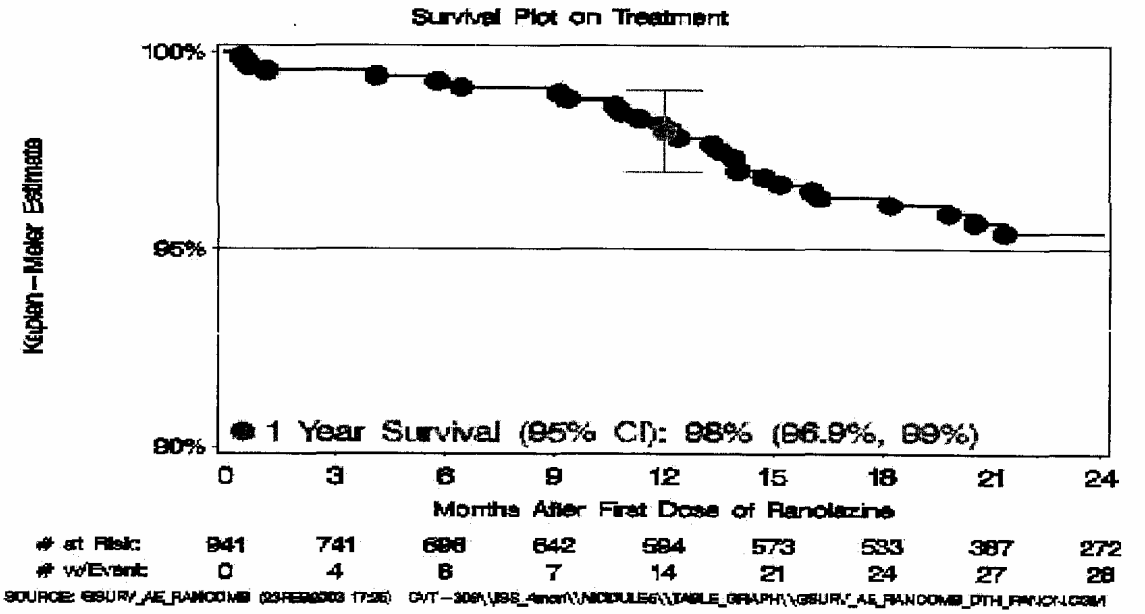
Deaths

Subject ID	Dose SR bid /duration (days)	Cause of death
3032/129/129 1082	1000 mg/1107	Liver carcinoma and sepsis
3032/505/505 1510+	1000 mg/1281	Non-Hodgkin's lymphoma
3032/506/506 1449	1000 mg/1159	Myocardial infarction
3034/141/141 8124	1000 mg/374	Elevated LFTs, jaundice, sepsis with biliary obstruction and probable cholangio-carcinoma
3034/182/182 9079	750 mg/740	Sudden death
3034/183/183 8354	750 mg/489	MI
3034/190/190 8006	1000 mg/864	Sudden death
3034/204/204 7021*	1000 mg/744	GI carcinoma, MI, UTI
3034/224/224 7300	1000 mg/650	Sudden death
3034/493/493 9516	1000 mg/83^	Collapse, prostatic carcinoma
3034/502/502 8117	750 mg/634	Sudden death
3034/512/512 8243	500 mg/666	MI
3034/519/519 9211	1000 mg/344	Angina, MI
3034/525/525 8258	750 mg/324	Sudden death
3034/706/706 8645	750 mg/178	Pulmonary embolism, endometrial carcinoma
3034/707/707 9604	1000 mg/176	Osteosarcoma
3034/710/710 9608	750 mg/202	MI
3034/712/712 7613	500 mg/117	Sudden death, Myocardial ischemia
3034/718/718 7643	1000 mg/46	Acute coronary syndrome
3034/721/721 9636	750 mg/192	Sudden death, hemopericardium
3034/728/728 9686	1000 mg/49	MI

+died after cut off date of 31 Oct 2002
*previous submitted, material updated
^ drug discontinued; patient died 44 days later

Survival curve
The updated version is shown below.

Figure 4R Survival of Chronic Angina Patients on Ranolazine SR; Studies CVT 3031–3034, on Treatment



Discontinuations for adverse events

An additional 30 patients were discontinued from treatment because of an adverse event, an increase of 0.8% compared to the original NDA.

Table 24R Number (%) of Subjects/Patients Who Discontinued Study Medication Due to Treatment-Emergent Adverse Events by Category and Treatment—All Treated Subjects/Patients

Category	Ranolazine				Placebo	
	Original Submission		4-Month Update		Original Submission	
	Total N	Number (%) of Subjects/ Patients[a]	Total N	Number (%) of Subjects/ Patients[a]	Total N	Number (%) of Subjects/ Patients[a]
All Treated Subjects/ Patients	2,955	240 (8.1)	3,020	270 (8.9)	1,688	38 (2.3)
ISS Database	2,682	237 (8.8)	2,783	267 (9.6)	1,529	35 (2.3)
Phase 2/3 SR Controlled Angina Studies	749	63 (8.4)	749	63 (8.4)	455	18 (4.0)
16 Early Studies not in the ISS Database	237	3 (1.3)	237	3 (1.3)	159	3 (1.9)
Bioequivalence Study (CVT 301-15)	36	0	Included in ISS database number	0	0	0

[a] Number of subjects/patients reflects number of subjects/patients who received at least one dose of study drug. See **Table 4R**.

Abstracted from **End-of-Text Table-1, Appendix III A, Table D-4.1, Appendix III F Table I-1.1, Appendix IV A Table D-4.2, Appendix V A Table D-4.3, Appendix V F Table I-1.3, Appendix VI A Table D-4.4, Appendix III G Table J-1.1, Appendix V G Table J-1.3.**

The adverse events most commonly resulting in discontinuation are shown below.

Table 25R Incidence of Most Common Treatment-Emergent Adverse Events Resulting in Discontinuation Reported for ≥ 1% of Subjects/Patients—ISS Database and Phase 2/3 SR Controlled Angina Studies Populations

Category	Number (%) of Subjects/Patients				
	ISS Database			Phase 2/3 SR Controlled Studies	
	Original Submission		4-Month Update	Original Submission	
	Ranolazine (N = 2,682)	Placebo (N = 1,529)	Ranolazine (N = 2,783)	Ranolazine (N = 749)	Placebo (N = 455)
Mean Duration of Exposure (Days)	160	24	225	66	53
Total Subjects/ Patients Who Discontinued Due to AEs	226 (8.4)	31 (2.0)	256 (9.2)	62 (8.3)	18 (4.0)
Cardiovascular System					
Angina Pectoris	36 (1.3)	11 (0.7)	41 (1.5)	10 (1.3)	6 (1.3)
Digestive System					
Nausea	26 (1.0)	1 (0.1)	27 (1.0)	10 (1.3)	0
Nervous System					
Dizziness	30 (1.1)	1 (0.1)	30 (1.1)	13 (1.7)	1 (0.2)

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

This is similar to what was previously reported.

ECG

There is no new information about the effect of ranolazine on QT interval prolongation and T wave morphology changes. The summary of QTc outliers is shown below.

Table 39R **Summary of Bazett QT_c Outliers by Treatment in Studies CVT 3031, CVT 3032, CVT 3033, and CVT 3034**

Treatment	Number of Patients Treated		Number (%) of Patients with a QT_c Increase ≥ 60 msec from Baseline		Number (%) of Patients with a QT_c > 500 msec		Either QT_c Increase > 60msec from baseline or QT_c > 500msec		Both QT_c Increase > 60msec from baseline and QT_c > 500msec	
	Original Submission	4-Month Update	Original Submission	4-Month Update	Original Submission	4-Month Update	Original Submission	4-Month Update	Original Submission	4-Month Update
Placebo	436	436	7 (1.6)	7 (1.6)	7 (1.6)	7 (1.6)	11 (2.5)	11 (2.5)	3 (0.7)	3 (0.7)
Placebo (Rebound Phase)	245	245	0	0	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0
Ranolazine 500 mg b.i.d.	500	694	12 (2.4)	11 (1.6)	11 (2.2)	11 (1.6)	17 (3.4)	16 (2.3)	6 (1.2)	6 (0.9)
Ranolazine 750 mg b.i.d.	611	720	9 (1.5)	12 (1.7)	2 (0.3)	3 (0.4)	10 (1.6)	13 (1.8)	1 (0.2)	2 (0.3)
Ranolazine 1000 mg b.i.d.	528	620	9 (1.7)	13 (2.1)	15 (3.0)	16 (2.6)	22 (4.2)	25 (4.0)	3 (0.6)	4 (0.6)
Ranolazine 1500 mg b.i.d.	173	173	11 (6.9)	12 (6.9)	13 (7.5)	13 (7.5)	21 (12.1)	21 (12.1)	4 (2.3)	4 (2.3)
Off-Treatment	112	85	0	0	1 (0.9)	0	1 (0.9)	0	0	0

Abstracted from **Appendix VII F Table N-23, and Appendix VII F Table N-28.1**.

There is a dose related increase in the incidence rate of QTc outliers.

Protocol CVT 3031

A Double-Blind, Placebo-Controlled, 4-Period Cross Over, Multiple-Dose Study of Ranolazine SR as Monotherapy for Chronic Stable Angina Pectoris at Doses of 500 mg bid, 1000 mg bid, and 1500 mg bid.

The primary objective of this study was to determine the effect of ranolazine SR monotherapy compared to placebo in patients with chronic stable angina on exercise treadmill test duration at the time of trough ranolazine plasma levels (12 hours post dose) when given at the following doses 500 mg bid, 1000 mg bid and 1500 mg bid. There was no washout phase between doses.

Demographics

Panel 11A
Demographic and Background Characteristics - Safety Population

Characteristic	Statistic	Total	Treatment Sequence ABCD	BDAC	CADB	DCBA	Comparison p-value
Total Number of Patients in Safety Population	N	191	47	49	50	45	
Gender:	n	191	47	49	50	45	0.050*
Male	n (%)	140 (73)	39 (83)	40 (82)	32 (64)	29 (64)	
Female	n (%)	51 (27)	8 (17)	9 (18)	18 (36)	16 (36)	
Mean Age (years)		64.3	64.7	65.0	64.0	63.2	0.807
Age Category:		191	47	49	50	45	0.817
<65 years	n (%)	90 (47)	23 (49)	20 (41)	24 (48)	23 (51)	
≥65 years	n (%)	101 (53)	24 (51)	29 (59)	26 (52)	22 (49)	
Race:	n	191	47	49	50	45	0.242
Caucasian	n (%)	174 (91)	45 (96)	46 (94)	43 (86)	40 (89)	
Black	n (%)	10 (5)	2 (4)	2 (4)	4 (8)	2 (4)	
Asian	n (%)	4 (2)	0	0	2 (4)	2 (4)	
Hispanic	n (%)	2 (1)	0	1 (2)	1 (2)	0	
Other	n (%)	1 (<1)	0	0	0	1 (2)	
Mean Weight	(kg)	83.3	85.3	86.8	80.7	80.2	0.076
Mean Height	(cm)	171.5	173.0	172.9	169.3	171.0	0.119

*0.010 < p-value ≤ 0.050; ** p-value ≤ 0.010.
Note: Treatment sequence comparison p-values for continuous variables are from an ANOVA with effects for treatment sequence and pooled site.
Note: Treatment sequence comparison p-values for categorical variables are based on a CMH test with pooled sites as strata.
Note: The treatment sequence comparison for race is for Caucasian versus Non-Caucasian.
Note: A = 500 mg bid; B = 1000 mg bid; C = 1500 mg bid; D = placebo.
Note: Percentages are based on the row totals for that category.
Data Source: Table 1.7.0

The majority of subjects were male, mean age was about 64 years, and most were white. Approximately half of the subjects were at least 65 years of age.

Study completion

Panel 10B
Patient Premature Discontinuation by Dose

			Treatment[2]			
	Statistic	Total[1]	Placebo	Ran SR 500mg	Ran SR 1000 mg	Ran SR 1500 mg
Total Number of Patients	N	191	179	181	180	187
Number of Patients Who Discontinued the Study Prematurely	n	23 (12%)	3	6	1	13
Primary Reason for Premature Discontinuation						
Unacceptable Adverse Event	n (%)	15 (8)	2 (67)	1 (17)	1 (100)	11 (85)
Inappropriate Enrollment	n (%)	1 (<1)	1 (33)	0	0	0
Non-compliance	n (%)	0	0	0	0	0
Elective Withdrawal	n (%)	4 (2)	0	2 (33)	0	2 (15)
Lost to Follow-up	n (%)	0	0	0	0	0
Death	n (%)	1 (<1)	0	1 (17)	0	0
Other	n (%)	2 (1)	0	2 (33)	0	0

[1] Percentages are based on the total number of patients randomized.
[2] Percentages are based on the total number of patients who discontinued the study prematurely.
Data Source: Table 1.2.0 and 1.2.1

There were 3 (1.7%) placebo subjects discontinued prematurely compared to 6 (3.3%) of the ranolazine 500 mg, 1 (0.5%) in the ranolazine 1000 mg, and 13 (7.0%) in the ranolazine 1500 mg groups.
Most of the discontinuations were the result of an adverse event.

Panel 10A (cont'd)
Patient Disposition

	Statistic	Total	Treatment Sequence ABCD	BDAC	CADB	DCBA
Primary Reason for Premature Discontinuation						
Unacceptable Adverse Event	n (%)	15 (8)	6 (13)	3 (6)	4 (8)	2 (4)
Inappropriate Enrollment	n (%)	1 (<1)	0	1 (2)	0	0
Non-compliance	n (%)	0	0	0	0	0
Elective Withdrawal	n (%)	4 (2)	1 (2)	0	2 (4)	1 (2)
Lost to Follow-up	n (%)	0	0	0	0	0
Death	n (%)	1 (<1)	0	1 (2)	0	0
Other	n (%)	2 (1)	0	0	1 (2)	1 (2)

[1]Defined as all randomized patients with evaluable efficacy measurements at baseline and for at least 3 of the 4 double-blind periods, irrespective of protocol violations.
[2]Defined as all randomized patients with evaluable efficacy measurements at baseline and for at least 1 double-blind treatment period, irrespective of protocol violations.
[3]Defined as all randomized patients with evaluable efficacy measurements at baseline and from the first double-blind period, irrespective of protocol violations.
[4]Defined as all randomized patients with an evaluable efficacy measurement at baseline and with at least 3 out of 4 treatment periods completed in accordance with the protocol.
[5]Defined as all randomized patients who receive at least 1 dose of double-blind study drug.
Note: Percentages are based on total number of patients randomized.
Note: A = 500 mg bid; B = 1000 mg bid; C = 1500 mg bid; D = placebo.
Data Source: Tables 1.0.0 and 1.2.0

All adverse events

Because of the cross over design of the study, it is very difficult to associate adverse event and dose. The following The table below shows the most common adverse events using the first period analysis (the analysis counting an AE in the period in which it occurred unless it worsened).

Panel 12C
Common Adverse Events*

	Statistic	Placebo (n=179)	500 mg Ran SR (n=181)	1000 mg Ran SR (n=180)	1500 mg Ran SR (n=187)
Total Number of Patients with at Least 1 AE	n (%)	26 (15)	28 (15)	37 (21)	62 (32)
Adverse Events:					
Dizziness	n (%)	1 (<1)	2 (1)	9 (5)	22 (12)
Nausea	n (%)	0	1 (<1)	2 (1)	16 (9)
Asthenia	n (%)	3 (2)	0	3 (2)	11 (6)
Angina Pectoris	n (%)	8 (4)	8 (4)	2 (1)	6 (3)

* Counting an AE only in the first period it occurred unless it worsened.
Data Source: Table 3.0.1

All of the reported events except angina pectoris were more frequent in the ranolazine 1500 mg group compare to lower dose groups and placebo.

Serious safety

Death

There was one death, the cause reported as ventricular fibrillation (sudden death), and the patient was on study drug for 17 days. He was taking ranolazine 500 mg at the time of death and in the previous weeks had received ranolazine 1000 mg and placebo in that order.

Serious adverse events

There were 12 patients who reported adverse events. The details of these events are shown below.

Panel 12H
Listing of Patients with Serious Adverse Events -
Safety Population

Site	Patient Number	Treatment Sequence	Treatment at Which SAE Occurred	SAE	Age/Sex/Race	Time From Baseline to Event (days)	Event Duration (days)	Frequency	Severity	Relation to Study Drug	Effect on Study Drug	Treatment	Outcome
124	1241034	ABCD	D	Atrial Fibrillation	76/M/C	28	1	Intermittent	Severe	Probably	Discontinued	Medication	Resolved
133	1331017	BDAC	A*	Ventricular Fibrillation	60/M/C	17	1	Single Episode	Severe	Possibly	None	None	Died
	1331018	CADB	C	Allergic Reaction	80/M/C	6	2	Single Episode	Severe	Probably Not	None	Medication	Resolved
137	1371132	BDAC	C**	Accidental Injury	71/M/B	37	2	Constant	Moderate	Probably Not	Discontinued	Other	Resolved
154	1541222	CADB	B	Shock	44/M/C	25		Constant	Severe	Probably Not	Discontinued	Medication	Ongoing
157	1571242	CADB	C	Postural Hypotension	63/M/C	8	1	Constant	Severe	Possibly	Interrupted	Other	Resolved
170	1701469	ABCD	C	Angina Pectoris	75/M/C	19	5	Intermittent	Moderate	Probably Not	None	Medication	Resolved
177	1771465	ABCD	C#	Syncope	76/F/C	20		Intermittent	Moderate	Probably Not	Discontinued	Other	Ongoing

* Patient 1331017 was dispensed drug for period 3 and died 2 days later. Information on tablets taken for that period is unknown.
**Patient 1371132 was dispensed drug for period 4, fractured his pelvis 10 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
Patient 1771465 was dispensed drug for period 3, experienced an SAE 4 days later, and withdrew from the study.
##Patient 1851529 experienced an SAE 4 days after completing period 4, the final visit in the double-blind treatment phase, and was no longer on study drug.
Note: For Race: C = Caucasian, B = Black, A = Asian, H = Hispanic, O = Other; For Sex: M = Male, F = Female.
Note: Ran SR = Ranolazine SR; A = 500 mg bid; B = 1000 mg bid; C = 1500 mg bid; D = Placebo
Note: SAE = Serious adverse event.
Note: One SAE not included in the table above is for patient 1551226, who had laboratory screening on Aug 10 98. He experienced chest pain on Aug 11 98 and was hospitalized for observation. He stabilized, had Visit 1 on Sep 22 98 and was subsequently randomized into the study.
Data Source: Table 3.1.1

Panel 12H (cont'd)
Listing of Patients with Serious Adverse Events -
Safety Population

Site	Patient Number	Treatment Sequence	Treatment at Which SAE Occurred	SAE	Age/Sex/Race	Time From Baseline to Event (days)	Event Duration (days)	Frequency	Severity	Relation to Study Drug	Effect on Study Drug	Treatment	Outcome
185	1851529	DCBA	A##	Coronary Artery Disorder	50/M/C	32	2	Single Episode	Severe	Probably Not	None	Other	Resolved
512	5121315	CADB	C	Angina Pectoris	58/F/C	3	4	Intermittent	Moderate	Probably Not	Discontinued	Medication	Controlled
519	5191362	BDAC	C	Dizziness	65/M/C	25	1	Single Episode	Severe	Possibly	Discontinued	Medication	Resolved
				Headache		25	1	Single Episode	Severe	Possibly	Discontinued	Medication	Resolved
				Vertigo		25	1	Single Episode	Severe	Possibly	Discontinued	Medication	Resolved
520	5201341	ABCD	A	Angina Pectoris	45/M/C	3	2	Intermittent	Moderate	Possibly	Discontinued	Medication	Controlled

* Patient 1331017 was dispensed drug for period 3 and died 2 days later. Information on tablets taken for that period is unknown.
**Patient 1371132 was dispensed drug for period 4, fractured his pelvis 10 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
Patient 1771465 was dispensed drug for period 3, experienced an SAE 4 days later, and withdrew from the study.
##Patient 1851529 experienced an SAE 4 days after completing period 4, the final visit in the double-blind treatment phase, and was no longer on study drug.
Note: For Race: C = Caucasian, B = Black, A = Asian, H = Hispanic, O = Other; For Sex: M = Male, F = Female.
Note: Ran SR = Ranolazine SR; A = 500 mg bid; B = 1000 mg bid; C = 1500 mg bid; D = Placebo.
Note: SAE = Serious adverse event.
Note: One SAE not included in the table above is for patient 1551226, who had laboratory screening on Aug 10 98. He experienced chest pain on Aug 11 98 and was hospitalized for observation. He stabilized, had Visit 1 on Sep 22 98 and was subsequently randomized into the study.
Data Source: Table 3.1.1

Serious events were reported more often in the ranolazine 1500 mg group (7/191, 4%), compared to placebo (1/191, <1%), ranolazine 500 mg (3/191, 2%), and ranolazine 1000 mg (1/191, <1%). The events reported in the 1500 mg group include allergic reaction (post flu shot), accidental injury (occupation related), postural hypotension, angina (2), syncope, and dizziness (and headache and vertigo).

Withdrawals for adverse events

There were 15 subjects who withdrew from the study because of an adverse event.

Panel 12I
Listing of Patients Who Withdrew from the Study Due to Adverse Events - Safety Population

Site	Patient Number	Treatment Sequence	Treatment at Which SAE Occurred	AE	Age/ Sex/ Race	Time From Baseline to Event (days)	Event Duration (days)	Frequency	Severity	Relation to Study Drug	Effect on Study Drug	Treatment	Outcome
124	1241034	ABCD	D	Atrial Fibrillation	76/M/C	28	1	Intermittent	Severe	Probably	Discontinued	Medication	Resolved
			D	Supraventricular Extrasystoles		28	1	Intermittent	Moderate	Possibly	Discontinued	Medication	Resolved
127	1271119	ABCD	D	Arrhythmia	76/M/C	25	5	Intermittent	Moderate	Probably	Discontinued	None	Resolved
128	1281076	CADB	C	Increased Salivation	67/F/H	4	10	Intermittent	Moderate	Probably	Discontinued	None	Resolved
			C	Nausea		3	13	Intermittent	Moderate	Probably	Discontinued	None	Resolved
			C	Paresthesia		7	2	Intermittent	Moderate	Possibly	Discontinued	None	Resolved
			C	Thirst		4	10	Intermittent	Moderate	Possibly	Discontinued	None	Resolved
			C	Urine Abnormality		6	8	Intermittent	Moderate	Possibly	Discontinued	None	Resolved
			C	Vomiting		4	10	Intermittent	Moderate	Probably	Discontinued	None	Resolved
133	1331024	DCBA	C	Hematuria	80/F/C	9	4	Constant	Moderate	Possibly	Discontinued	Medication	Resolved
			C	Nausea		10	6	Constant	Moderate	Possibly	Discontinued	Medication	Resolved
137	1371132	BDAC	C*	Accidental Injury	71/M/B	37	2	Constant	Moderate	Probably Not	Discontinued	Other	Resolved
140	1401138	ABCD	A	Tremor	77/M/C	6	16	Constant	Moderate	Probably Not	Discontinued	Medication	Controlled
154	1541222	CADB	B	Congestive Heart Failure	44/M/C	25	1	Single Episode	Moderate	Probably Not	Discontinued	Medication	Resolved
			B	Shock		25		Constant	Severe	Probably Not	Discontinued	Medication	Ongoing

* Patient 1371132 was dispensed drug for period 4, fractured his pelvis 10 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
** Patient 1771465 was dispensed drug for period 3, began experiencing an SAE 4 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
Note: For Race: C = Caucasian, B = Black, A – Asian, H = Hispanic, O = Other; (Specify) For Sex: M = Male, F = Female.
Note: Ran SR = Ranolazine SR; A = 500 mg bid; B = 1000 mg bid; C – 1500 mg bid; D = Placebo.
Note: AE = Adverse event
Data Source: Table 3.1.2

Panel 12I (cont'd)
Listing of Patients Who Withdrew From the Study Due to Adverse Events - Safety Population

Site	Patient Number	Treatment Sequence	Treatment at Which SAE Occurred	AE	Age/ Sex/ Race	Time From Baseline to Event (days)	Event Duration (days)	Frequency	Severity	Relation to Study Drug	Effect on Study Drug	Treatment	Outcome
155	1551225	CADB	C	Abnormal Vision	68/F/C	2	1	Single Episode	Mild	Probably Not	Discontinued	Other	Resolved
			C	Constipation		4	6	Constant	Moderate	Probably Not	Discontinued	Other	Resolved
			C	Hypesthesia		5	5	Intermittent	Mild	Probably Not	Discontinued	Other	Resolved
			C	Hypesthesia		5	5	Intermittent	Mild	Probably Not	Discontinued	Other	Resolved
			C	Nausea		5	9	Constant	Moderate	Probably Not	Discontinued	Other	Resolved
			C	Vomiting		6	1	Single Episode	Mild	Probably Not	Discontinued	Other	Resolved
	1551227	DCBA	C	Abnormal Gait	78/F/C	10	3	Intermittent	Moderate	Possibly	Discontinued	None	Resolved
			C	Confusion		10	3	Intermittent	Mild	Possibly	Discontinued	None	Resolved
			C	Constipation		10	4	Constant	Moderate	Possibly	Discontinued	None	Resolved
			C	Headache		11	1	Constant	Severe	Possibly	Discontinued	None	Resolved
			C	Myasthenia		11	3	Intermittent	Severe	Possibly	Discontinued	None	Resolved
			C	Twitching		11	1	Single Episode	Moderate	Possibly	Discontinued	None	Resolved
170	1701469	ABCD	C	Asthenia	75/M/C	13	2	Constant	Moderate	Probably	Discontinued	None	Resolved
			C	Dizziness		13	27	Constant	Severe	Probably	Discontinued	None	Resolved

* Patient 1371132 was dispensed drug for period 4, fractured his pelvis 10 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
** Patient 1771465 was dispensed drug for period 3, began experiencing an SAE 4 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
Note: For Race: C = Caucasian, B = Black, A = Asian, H = Hispanic, O = Other; (Specify) For Sex: M = Male, F = Female.
Note: Ran SR = Ranolazine SR; A = 500 mg bid; B = 1000 mg bid; C = 1500 mg bid; D = Placebo.
Note: AE = Adverse event
Data Source: Table 3.1.2

Panel 12I (cont'd)
Listing of Patients Who Withdrew From the Study Due to Adverse Events - Safety Population

Site	Patient Number	Treatment Sequence	Treatment at Which SAE Occurred	AE	Age/ Sex/ Race	Time From Baseline to Event (days)	Event Duration (days)	Frequency	Severity	Relation to Study Drug	Effect on Study Drug	Treatment	Outcome
177	1771465	ABCD	C**	Syncope	76/F/C	20		Intermittent	Moderate	Probably Not	Discontinued	Other	Ongoing
			C**	Congestive Heart Failure		26	5	Single Episode	Moderate	Probably Not	Discontinued	Medication	Resolved
512	5121315	CADB	C	Angina Pectoris	58/F/C	3	4	Intermittent	Moderate	Probably Not	Discontinued	Medication	Controlled
	5121365	BDAC	C	Dizziness	49/M/C	23	2	Intermittent	Moderate	Probably	Discontinued	None	Resolved
			C	Headache		23	2	Constant	Moderate	Probably	Discontinued	None	Resolved
			C	Nausea		23	2	Single Episode	Mild	Probably	Discontinued	None	Resolved
519	5191362	BDAC	C	BUN Increased	65/M/C	25	6	Constant	Severe	Possibly	Discontinued	Medication	Resolved
			C	Dizziness		25	1	Single Episode	Severe	Possibly	Discontinued	Medication	Resolved
			C	Headache		25	1	Single Episode	Severe	Possibly	Discontinued	Medication	Resolved
			C	Vertigo		25	1	Single Episode	Severe	Possibly	Discontinued	Medication	Resolved
520	5201341	ABCD	A	Angina Pectoris	45/M/C	3	2	Intermittent	Moderate	Possibly	Discontinued	Medication	Controlled

* Patient 1371132 was dispensed drug for period 4, fractured his pelvis 10 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
** Patient 1771465 was dispensed drug for period 3, began experiencing an SAE 4 days later, and withdrew from the study. Information on tablets taken for that period is unknown.
Note: For Race: C = Caucasian, B = Black, A = Asian, H = Hispanic, O = Other; (Specify) For Sex: M = Male, F = Female.
Note: Ran SR = Ranolazine SR; A = 500 mg bid; B = 1000 mg bid; C = 1500 mg bid; D = Placebo.
Note: AE = Adverse event
Data Source: Table 3.1.2

Of the 15 patients who withdrew, 10 (5%) were receiving ranolazine 1500 mg, 1 (<1%) was receiving 1000 mg, 2 (1%) were receiving 500 mg, and 2 (1%) were receiving placebo. The 10 subjects on the highest ranolazine dose withdrew because of increased salivation (and nausea, paresthesia, thirst, urine abnormality, vomiting), hematuria (and nausea), abnormal vision (and constipation, hypesthesia, nausea, vomiting), abnormal gait (and confusion, constipation, headache, myasthenia, twitching), asthenia (and dizziness), syncope (and CHF), angina, dizziness (and headache, nausea), BUN increased (and dizziness, headache, vertigo).

QT/QTc intervals
The frequency of QTc interval changes are shown below.

Panel 12N

Frequency of QTc (Bazett) Change from Baseline to ≥60 msec and to >500 msec, n (%) of Patients

	Placebo	RAN SR 500 mg	RAN SR 1000 mg	RAN SR 1500 mg
Trough	1/176 (0.6)	2/177 (1.1)	2/178 (1.1)	2/171 (1.2)
Peak	0/177 (0)	4/177 (2.3)	0/177 (0)	4/169 (2.4)

There were 9 subjects with 15 ECGs that matched the criteria of ≥ 60 msec from baseline to values to >500 msec.

Pt number/dose	Baseline QTc (msec)	Highest QTc (msec)	Change (msec)
1231001/500 mg	461	543	82
1411161/500 mg	482	583	101
1411161/1500 mg	482	561	79
1491198/1000 mg	460	528	68
1561230/placebo	465	527	62
1561230/1500 mg	438	535	97
5011437/1000 mg	426	503	77
5011441/1500 mg	438	558	120
5071428/1500 mg	433	522	89
5101417/500 mg	446	539	93
5251309/500 mg	506	571	65

T wave morphology

The frequency of notched T waves is shown below by treatment group at peak and trough concentrations.

% of subjects with notched T waves

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

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

Vital signs

The table below shows the mean blood pressure and heart rate at rest.

Panel 12L
LS Mean (SE) Standing BP, HR, and RPP

	Placebo (N=179)		Ranolazine Treatment 500 mg bid (N=181)		1000 mg bid (N=180)		1500 mg bid (N=187)	
	Trough	Peak	Trough	Peak	Trough	Peak	Trough	Peak
At Rest								
Systolic blood pressure (mm Hg)	138.9 (0.9)	134.8 (0.8)	136.6 (0.9)	134.4 (0.8)	137.9 (0.8)	134.5 (0.8)	137.1 (0.9)	132.5 (0.8)*
Diastolic blood pressure (mm Hg)	80.3 (0.5)	79.2 (0.5)	79.9 (0.5)	78.2 (0.5)	80.4 (0.5)	78.8 (0.5)	80.2 (0.5)	77.7 (0.5)*
Heart rate (bpm)	81.2 (0.5)	84.2 (0.6)	81.6 (0.5)	84.5 (0.6)	79.7 (0.5)*	82.7 (0.6)	78.4 (0.5)**	81.6 (0.6)**
Rate pressure product (mm Hg x bpm)	11243.7 (96.0)	11326.7 (99.5)	11088.9 (95.6)	11339.3 (99.7)	10946.1 (94.8)*	11065.7 (98.7)	10717.0 (97.7)**	10783.1 (102.0)**

At doses less than 1500 mg, there were no statistically significant differences between ranolazine and placebo for changes in blood pressure. There were significant decreases for the 1500 mg dose at peak drug concentrations (reductions were in the order of 2-3 mmHg[27]).

Heart rate reductions were significant for the 1500 mg dose at both peak and trough drug concentrations. Mean reductions in heart rate were 3 bmp or less.

[27] See page 170 item 8 vol 146

Protocol CVT 3033

A Double-Blind, Randomized, Stratified, Placebo-Controlled, Parallel Study of Ranolazine SR at Doses of 750 mg Twice a Day and 1000 mg Twice a Day in Combination with Other Anti-Anginal Medications in Patients with Chronic Stable Angina Pectoris.

The primary objective of this study was to determine the effect of ranolazine SR at doses of 750 mg twice a day and 1000 mg twice a day compared to placebo on symptom-limited treadmill exercise over 12 week treatment period. Study patients had chronic stable angina and were receiving a stable dose of a single concomitant anti-anginal medication (diltiazem 180 mg once a day in a formulation intended for once-a-day dosing, atenolol 50 mg once a day, or amlodipine 5 mg once a day).

A 2-day rebound assessment for possible increase in anginal events, as measured by exercise treadmill test duration, was included following discontinuation of ranolazine SR at doses of 750 mg twice a day or 1000 mg twice a day compared to patients who were maintained on placebo during a 12 week treatment period.

Demographics

Table 11B Demography by Treatment: Safety Population

		Treatment			Total n = 823***	P-value
		Placebo n = 269	Ranolazine SR 750 mg n = 279	Ranolazine SR 1000 mg n = 275**		
Gender	Male n (%)	202 (75.1)	217 (77.8)	219 (79.6)	638 (77.5)	0.45
	Female n (%)	67 (24.9)	62 (22.2)	56 (20.4)	185 (22.5)	
Age (years)	Mean	63.7	64.3	63.9	64.0	0.73
	SD	8.9	9.3	9.3	9.2	
	Min	36	38	36	36	
	Max	84	92	86	92	
Age Category	<65 years n (%)	129 (48.0)	141 (50.5)	138 (50.2)	408 (49.6)	0.80
	≥65 years n (%)	140 (52.0)	138 (49.5)	137 (49.8)	415 (50.4)	
Race	Asian n (%)	1 (0.4)	3 (1.1)	1 (0.4)	5 (0.6)	0.26*
	Black n (%)	0	1 (0.4)	2 (0.7)	3 (0.4)	
	Caucasian n (%)	265 (98.5)	269 (96.4)	269 (97.8)	803 (97.6)	
	Hispanic n (%)	1 (0.4)	4 (1.4)	0	5 (0.6)	
	Other n (%)	2 (0.7)	2 (0.7)	3 (1.1)	7 (0.9)	
Weight (kg)	Mean	79.7	80.2	81.9	80.6	0.13
	SD	12.4	13.0	13.0	12.8	
	Min	41	50	50	41	
	Max	122	124	150	150	
Height (cm)	Mean	169.3	169.7	170.7	169.9	0.14
	SD	8.6	8.3	8.7	8.5	
	Min	150	149	149	149	
	Max	192	190	195	195	

Note: Data summarized in the above table are located in Table 1.5.0.1.
*The treatment comparison p-value for race is for Caucasian vs non-Caucasian.
** n=274 for the weight variable in the ranolazine SR 1000 mg group.
*** n=822 for the weight variable.

Most patients were male, around 64 years of age, and almost completely white. The groups were similar in these characteristics.

Table 11C Cardiovascular History by Treatment, N (%): Safety Population

Cardiovascular History			Placebo n = 269	Ranolazine SR 750 mg n = 279	Ranolazine SR 1000 mg n = 275	Total n = 823	P-value
Unstable Angina >Two Months Before Randomization			**54 (20.1)**	**58 (20.8)**	**65 (23.6)**	**177 (21.5)**	**0.54**
Congestive Heart Failure			**77 (28.6)**	**87 (31.2)**	**78 (28.4)**	**242 (29.4)**	**0.72**
Congestive Heart Failure	NYHA Class I		33 (12.3)	35 (12.5)	35 (12.7)	103 (12.5)	0.68
	NYHA Class II		44 (16.4)	52 (18.6)	43 (15.6)	139 (16.9)	
Prior Myocardial Infarction			**150 (55.8)**	**166 (59.5)**	**158 (57.5)**	**474 (57.6)**	**0.67**
Number of Prior Myocardial Infarctions		0	119 (44.2)	113 (40.5)	117 (42.5)	349 (42.4)	0.55
		1	121 (45.0)	129 (46.2)	128 (46.5)	378 (45.9)	
		2	22 (8.2)	26 (9.3)	27 (9.8)	75 (9.1)	
		3	3 (1.1)	7 (2.5)	3 (1.1)	13 (1.6)	
		>3	4 (1.5)	4 (1.4)	0	8 (1.0)	
Prior CABG >Two Months Before Randomization			**36 (13.4)**	**53 (19.0)**	**56 (20.4)**	**145 (17.6)**	**0.067**
Number of Prior CABGs		0	233 (86.6)	226 (81.0)	219 (79.6)	678 (82.4)	0.13
		1	21 (7.8)	39 (14.0)	43 (15.6)	103 (12.5)	
		2	7 (2.6)	11 (3.9)	10 (3.6)	28 (3.4)	
		>2	8 (3.0)	3 (1.1)	2 (0.7)	13 (1.6)	
		Unknown	0	0	1 (0.4)	1 (0.1)	
Prior PTCA >Two Months Before Randomization			**53 (19.7)**	**46 (16.5)**	**53 (19.3)**	**152 (18.5)**	**0.57**
Number of PTCA Procedures		0	216 (80.3)	233 (83.5)	222 (80.7)	671 (81.5)	0.69
		1	35 (13.0)	25 (9.0)	40 (14.5)	100 (12.2)	
		2	13 (4.8)	14 (5.0)	8 (2.9)	35 (4.3)	
		>2	5 (1.9)	7 (2.5)	5 (1.8)	17 (2.1)	
Intermittent Claudication			**19 (7.1)**	**23 (8.2)**	**20 (7.3)**	**62 (7.5)**	**0.86**
Arrhythmias	**Atrial**		**20 (7.4)**	**22 (7.9)**	**23 (8.4)**	**65 (7.9)**	**0.91**
	Ventricular		**19 (7.1)**	**25 (9.0)**	**27 (9.8)**	**71 (8.6)**	**0.48**
	Other		**2 (0.7)**	**5 (1.8)**	**4 (1.5)**	**11 (1.3)**	**0.64**
Atrial Arrhythmias	**Ectopy**		**8 (3.0)**	**9 (3.2)**	**11 (4.0)**	**28 (3.4)**	**0.76**
	Tachycardia		**2 (0.7)**	**1 (0.4)**	**4 (1.5)**	**7 (0.9)**	**0.37**
	Fibrillation or Flutter		**10 (3.7)**	**13 (4.7)**	**12 (4.4)**	**35 (4.3)**	**0.85**
Ventricular Arrhythmias	**Ectopy**		**16 (5.9)**	**23 (8.2)**	**25 (9.1)**	**64 (7.8)**	**0.35**
	Tachycardia		**3 (1.1)**	**2 (0.7)**	**1 (0.4)**	**6 (0.7)**	**0.54**
	Fibrillation or Flutter		**3 (1.1)**	**1 (0.4)**	**1 (0.4)**	**5 (0.6)**	**0.46**
Clinically Significant Valvular Disease			**19 (7.1)**	**23 (8.2)**	**12 (4.4)**	**54 (6.6)**	**0.17**
Clinically Significant Valvular Disease	Aortic Stenosis		2 (0.7)	4 (1.4)	0	6 (0.7)	0.13
	Aortic Insufficiency		6 (2.2)	7 (2.5)	5 (1.8)	18 (2.2)	0.88
	Aortic Insufficiency Repaired		1 (0.4)	0	1 (0.4)	2 (0.2)	0.55
	Mitral Insufficiency		12 (4.5)	17 (6.1)	9 (3.3)	38 (4.6)	0.27
	Mitral Insufficiency Repaired		0	2 (0.7)	1 (0.4)	3 (0.4)	0.78
	Other		2 (0.7)	6 (2.2)	3 (1.1)	11 (1.3)	0.41
	Other Repaired		0	0	1 (0.4)	1 (0.1)	0.66
Cardiac Arrest			**6 (2.2)**	**6 (2.2)**	**1 (0.4)**	**13 (1.6)**	**0.13**
Hypertension			**173 (64.3)**	**177 (63.4)**	**177 (64.4)**	**527 (64.0)**	**0.97**
Stroke			**11 (4.1)**	**15 (5.4)**	**15 (5.5)**	**41 (5.0)**	**0.73**
Pulmonary Embolism			**2 (0.7)**	**4 (1.4)**	**1 (0.4)**	**7 (0.9)**	**0.47**

Note: Data summarized in the above table are located in Table 1.6.0.

About one fifth of the population had unstable angina at least 2 months prior to study enrollment, about 30% had congestive heart failure (NYHA class I or II), and more than half had a prior MI. The groups were well balanced with rare exception.

Study completion

No. and (percent) of patients

	Placebo N=269	Ran 750 mg N=279	Ran 1000 mg N=275
Completed trial	243 (90.3)	250 (89.6)	238 (86.5)
Early withdrawal	26 (9.7)	29 (10.4)	37 (13.5)
For AE	16 (5.9)	22 (7.9)	25 (9.1)
Death	2 (0.7)	2 (0.7)	1 (0.4)
Elective withdrawal	4 (1.5)	1 (0.4)	5 (1.8)
Other^	7 (2.9)	6 (2.2)	7 (2.5)

^ includes non compliance, lost to follow up
table 12B, Table 1.4.1 study report

More patients failed to complete the study in the high dose ranolazine group (13.5%) compared to low dose ranolazine (10.4%) and placebo (9.7%). The main reason for discontinuation for all treatment groups was an adverse event. The high dose group had more discontinuations for adverse events (8.7%) compared to low dose (7.2%) and placebo (4.8%). The percent of reported deaths were similar across treatment groups.

Withdrawals by concomitant anti-anginal medication.

Percent of patients who withdrew early: placebo subtracted

	Ran 750 mg			Ran 1000 mg		
	Dilt N=74	Aten N=119	Amlo N=86	Dilt N=69	Aten N=117	Amlo N=89
Early withdrawal	3.3	5	-7.6	4.5	9.4	-4.4
For AE	6.5	5.1	-5.1	8.8	6.9	-4.0
Death	0	-0.8	1.2	-1.4	-0.8	1.1
Elective withdrawal	0	-1.7	-1.2	0	0.9	-0.1

There were more withdrawals for adverse events by patients taking diltiazem in all treatment groups including placebo (table 1.4.3).

N.B. Diltiazem (180-360 mg) in previous studies (CVT 3012, RAN0121, and RAN068) was shown to increase ranolazine average steady-state plasma concentrations of 1.5-2.4 fold.

Individual adverse events
Adverse events reported by at least 4 subjects in at least 1 of the ranolazine groups and more than the placebo group are shown below.

No. and (percent) of patients

Adverse event	Placebo N=269	Ran 750 mg N=279	% Pl subtracted	Ran 1000 mg N=275	% Pl subtracted
Any event	71 (26.4)	87 (31.2)	4.8	90 (32.7)	6.6
Constipation	2 (0.7)	18 (6.5)	5.8	20 (7.3)	6.6
Dizziness	5 (1.9)	10 (3.6)	1.7	19 (6.9)	5.0
Nausea	2 (0.7)	9 (3.2)	2.5	14 (5.1)	4.4
Asthenia	6 (2.2)	5 (1.8)	-0.4	13 (4.7)	2.5

Syncope	0	0	0	5 (1.8)	1.8
Abdominal pain	2 (0.7)	2 (0.7)	0	7 (2.5)	1.8
Sweating	0	3 (1.1)	1.1	4 (1.5)	1.5
Vomiting	1 (0.4)	2 (0.7)	0.3	4 (1.5)	1.1
Diabetes mellitus	0	5 (1.8)	1.8	2 (0.7)	0.7
Headache	4 (1.5)	7 (2.5)	1.0	6 (2.2)	0.7
Myocardial infarct	0	4 (1.4)	1.4	1 (0.4)	0.4
Dyspepsia	4 (1.5)	7 (2.5)	1.0	5 (1.8)	0.3
Dyspnea	4 (1.5)	5 (1.8)	0.3	1 (0.4)	-1.1

Table 3.0.1

Constipation was the most frequently reported adverse event for patients randomized to ranolazine with the 1000 mg dose group reporting more (6.6%) than the 750 mg dose (5.8%). Dizziness was the next most frequently reported event with the 1000 mg dose group reporting more (5.0%) than the 750 mg dose group (1.7%). Syncope was reported by 5 subjects, all from the 1000 mg dose group and 4 of these 5 subjects were taking concomitant diltiazem.

Serious safety

The table below shows the number and percent of patients how reported early withdrawal for an adverse event, a serious adverse event, and/or death.

No. and (percent) of patients

	Placebo N=269	Ran 750 mg N=279	Placebo subtracted (%)	Ran 1000 mg N=275	Placebo subtracted (%)
Death	3 (1.1)	2 (0.7)	-0.4	1 (0.4)	-0.7
Serious adverse event	15 (5.6)	20 (7.2)	1.6	19 (6.9)	1.3
Early withdrawal for AE	16 (5.9)	22 (7.9)	2.0	25 (9.1)	3.2

Table 3.0.0

There were 6 reported deaths with half occurring in the placebo group (3 placebo, 2 ranolazine 750 mg and 1 ranolazine 1000 mg).

There were more reported serious events in the ranolazine 1000 mg group (6.9%) and ranolazine 750 mg (7.2%), compared to placebo (5.6%). In addition, compared to placebo, there were more reported withdrawals for adverse event in the ranolazine 1000 mg group (9.1%) and the ranolazine 750 mg group (7.9%).

Deaths

There were 6 deaths and they are listed in the table below.

Patient ID	Treatment group/background med	Duration of treatment (days)	Cause of death
177/9027	Ranol 750 mg/amlodipine	33	Acute MI
704/7600	Ranol 750 mg/diltiazem	18	Sudden death
706/9575	Ranol 1000	13	Sudden death

	mg/amlodipine		
710/7631	Placebo diltiazem	18	Sudden death
717/8668	Placebo/atenolol	6	Acute coronary insufficiency
751/9386	Placebo/amlodipine	83	Cardiac arrest

Tables 3.2.0 and 3.2.1

There were 3 deaths reported in the placebo group, 2 in the ranolazine 750 mg group and 1 in the ranolazine 1000 mg group. The causes of deaths are not unusual for this type of patient population.

Serious adverse events
The numbers and percents of patients reporting a serious event are shown below by event.

Table 12G Incidence of Serious Adverse Events Occurring on or after Visit 2 by Body System and Preferred Term, N (%): Safety Population

COSTART Body System and Preferred Term	Treatment		
	Placebo (n=269)	Ranolazine SR 750 mg (n=279)	Ranolazine SR 1000 mg (n=275)
Patients with at least one SAE	**15 (5.6)**	**20 (7.2)**	**19 (6.9)**
Body as a whole	**2 (0.7)**	**2 (0.7)**	**3 (1.1)**
Asthenia	0	0	1 (0.4)
Carcinoma	0	1 (0.4)	0
Death	1 (0.4)	0	0
Headache	0	0	2 (0.7)
Sudden Death	1 (0.4)	1 (0.4)	1 (0.4)
Cardiovascular	**10 (3.7)**	**15 (5.4)**	**13 (4.7)**
Angina Pectoris	8 (3.0)	7 (2.5)	3 (1.1)
Bradycardia	0	0	1 (0.4)
Cerebral Ischemia	0	0	1 (0.4)
Cerebrovascular Accident	0	0	1 (0.4)
Coronary Artery Disorder	2 (0.7)	2 (0.7)	1 (0.4)
Heart Arrest	0	0	1 (0.4)
Hypotension	0	0	1 (0.4)
Myocardial Infarct	0	4 (1.4)	1 (0.4)
Myocardial Ischemia	0	2 (0.7)	0
Sinus Bradycardia	0	0	1 (0.4)
Syncope	0	0	3 (1.1)
Digestive	**0**	**1 (0.4)**	**2 (0.7)**
Cholecystitis	0	0	1 (0.4)
Colitis	0	1 (0.4)	0
Nausea	0	0	1 (0.4)
Metabolic and Nutritional	**0**	**1 (0.4)**	**0**
Dehydration	0	1 (0.4)	0
Musculoskeletal	**1 (0.4)**	**0**	**0**
Arthritis	1 (0.4)	0	0
Nervous	**0**	**1 (0.4)**	**3 (1.1)**
Dizziness	0	0	2 (0.7)
Meningitis	0	1 (0.4)	0
Vertigo	0	0	1 (0.4)
Respiratory	**2 (0.7)**	**0**	**1 (0.4)**
Bronchitis	1 (0.4)	0	0
Pneumonia	1 (0.4)	0	1 (0.4)
Special	**0**	**0**	**1 (0.4)**
Tinnitus	0	0	1 (0.4)

Note: Data presented in this table are located in Tables 3.0.0 and 3.0.4.
Multiple occurrences of the same event are counted once per patient using the maximum severity.

Cardiovascular events combined were reported by ranolazine subjects more often than placebo (3.7%) compared to the ranolazine groups (5.4% and 4.7% for 750 mg and 1000 mg, respectively).

Serious adverse events reported by 3 or more subjects in 1 or both of the ranolazine groups and reported by more ranolazine subjects than placebo subjects include myocardial infarct and syncope. On the other hand, angina pectoris was reported more often by placebo patients. No particular event, other than syncope (all in ranolazine 1000 mg), was convincingly reported more often in the ranolazine group compared to placebo.

The patients taking concomitant diltiazem with ranolazine had more serious adverse events compared to patients taking atenolol or amlodipine (table 3.0.6).

Withdrawals for adverse events

Table 12H Number of Patients with Adverse Events Leading to Discontinuation of Study Drug: Safety Population

	Treatment			
	Placebo	Ranolazine SR 750 mg	Ranolazine SR 1000 mg	Total
Number (%) of patients with adverse events leading to study drug discontinuation	16 (5.9)	22 (7.9)	25 (9.1)	63 (7.6)
Number of events leading to study drug discontinuation	17	41	47	105

Note: Data summarized above is presented in Table 3.0.0.

Adverse events leading to discontinuation reported for more than one subject included nausea, headache, asthenia, dyspnea, dyspepsia, palpitations, syncope, angina pectoris, dizziness, atrial fibrillation, myocardial infarction, constipation, myasthenia, abdominal pain, tinnitus, vomiting, coronary artery disorder, myocardial ischemia and sudden death.

The table below shows the adverse event leading to discontinuation in 3 or more ranolazine subjects and more in the ranolazine than the placebo subjects are shown below.

No. and (percent) who discontinued for adverse event

	Placebo N=269	Ran 750 mg N=279	Ran 1000 mg N=275	Total ranol N=554	% Placebo subtracted
Total discont	16 (5.9)	22 (7.9)	25 (9.1)	47 (8.5)	2.6
Nausea/N&V/vomiting	0	2 (0.7)	6 (2.2)	8 (2.9)	2.9
Dizziness	1 (0.4)	2 (0.7)	7 (2.5)	9 (1.6)	1.2
Constipation	0	2 (0.7)	2 (0.7)	4 (0.7)	0.7
Asthenia	0	1 (0.4)	3 (1.1)	4 (0.7)	0.7
Syncope	0	0	3 (1.1)	3 (0.5)	0.5
Headache	0	1 (0.4)	2 (0.7)	3 (0.5)	0.5
MI	0	2 (0.7)	1 (0.4)	3 (0.5)	0.5
Myocardial ischemia	1 (0.4)	2 (0.7)	1 (0.4)	3 (0.5)	0.1

Attachment 6 dated 3-18-03

Nausea (with the addition of nausea & vomiting and vomiting) was the leading adverse event resulting in discontinuation for the ranolazine group (2.9%), compared to placebo (0). Dizziness was the next most cited adverse event followed by constipation and asthenia. Syncope was reported only by the high dose group.

Patients were more likely to discontinue study early because of an adverse event if they were receiving diltiazem and ranolazine (table 3.0.6).

Syncope

There were patients reporting serious syncope/dizziness and they are listed in the table below.

Patient ID	Treatment group/background med	Days on drug at time of event	Comments
174/7012	Ranolazine 1000/diltiazem	3	Lab tests and ECG were reported as normal. Withdrawn from study
530/7169	Ranolazine 1000/diltiazem	9	Experienced dizziness on day 7 followed by syncope 2 days later
549/7219	Ranolazine 1000/diltiazem	5	Witnessed event with loss of consciousness and "jerking movements" and "snorting breathing" Pulse not palpable, systolic BP 88 mmHg. Remained on drug.
562/8071	Ranolazine 1000/atenolol	70	This 86 year old female was hospitalized for syncope reported as mild. Withdrawn from drug.
569/7065	Ranolazine 1000/diltiazem	17 and 33	Treatment interrupted
177/7406	Ranolazine 1000/diltiazem	18	Nausea and vomiting followed by syncope. Withdrawn from study

Appendix 14.7.2

There were 5 patients reporting syncope as an adverse event. Of the 5, 4 were receiving ranolazine 1000 mg plus diltiazem and 1 was receiving ranolazine 1000 mg plus atenolol.

Clinical Laboratory

Hematology

The mean changes from baseline at the last double blind visit are shown below by treatment group.

Table 12l Mean Change from Baseline Hematology Results at the Last Double-Blind Visit: Safety Population

Parameter	Statistic	Treatment		
		Placebo	Ranolazine SR 750 mg	Ranolazine SR 1000 mg
Hemoglobin (g/dL)	N	213	236	221
	Mean	-0.11	-0.55	-0.56
	SE	0.06	0.06	0.05
	Range	-3.1, 2.1	-4.5, 2.2	-3.0, 1.8
Hematocrit (%)	N	211	229	218
	Mean	0.1	-1.0	-1.2
	SE	0.2	0.2	0.2
	Range	-10, 11	-11, 10	-9, 6
WBC ($x10^3$/uL)	N	213	236	221
	Mean	-0.190	-0.159	-0.265
	SE	0.102	-0.16	0.105
	Range	-7.28, 3.22	-5.45, 10.13	-5.11, 6.73
Neutrophils (%)	N	213	236	221
	Mean	0.21	1.73	1.67
	SE	0.47	1.7	0.44
	Range	-29.2, 19.0	-18.0, 27.2	-20.0, 22.0
Lymphocytes (%)	N	213	236	221
	Mean	0.07	-1.61	-1.39
	SE	0.40	0.41	0.39
	Range	-15.7, 19.5	-24.3, 19.4	-19.0, 15.5
Monocytes (%)	N	213	236	221
	Mean	-0.14	-0.05	-0.07
	SE	0.11	0.12	0.11
	Range	-6.3, 7.8	-7.2, 9.4	-6.0, 4.8
Eosinophils (%)	N	213	236	221
	Mean	-0.16	-0.04	-0.11
	SE	0.10	0.12	0.11
	Range	-6.5, 6.5	-6.0, 13.2	-9.3, 5.9
Basophils (%)	N	213	236	221
	Mean	0.01	-0.04	-0.10
	SE	0.04	0.04	0.04
	Range	-2.1, 2.7	-2.6, 2.2	-2.2, 2.0
Bands (%)	N	213	236	221
	Mean	0.00	0.00	0.00
	SE	0.00	0.0	0.0
	Range	-0.3, 0.0	0.0, 0.0	0.0, 0.0
RBC ($x10^6$/uL)	N	213	236	221
	Mean	-0.03	-0.25	-0.30
	SE	0.02	0.02	0.02
	Range	-1.1, 0.8	-2.3, 0.8	-1.2, 0.4
Platelets ($x10^3$/uL)	N	204	228	215
	Mean	5.8	11.8	7.1
	SE	3.2	2.6	2.5
	Range	-166, 273	-132, 135	-127, 154

Note: Baseline is the visit closest to Visit 1
Data presented in this table are located in Tables 3.3.0.1.1 to 3.3.0.1.11

There were decreases in hemoglobin, hematocrit, and RBCs in all three treatment groups but more so in the ranolazine groups.

Mean changes from baseline at endpoint and (SE)

Parameter	Means		
	Placebo	Ranol 750 mg	Ranol 1000 mg
Hemoglobin g/dl	-0.11 (0.06)	-0.55 (0.06)	-0.56 (0.05)
Hematocrit %	0.1 (0.2)	-1.0 (0.2)	-1.2 (0.2)
RBC (10^6/uL)	-0.03 (0.02)	-0.25 (0.02)	-0.3 (0.02)

Table 12I

Shift changes for the 3 hematology parameters are shown below.

CVT 3033

TABLE 3.3.0.2.1

Hematology Results
Hemoglobin (g/dL)
Shift Values by Treatment and Visit
Summary Statistics: Safety Population

Baseline	Last Double Blind Visit	Placebo n	Placebo (%)	Ran SR 750 mg n	Ran SR 750 mg (%)	Ran SR 1000 mg n	Ran SR 1000 mg (%)
Low	Low	7	(3.3)	7	(3.0)	9	(4.1)
	Normal	4	(1.9)	2	(0.8)	1	(0.5)
	High	0		0		0	
Normal	Low	3	(1.4)	9	(3.8)	6	(2.7)
	Normal	192	(90.1)	210	(89.0)	200	(90.5)
	High	2	(0.9)	0		1	(0.5)
High	Low	0		0		0	
	Normal	4	(1.9)	7	(3.0)	2	(0.9)
	High	1	(0.5)	1	(0.4)	2	(0.9)

CVT 3033

TABLE 3.3.0.2.1

Hematology Results
Hemoglobin (g/dL)
Shift Values by Treatment and Visit
Summary Statistics: Safety Population

Baseline	Last Double Blind Visit	Placebo n	Placebo (%)	Ran SR 750 mg n	Ran SR 750 mg (%)	Ran SR 1000 mg n	Ran SR 1000 mg (%)
Low	Low	7	(3.3)	7	(3.0)	9	(4.1)
	Normal	4	(1.9)	2	(0.8)	1	(0.5)
	High	0		0		0	
Normal	Low	3	(1.4)	9	(3.8)	6	(2.7)
	Normal	192	(90.1)	210	(89.0)	200	(90.5)
	High	2	(0.9)	0		1	(0.5)
High	Low	0		0		0	
	Normal	4	(1.9)	7	(3.0)	2	(0.9)
	High	1	(0.5)	1	(0.4)	2	(0.9)

CVT 3033

TABLE 3.3.0.2.10

Hematology Results
RBC (x10^6/uL)
Shift Values by Treatment and Visit
Summary Statistics: Safety Population

Baseline	Last Double Blind Visit	Placebo n	Placebo (%)	Ran SR 750 mg n	Ran SR 750 mg (%)	Ran SR 1000 mg n	Ran SR 1000 mg (%)
Low	Low	7	(3.3)	7	(3.0)	5	(2.3)
	Normal	5	(2.3)	3	(1.3)	0	
	High	0		0		0	
Normal	Low	3	(1.4)	14	(5.9)	20	(9.0)
	Normal	198	(93.0)	211	(89.4)	196	(88.7)
	High	0		0		0	
High	Low	0		0		0	
	Normal	0		0		0	
	High	0		1	(0.4)	0	

There were more subjects in the ranolazine groups compared to placebo who were normal at baseline and became abnormally low at endpoint.

Clinical chemistry

The mean changes from baseline at the last double blind visit are shown below by treatment group.

Table 12K Mean Change from Baseline Clinical Chemistry at the Last Double-Blind Visit: Safety Population

Parameter	Statistic	Treatment		
		Placebo	Ran SR 750mg	Ran SR 1000mg
Urea Nitrogen (mg/dL)	N	250	263	256
	Mean	-0.1	1.1	1.1
	SE	0.3	0.3	0.3
	Range	-14, 15	-18, 12	-16, 16
Glucose (mg/dL)	N	235	252	246
	Mean	0.9	2.7	0.6
	SE	1.9	2.4	1.9
	Range	-135, 162	-224, 216	-184, 135
AST (U/L)	N	238	256	246
	Mean	0.3	-1.4	-2.3
	SE	0.9	0.7	0.4
	Range	-93, 101	-38, 109	-35, 18
ALT (U/L)	N	238	256	246
	Mean	-0.6	-2.5	-4.0
	SE	1.0	0.7	0.7
	Range	-100, 122	-46, 88	-46, 35
Alk Phos (U/L)	N	247	262	254
	Mean	-0.1	-3.3	-6.0
	SE	0.7	0.8	0.9
	Range	-42, 50	-90, 43	-144, 30
LDH (U/L)	N	243	254	251
	Mean	2.8	1.9	-3.4
	SE	2.2	2.4	1.5
	Range	-102, 294	-72, 391	-87, 81
Sodium (mEq/L)	N	250	263	254
	Mean	0.0	-0.6	-0.7
	SE	0.2	0.2	0.2
	Range	-8, 11	-13, 6	-9, 9
Potassium (mEq/L)	N	246	258	252
	Mean	-0.06	0.03	-0.02
	SE	0.03	0.03	0.03
	Range	-1.2, 1.5	-1.6, 1.2	-1.0, 1.2
Bicarbonate (mEq/L)	N	237	253	245
	Mean	-0.10	-0.03	0.13
	SE	0.18	0.17	0.18
	Range	-9.5, 10.3	-8.1, 8.9	-10.3, 9.1
Chloride (mEq/L)	N	250	263	254
	Mean	0.0	-0.7	-0.6
	SE	0.2	0.2	0.2
	Range	-11, 8	-10, 7	-10, 7
Creatinine (mg/dL)	N	250	264	256
	Mean	0.02	0.09	0.06
	SE	0.01	0.01	0.01
	Range	-0.6, 0.7	-0.4, 1.3	-0.8, 0.5

Note: Baseline is the visit closest to Visit 1
Data presented in this table are located in Tables 3.3.2.1.1 to 3.3.2.1.22

Table 12K (continued): Mean Change from Baseline Clinical Chemistry at the Last Double Blind Visit: Safety Population

Parameter	Statistic	Treatment		
		Placebo	Ran SR 750mg	Ran SR 1000mg
Phosphorus (mg/dL)	N	246	258	254
	Mean	0.02	0.08	0.08
	SE	0.03	0.03	0.04
	Range	-1.7, 1.5	-2.0, 1.4	-2.5, 2.0
Calcium (mg/dL)	N	250	264	256
	Mean	0.03	-0.01	-0.02
	SE	0.03	0.03	0.03
	Range	-1.1, 1.2	-1.4, 1.4	-1.1, 1.2
Total Bilirubin (mg/dL)	N	235	255	246
	Mean	0.00	0.01	-0.01
	SE	0.01	0.01	0.01
	Range	-0.6, 0.8	-0.7, 1.3	-0.7, 0.5
GGT (U/L)	N	250	264	256
	Mean	-1.8	-10.8	-12.2
	SE	1.1	1.6	1.9
	Range	-111, 71	-291, 71	-329, 47
CPK (U/L)	N	238	255	246
	Mean	8.8	-5.6	-12.4
	SE	8.7	4.7	4.0
	Range	-1636, 486	-355, 802	-496, 327
Uric Acid (mg/dL)	N	250	264	256
	Mean	0.07	-0.32	-0.41
	SE	0.05	0.05	0.06
	Range	-2.4, 5.2	-4.6, 2.9	-3.7, 2.7
Triglycerides (mg/dL)	N	250	262	255
	Mean	2.9	17.1	7.8
	SE	5.8	5.8	4.7
	Range	-218, 987	-331, 448	-292, 271
Cholesterol (mg/dL)	N	250	263	255
	Mean	-4.0	13.7	10.5
	SE	1.7	2.0	2.0
	Range	-102, 82	-95, 169	-107, 169
VLDL (mg/dL)	N	250	262	255
	Mean	0.6	3.4	1.6
	SE	1.2	1.2	0.9
	Range	-44, 197	-66, 89	-58, 54
LDL (mg/dL)	N	242	243	242
	Mean	-3.6	8.2	3.6
	SE	1.6	1.8	1.7
	Range	-105, 60	-80, 162	-106, 89
HDL (mg/dL)	N	250	262	255
	Mean	-0.3	2.4	3.6
	SE	0.4	0.5	0.5
	Range	-43, 21	-41, 63	-26, 33

Note: Baseline is the visit closest to Visit 1
Data presented in this table are located in Tables 3.3.2.1.1 to 3.3.2.1.22

Nothing seems alarming.

Resting ECG

Standard supine 12-lead ECGs were obtained at Screening (Visit 1), at trough at Visits 2-6 (or early withdrawal), and peak at Visits 2, 3,and 5, and whenever clinically indicated. The ECG was to be inspected by the investigator to ensure patient safety. The QT interval was to be examined for evidence of prolongation. Any other new clinically significant ECG findings appearing during treatment with study medication was to be discussed with a study monitor to determine whether the patient should continue in the study.

Official reading of each ECG for analysis was measured on the supine rest electrocardiogram and performed by the ECG core laboratory. The patient was to be withdrawn from the study and monitored to ensure the QTc returned to baseline if, at any point during the study, the QTc interval widened to 130% of its duration at Visit 2 and was longer than 500 msec.

In the ECG safety population, key parameters from the centrally coded electrocardiogram (e.g., corrected QT interval, T wave amplitude, T wave notching) were to be analyzed using analysis of variance for continuous measures or Cochran-Mantel-Haenszel tests for categorical measures.

ECG Interval changes

Mean ECG changes from baseline at week 12 at peak (4 hrs $\pm$ 0.5 after dosing) drug concentrations are shown below.

Table 12S Statistical Analysis of ECG Variables at Peak at Week 12 by Treatment: Safety Population

Variable		Treatment	
		Ranolazine SR 750 mg vs Placebo	Ranolazine SR 1000 mg vs placebo
Heart Rate	Mean difference (b.p.m)	-1.5	-0.8
	SE of mean difference	0.8	0.8
	Confidence interval	-3.0, 0.1	-2.4, 0.8
	p-value	0.066	0.33
PR Interval	Mean difference (ms)	2.3	2.4
	SE of mean difference	1.5	1.5
	Confidence interval	-0.6, 5.3	-0.6, 5.4
	p-value	0.12	0.12
QRS Interval	Mean difference (ms)	2.2	2.0
	SE of mean difference	0.9	0.9
	Confidence interval	0.4, 3.9	0.2, 3.7
	p-value	0.014	0.030
T amplitude	Mean difference (ms)	-0.6	-0.8
	SE of mean difference	0.1	0.1
	Confidence interval	-0.8, -0.3	-1.0, -0.5
	p-value	<0.001	<0.001
QT Interval	Mean difference (ms)	11.2	11.7
	SE of mean difference	2.3	2.3
	Confidence interval	6.7, 15.7	7.1, 16.2
	p-value	<0.001	<0.001
QTc Interval (Bazett)	Mean difference (ms)	6.1	9.2
	SE of mean difference	1.3	1.4
	Confidence interval	3.5, 8.8	6.5, 11.9
	p-value	<0.001	<0.001
QT Dispersion	Mean difference (ms)	2.2	0.0
	SE of mean difference	1.3	1.3
	Confidence interval	-0.3, 4.7	-2.5, 2.6
	p-value	0.079	0.97

Note: Data summarized above are located in Tables 3.8.5.0, 3.8.6.0, 3.8.7.0, 3.8.8.0, 3.8.9.0, 3.8.13.0 and 3.8.14.0.

Heart rate was essentially unchanged by ranolazine. Mean changes in QT and QTc intervals were significantly longer ($p<0.001$) in the ranolazine 750 mg and ranolazine 1000mg groups compared to placebo.

T wave amplitude decreased significantly ($p<0.001$) from baseline in both ranolazine groups compared to placebo.

The table below shows the QT interval changes at weeks 2 and 12 comparing the ranolazine groups to placebo using ANCOVA model.

CVT 3033

TABLE 3.8.8.0
ECG Safety Analysis: QT Interval at Peak at Week 2 and 12
Comparison of Treatment Differences from ANCOVA Model 1
Statistical Analysis: ECG Safety Population

Assessment	Statistic	Ran SR 750 mg vs Placebo	Ran SR 1000 mg vs Placebo
Week 2	Mean Difference	7.5	8.6
	S.E. of Mean Difference	2.0	2.0
	95% Confidence Interval	(3.6,11.4)	(4.6,12.6)
	P-value	<0.001	<0.001
Week 12	Mean Difference	11.2	11.7
	S.E. of Mean Difference	2.3	2.3
	95% Confidence Interval	(6.7,15.7)	(7.1,16.2)
	P-value	<0.001	<0.001

Note: Model 1 for Week 2 includes effects for treatment (p=<0.001), baseline covariate (p=<0.001), pooled site(p= 0.083) and background therapy (p=<0.001) using TYPE III sum of squares
Note: Model 1 for Week 12 includes effects for treatment (p=<0.001), baseline covariate (p=<0.001), pooled site(p= 0.034), and background therapy (p=<0.001) using TYPE III sum of squares
Note: P values obtained from ANCOVA model adjusted for stated effects
Note: Mean difference and SE of mean difference are Least Squares mean estimates from ANCOVA model
Note: Baseline covariate is the QT Interval at peak obtained from Visit 2

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Mean differences of ranolazine versus placebo for QT interval at peak were 7.5 msec at week 2 and 11.2 msec at week 12 for ranolazine 750 mg and 8.6 msec for ranolazine 1000 mg at week 2 and 11.7 msec at week 12. Both doses at both time points were statistically significantly different from placebo (p<0.001).

The upper limits of the 95% confidence interval for change at peak at week 12 were 15.7 msec for the 750 mg dose and 16.2 msec for the 1000 mg dose.

The table below shows the number and percent of patients with selected QT changes from baseline, by treatment group.

No. and (percent) of patient with selected QT changes

QT changes from baseline msec	Placebo N=257		Ranolazine 750 mg N=271		Ranolazine 1000 mg N=255	
	Week 2	Week 12	Week 2	Week 12	Week 2	Week 12
0-<30	123 (48)	102 (42)	125 (46)	121 (48)	134 (53)	112 (47)
30-<60	9 (4)	12 (5)	29 (11)	33 (13)	26 (10)	34 (14)
≥60	4 (2)	5 (2)	12 (4)	13 (5)	9 (4)	12 (5)

Attachment 3 dated 3-18-03

The percents of patients with prolonged QT intervals at Weeks 2 and 12 are at least twice as high in the ranolazine groups compared to placebo. There is little difference between the ranolazine groups.

Trough changes

Mean ECG changes from baseline at week 12 at trough drug concentrations are shown below.

Table 12Q Statistical Analysis of ECG Variables at Trough at Week Treatment: Safety Population

Variable		Treatment	
		Ranolazine SR 750 mg vs Placebo	Ranolazine SR 1000 mg vs placebo
Heart Rate	Mean difference (b.p.m)	-1.1	-0.5
	SE of mean difference	0.8	0.8
	Confidence interval	-2.6, 0.4	-2.0, 1.1
	p-value	0.14	0.56
PR Interval	Mean difference (ms)	0.9	0.6
	SE of mean difference	1.4	1.4
	Confidence interval	-1.8, 3.7	-2.2, 3.4
	p-value	0.51	0.66
QRS Interval	Mean difference (ms)	0.8	1.3
	SE of mean difference	0.9	0.9
	Confidence interval	-0.9, 2.5	-0.5, 3.0
	p-value	0.36	0.16
T amplitude	Mean difference (ms)	-0.4	-0.6
	SE of mean difference	0.1	0.1
	Confidence interval	-0.7, -0.2	-0.8, -0.4
	p-value	<0.001	<0.001
QT interval	Mean difference (ms)	8.5	10.0
	SE of mean difference	2.0	2.1
	Confidence interval	4.5, 12.5	5.9, 14.1
	p-value	<0.001	<0.001
QTc Interval (Bazett)	Mean difference (ms)	4.5	7.7
	SE of mean difference	1.1	1.2
	Confidence interval	2.3, 6.7	5.4, 10.0
	p-value	<0.001	<0.001
QT Dispersion	Mean difference (ms)	0.5	-0.5
	SE of mean difference	1.2	1.2
	Confidence interval	-1.9, 2.8	-2.9, 1.9
	p-value	0.70	0.70

Note: Data summarized above are located in Tables 3.7.6.0, 3.7.7.0, 3.7.8.0, 3.7.9.0, 3.7.10.0, 3.7.14.0 and 3.7.15.0.

As with peak effects, the mean changes at week 12 for QT and QTc intervals at trough were statistically significantly greater compared to placebo (8.5 msec and 4.5 msec for ranolazine 750 mg, respectively, and 10.0 msec and 7.7 msec for ranolazine 1000mg, respectively). There was little effect on heart rate, but the effect on T wave amplitude was significantly different from placebo for both treatment groups.

The table below shows the number and percent of patients with selected QTc changes from baseline, by treatment group, at weeks 2, 6 and 12.

No. and (percent) of patient with selected QTc changes

	Placebo		Ranolazine 750 mg		Ranolazine 1000 mg	
QT changes from baseline msec	Week 6	Week 12	Week 6	Week 12	Week 6	Week 12
<0	141 (56)	134 (54)	102 (38)	112 (44)	89 (35)	78 (33)
0-<30	110 (43)	112 (45)	156 (59)	134 (52)	154 (61)	152 (63)
30-<60	1 (0)	0	4 (2)	8 (3)	4 (2)	6 (3)

Table 3.7.10.6.1

The incidence rates for QTc changes less than 0 msec at weeks 6 and 12 were higher for placebo than for the 2 ranolazine groups. For changes greater than 0 msec, incidence rates greater than 0 msec at both weeks were higher for the ranolazine groups than placebo groups.

T wave morphology

Changes in T wave morphology by drug group are shown below.

CVT 3033 TABLE 3.8.0 Page 2 of 3

ECG Characteristics at Peak Levels of Ranolazine SR
By Treatment and Week
Summary Statistics: ECG Safety Population

	Stati	Placebo		Ran SR 750 mg		Ran SR 1000 mg	
	stic	2	12	2	12	2	12
T Wave Morphology							
Positive	N (%)	237(92.2)	224(91.8)	228(84.1)	221(87.7)	237(92.9)	207(87.0)
Negative	N (%)	6(2.3)	5(2.0)	18(6.6)	13(5.2)	4(1.6)	5(2.1)
Flat	N (%)	3(1.2)	5(2.0)	4(1.5)	5(2.0)	0	5(2.1)
Biphasic (+/-)	N (%)	6(2.3)	4(1.6)	4(1.5)	4(1.6)	6(2.4)	6(2.5)
Biphasic (-/+)	N (%)	3(1.2)	5(2.0)	4(1.5)	4(1.6)	2(0.8)	7(2.9)
Notched	N (%)	1(0.4)	0	11(4.1)	3(1.2)	5(2.0)	8(3.4)
Major T Wave							
Yes	N (%)	42(16.3)	37(15.2)	43(15.9)	39(15.5)	31(12.2)	28(11.8)
No	N (%)	215(83.7)	207(84.8)	228(84.1)	213(84.5)	224(87.8)	210(88.2)
Minor T Wave							
Yes	N (%)	67(26.1)	76(31.1)	89(32.8)	80(31.7)	68(26.7)	68(28.6)
No	N (%)	190(73.9)	168(68.9)	182(67.2)	172(68.3)	187(73.3)	170(71.4)
Left Ventricular Hypertrophy	N (%)	32(12.5)	24(9.8)	19(7.0)	21(8.3)	29(11.4)	27(11.3)

Note: Data summarised in the above table are listed in data listings 9.2.3.1, 9.2.3.2 and 9.3

03APR2002 08:50

The numbers of patients with notched T waves were greater in the ranolazine groups.

No of patients with notched T waves

	Placebo		Ranolazine 750 mg		Ranolazine 1000 mg	
	peak	trough	peak	trough	peak	trough
Week 2	1	1	11^	7	5#	8
Week 6	-	0	-	4	-	6
Week 12	0	1	3	2	8	4

^2 patients also had notched T waves at baseline/screening
1 patient also had notched T waves at baseline/screening

Subject 218/7250 (ranolazine 1000 mg) was withdrawn on day 12 because of an increase of >25% QTc, asthenia, nausea, and dizziness. Events started on day 1 of study drug dosing.