CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-526/S004

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Memo

Date	October 23, 2008
From	Thomas A. Marciniak, M.D.
Subject	Cross-Discipline Team Leader Review - Updated
NDA/BLA # **Supp #**	NDA 21,526 S-004 (b) (4)
Proprietary / Established (USAN) names	Ranexa® / ranolazine
Dosage forms / strength	extended release tablets / 500 and 1000 mg
Proposed Indication	1. Primary use for the treatment of chronic angina (S-004) (b) (4)
Recommended:	1. Approval for the treatment of chronic angina (S-004) (b) (4)

1. Introduction to Review

Ranexa® (ranolazine) is an oral drug approved on January 27, 2006, for the treatment of chronic angina in patients who have not achieved an adequate response with other antianginal drugs. We specified the secondary use because of concerns about QTc prolongation. While its mechanism of action in angina is not known, ranolazine does affect various cardiac ion currents, including inhibition of the late I_{Na} and I_{Kr}. We believe the QTc prolongation is related to the I_{Kr} inhibition, and other drugs that inhibit I_{Kr} produce both QTc prolongation and torsades de pointes (TdP). The sponsor argues that, despite the I_{Kr} inhibition and QTc prolongation, ranolazine should not cause TdP because of its effects upon other cardiac ion currents. The effect upon QTc is moderate. With repeat dosing, the mean effect on QTc of ranolazine 1000 mg BID at T_{max}, is about 6 msec. In 5% of the population the prolongation of QTc is 15 msec. TdP was not a problem in the clinical trials involving 2,018 patients treated for angina for the original approval.

To secure a first line indication, the sponsor proposed doing a large outcome study (CVT 3036 or MERLIN or TIMI-36) in patients with non-ST segment elevation acute coronary syndrome (ACS). While improvement in the primary efficacy endpoint for this study (the combined endpoint of cardiovascular (CV) death, myocardial infarction (MI), and recurrent ischemia) was not statistically significant, we agreed in a special protocol assessment prior to initiation of the trial that, regardless of winning on the primary efficacy endpoint, no adverse trend in death and arrhythmia would be assuring and could support approval of ranolazine as first-line therapy for long-term treatment of chronic angina. This submission provides the CVT 3036 trial results to support the primary use indication. It also summarizes the results of six other smaller studies to support primary use. (b) (4)

Because the limiting factor for primary use for this drug is safety and because the large outcome trial in this submission provides an unusual opportunity to dissect the safety of a

drug, I summarize the primary clinical and statistical reviewers' conclusions regarding the primary endpoint, and I also discuss briefly the primary clinical reviewer's presentation of the [redacted] (b) (4) I address in detail in this review safety findings. These safety findings include ones suggested by pre-clinical and prior clinical studies as well as new ones suggested by the CVT 3036 results.

The safety issues suggested by prior studies, in addition to the presumed potential for TdP, are the following:

- Ranolazine is metabolized mainly by CYP3A and to a lesser extent by CYP2D6. Plasma levels are increased about 2-fold by the moderate CYP3A4 inhibitors diltiazem and verapamil, drugs used to treat angina. I analyzed the adverse effects by diltiazem and verapamil use to ascertain whether there is any interaction.

- One preclinical study performed by an investigator independent from the sponsor suggests that ranolazine may be carcinogenic: Ranolazine promoted the development of intestinal tumors in APC(Min/+) mice. (Suckow, Gutierrez et al. 2004) Because of these preclinical findings I examined cancer rates in CVT 3036.

- Ranolazine increased serum creatinine by about 0.1 mg/dL in angina patients in the earlier clinical trials. A special study did not confirm decreases in glomerular filtration rate despite the increased creatinines, so the current label concludes that the increased serum creatinine is due to a blockage of creatinine's tubular secretion by ranolazine or one of its metabolites. However, as the IND reviewer, I received many serious adverse event reports of acute renal failure (ARF) from CVT 3036. Because of these reports I scrutinized creatinine changes and renal adverse events in CVT 3036. [redacted] (b) (4)

In addition, the pre-NDA presentations raised an issue relevant to confidence in any safety (or efficacy) findings:

- The pre-NDA meeting materials suggested that there were problems with complete treatment and follow-up, i.e., about 15% of ranolazine and 13% of placebo patients withdrew consent to treatment and about 5% in each group also withdrew consent to follow-up. These withdrawals are high compared to other ACS studies. Our pre-NDA meeting preliminary responses cautioned as follows: "The apparent impediment to interpretation of CVT 3036 is the high rate of early terminations for withdrawal of consent. We would appreciate hearing a brief discussion of why withdrawals of consent, including in the placebo group, were high. In your submission you should document well the circumstances and statuses of all patients terminating early for withdrawal of consent. We note that about 5% of patients lacked follow-up due to withdrawal of consent. If any options are available for securing vital status on these patients, e.g., investigator queries, national registries or death indexes, you should use them and provide the follow-up data in the NDA submission." Hence I scrutinized

There are other safety signals that I detected only after analyzing the trial data. I discuss them under Safety below.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

As discussed in the Introduction to Review, we agreed in a special protocol assessment prior to initiation of the CVT 3036 trial that, regardless of winning on the primary efficacy endpoint, no adverse trend in death and arrhythmia would be assuring and could support approval of ranolazine as first-line therapy for long-term treatment of chronic angina. We also noted in the pre-NDA submission discussions that completeness of follow-up was an issue for this trial.

[redacted] (b) (4) I also incorporate into this updated review my findings from reviews of Holter recordings and discussions with the staff of the TIMI Group responsible for scientific oversight of the study.

3. CMC/Microbiology/Device

There are no outstanding CMC issues for this approved product and the product is an oral drug not requiring special microbiological evaluation. The only CMC document for this submission is an environmental assessment. Please see the FDA chemist's review of that document.

4. Nonclinical Pharmacology/Toxicology

4.1. General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

The general unanswered pharmacologic property for this drug is its mechanism of action in angina.

4.2. Carcinogenicity

As mentioned in the Introduction to Review, ranolazine promoted the development of intestinal tumors in a knockout mouse strain, although it is not mutagenic and was not carcinogenic in mouse and rat long-term carcinogenicity studies. Because of the positive preclinical cancer promoter study, I examined cancer rates in CVT 3036.

4.3. Reproductive toxicology

Ranolazine is pregnancy category C. There are no adequate pre-clinical or clinical studies regarding effects upon fertility, reproductive capacity, fetal development, or pregnancy. However, chronic angina due to atherosclerotic heart disease is a rare disorder in women of child-bearing potential.

4.4. Other notable issues

There are no other notable nonclinical pharmacology or toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

5.1. General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

The general unanswered pharmacologic property for this drug is its mechanism of action in angina.

5.2. Drug-drug interactions

Because of its CYP metabolism and Pgp substrate status, ranolazine interacts with various drugs affecting these pathways. The most relevant question regarding known ranolazine-drug interactions is regarding safety in patients taking the moderate CYP3A4 inhibitors used in angina patients, diltiazem and verapamil. Ranolazine appears to be a CYP3A inhibitor and, at the 1000 mg BID dosage, increases levels of simvastatin (a CYP3A4 substrate) 80 mg about twofold. (b) (4)

5.3. Pathway of elimination

Ranolazine is eliminated partly by CYP3A and CYP2D6 as well as excreted in the urine. Its metabolism is relevant to drug-drug interactions mentioned above. Its excretion in the urine is relevant to the issue of acute renal failure. I show the proposed metabolic pathways of ranolazine in Figure 1. I also show, for comparison, the structures of creatinine in Figure 2 and a typical ACE inhibitor (captopril) in Figure 3—I discuss the relevance of these latter structures under Safety below.

Figure 1: Ranolazine Metabolism

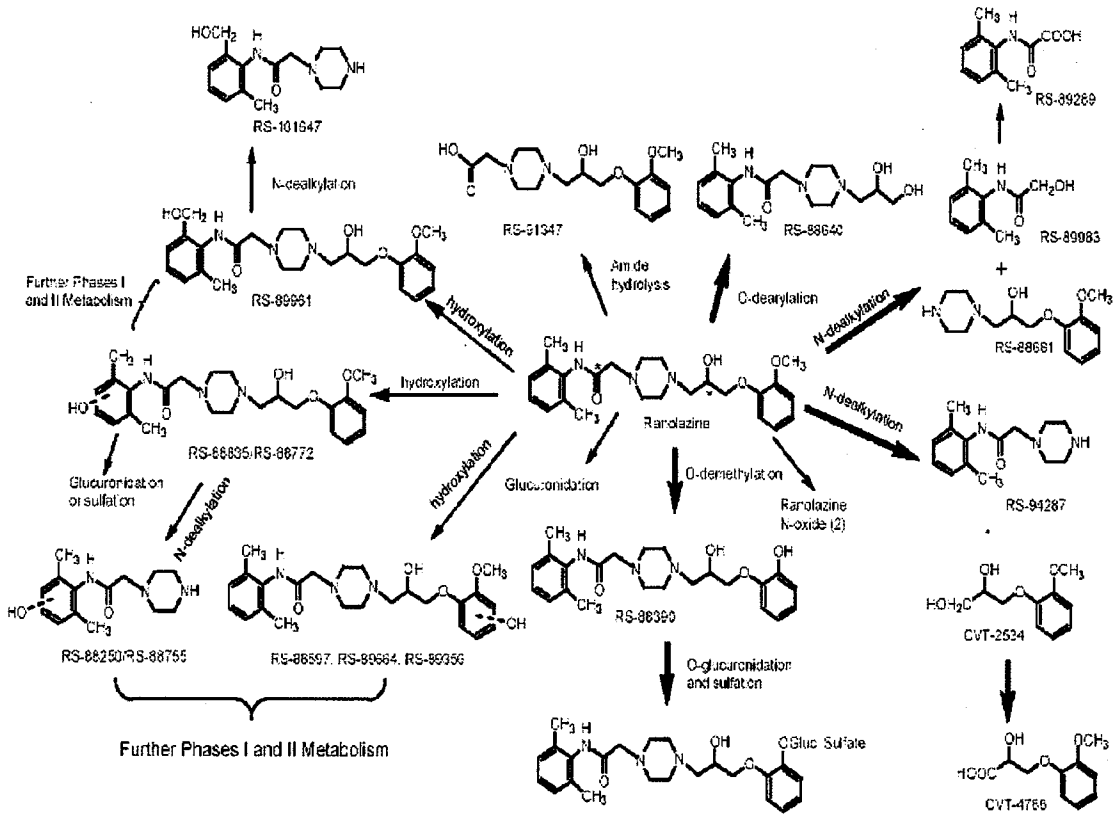


Figure 2: Chemical Structure of Creatinine

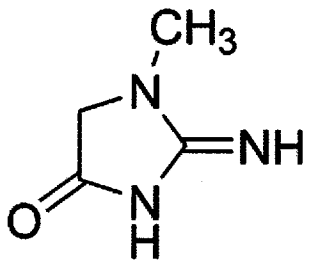
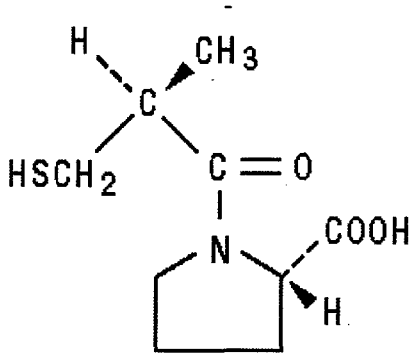


Figure 3: Chemical Structure of Captopril



5.4. Demographic interactions/special populations

Effects on angina frequency and exercise tolerance were considerably smaller in women than in men in the ranolazine angina studies. Because the major trial CVT 3036 for this submission failed for its primary efficacy endpoint, it may not be useful for discerning differential efficacy effects by sex.

5.5. Thorough QT study or other QT assessment

Ranolazine prolongs the QTc interval but has not led to TdP in earlier, smaller clinical studies. CVT 3036 (the large, longer-term clinical trial in this submission) provides the higher exposures needed to document a lack of torsadagenic potential as well as an initial Holter monitoring phase to explore all possible arrhythmogenic effects.

5.6. Other notable issues

There are no other notable clinical pharmacology or biopharmaceutics issues

6. Clinical Microbiology

Ranolazine is an oral non-antimicrobial drug for which there are no clinical microbiology concerns.

7. Clinical/Statistical

7.1. Efficacy

7.1.1. Primary clinical and statistical reviewers' findings and conclusions

7.1.1.1. First line treatment of chronic angina

The primary efficacy endpoint for CVT 3036, a trial in a new population for this drug of non-ST segment elevation acute coronary syndromes (ACS), was a combined endpoint of CV mortality, MI, and recurrent ischemia. The primary clinical and statistical reviewers, as well as the sponsor, agree that this trial failed on this primary endpoint: There were slightly fewer primary endpoint events in the ranolazine group (695 vs. 753), a relative risk of about 0.92 with an insignificant p value of 0.11 by pre-specified time-to-event analysis. Of the components, there were slightly more CV deaths with ranolazine (87 to 78) but less recurrent ischemia (400 vs. 465). Because there is no disagreement that this study failed on its primary endpoint and because the results do not suggest any additional efficacy or safety issues, I will not discuss the primary endpoint or the secondary efficacy endpoints further.

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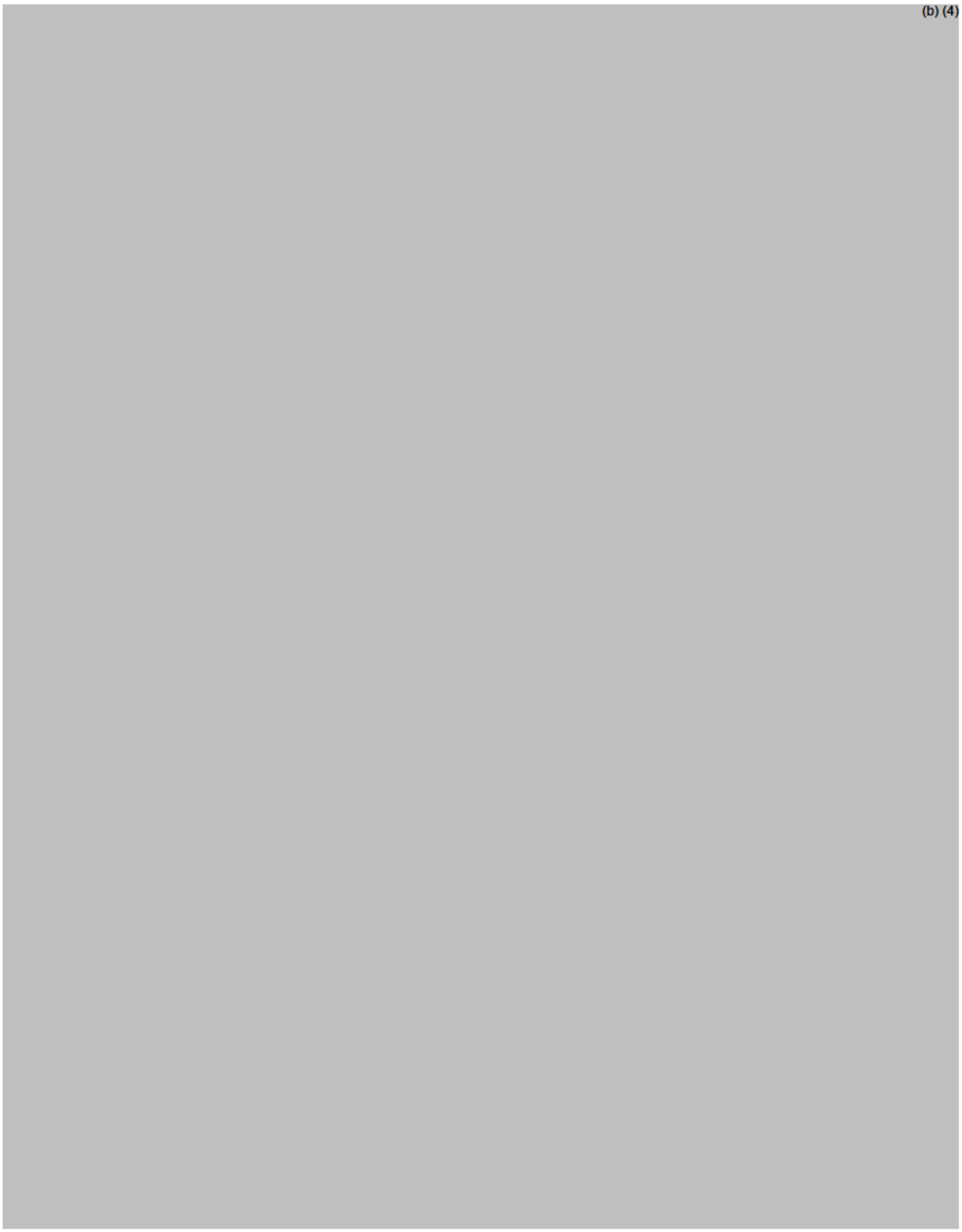


7.1.3. Pediatric use

Stable angina is extremely rare in children, so I am recommending a waiver of pediatric studies.

7.2. Safety

7.2.1. Primary clinical reviewer's findings and conclusions

The primary clinical reviewer makes the following pertinent observations about safety:

- All cause mortality was virtually identical in both treatment groups (5.3%).
- Sudden death rates were also similar (1.7% for ranolazine and 2% for placebo.)
- Rates of symptomatic documented arrhythmias were similar (3.1% and 3.0%).
- Dizziness, constipation, nausea, asthenia, and hypotension were AEs more frequent than 3% and occurring more frequently with ranolazine than placebo.
- Serum creatinine increased slightly and hemoglobin decreased slightly with ranolazine.
- Renal dysfunction (defined as renal failure, renal failure acute, renal impairment, renal failure chronic) was higher with ranolazine (3% vs. 2%).
- In the high dose tolerability study CVT 3023, many subjects were unable to tolerate doses 1500 mg bid and above. Dose limiting adverse events included syncope, nausea, dizziness, and vomiting (25%).

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

7.2.2. Discussion of notable safety issues

One issue regarding the interpretation of this study is data completeness. I discuss it first below, followed by other safety issues that deserve additional comment. They include the ones raised by previous studies and mentioned in the Introduction to Review above. There were also some surprising findings.

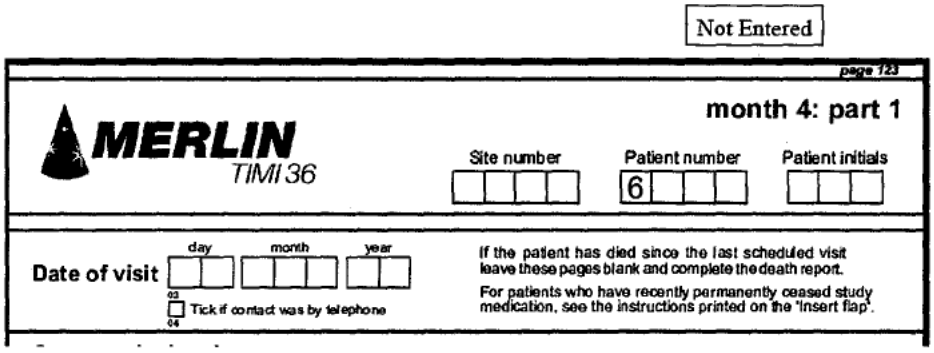
7.2.2.1. Data completeness and quality

The editorial in JAMA (Newby and Peterson 2007) on the CVT 3036 primary results article (Morrow, Scirica et al. 2007) described the study as a "well-designed and rigorously conducted clinical trial." The design is appropriate and most aspects of trial conduct appear good, e.g., the SAE reports are consistent between the IND and the NDA, the case report forms are reasonably detailed and accurate, and the CRFs, SAS data sets, and reports are consistent. However, there is one significant

limitation of the data collection in CVT 3036: a substantial number of patients are reported as withdrew consent to treatment (ranolazine 14%, placebo 12%) and a smaller but still not inconsequential number are reported as withdrew consent to follow-up (about 5% in each group). These numbers are higher than we have seen in other ACS trials. Because withdrawal of consent has not been a major problem for previous trials, the TIMI Group did not monitor statistics regarding it during the trial. They are now working to minimize problems in other on-going trials, but withdrawal of consent remains a problem for CVT 3036.

CVT 3036 was an event-driven trial. The study report notes that the pre-specified number of events was reached and final visits for patients were scheduled starting September 25, 2006. Hence the most relevant follow-up statistic (particularly for more complex determinations such as adverse event evaluations) is the percentage of patients who are not known to be dead and who did not have a follow-up visit on or after September 25, 2006. Determining the dates of follow-up visits is complicated by another problem: The CRF has 116 different forms with some forms completed at multiple visits. There are a vast number of fields, the majority of which the sponsor entered into the study data sets. Two critical fields that the sponsor reports not to have entered are the dates of the visits and whether the contact was by phone. I have show an excerpt from a typical visit form from the sponsor's annotated blank CRFs in Figure 5.

Figure 5 : Typical Visit CRF Header from the Sponsor's Annotated Blank CRFs for CVT 3036



The sponsor provided this surrogate for documentation of a visit: "a study visit was defined by evaluable (non-missing) data from at least one test or procedure that required the patient to be present at the study site or at a hospital. A test or procedure could include physical examination, vital signs, 12-lead ECG, Holter monitor, laboratory test, exercise tolerance test, quality-of-life questionnaire, hospitalization, angiogram, or a revascularization procedure. A test or procedure with partial dates was not considered as a "known" visit." I calculated that 14% of ranolazine and 13% of placebo patients had incomplete follow-up using the sponsor's dates for a last visit by this surrogate, counting patients not known to be dead as having incomplete follow-up if their last visits were prior to September 25, 2006.

The subgroups with complete and incomplete follow-up differ substantially: The mean duration of follow-up patients with incomplete follow-up was about 4.1 months compared to 11.6 months for patients with complete follow-up in both treatment groups. The patients with incomplete follow-up were similar in age but included more women (40% vs. 35%). Rates of AEs leading to withdrawals were substantially different among the subgroups as shown in Table 2 as were rates of SAEs as shown in Table 3.

Table 2: Rates of AEs Leading to Withdrawals by Treatment and Follow-up Status in CVT 3036

	follow-up	
	incomplete	complete
placebo	20%	9%
ranolazine	27%	14%

Table 3: Rates of SAEs by Treatment and Follow-up Status in CVT 3036

	follow-up	
	incomplete	complete
placebo	32%	38%
ranolazine	26%	39%

While it is slightly reassuring that the percentage in each group is about the same, 17% incomplete follow-up could obscure many problems—it is substantially greater than the absolute rates of some the serious AEs identified below (angioedema, leucopenia) and greater than the differences in most serious AEs (e.g., cancer). The differences sex and particularly the differences in AE withdrawals and SAE rates confirm that the incomplete follow-up subjects can not be considered missing completely at random. Any observed differences in AEs must be interpreted in view of the possibilities that the differences are underestimated.

Completeness of follow-up is not the only data quality issue for CVT 3036. I requested lot numbers of drugs with the intention of checking whether any variations in AE rates could be related to specific lot numbers. However patients in CVT 3036 were not dispensed consistent lot numbers even at the same visit. I show the distributions of lot numbers for the oral study drugs in Table 4.

Table 4: Distributions of Oral Study Drug Lot Numbers Dispensed at One Visit in CVT 3036

	placebo		ranolazine	
	n	%	n	%
2H2794, 3E2720	37	0.2%		
A01548, A01645	202	1.1%		
2H2795	237	1.3%		
2H2795, 3E2718	616	3.3%		

	placebo		ranolazine	
	n	%	n	%
A09761, A09762, A09763, A09765	1410	7.5%		
3I2776, 3I2778, 3I2779, A01550	5609	29.7%		
3I2773, 3I2774, A01548	476	2.5%	2	0.01%
A01549, A01701, A02041, A02289, A03295	10276	54.5%	8	0.04%
2I2799			51	0.3%
3E2724			203	1.1%
A13942			389	2.1%
3E2724, 3E2725			612	3.3%
A10395, A10397			768	4.2%
3H3023, 3H3024, 3K3050			936	5.1%
A02036, A02037, A02038			4745	25.9%
A10381, A10382, A1039			5013	27.3%
3H3026, 3K3043, 3K3044, 3K3045	3	0.02%	5619	30.6%

Note that five (for placebo) and four (for ranolazine) lot numbers were the modes of lot numbers dispensed at one visit. Visits were typically every four months, so the mode of four for ranolazine appears to be explained by dispensing four bottles. However, the wide variation in lot numbers dispensed makes it virtually impossible to correlate lot numbers with AEs. Conversely, while the lot numbers appear randomly assigned, the lot number groupings appear less random.

7.2.2.2. Interaction with diltiazem, verapamil, and other CY3A/Pgp inhibitors

About 7.5% of patients took diltiazem or verapamil in-hospital and 7% took diltiazem or verapamil post-hospital, slightly higher in ranolazine patients. The sponsor alleges that AEs were slightly higher in the patients taking diltiazem or verapamil and that the AEs had similar patterns with the exception of substantially more dizziness in the ranolazine patients also taking diltiazem or verapamil. I note that other common ranolazine adverse reactions, such as asthenia, were also increased by this combination, and I show my analyses for dizziness in Table 5 and asthenia in Table 6.

Please note: I present here the results only for combined diltiazem or verapamil use. The results for diltiazem or verapamil analyzed separately are similar, although the verapamil results show more variability because of the smaller number of patients who received verapamil.

Table 5: Patients with Dizziness AEs by Post-Hospital Diltiazem/Verapamil Use in CVT 3036

	diltiazem/verapamil	
	no	yes
placebo	7%	10%
ranolazine	13%	22%

Table 6: Patients with Asthenia AEs by Post-Hospital Diltiazem/Verapamil Use in CVT 3036

	diltiazem/verapamil	
	no	yes
placebo	3%	3%
ranolazine	5%	8%

By logistic regression both ranolazine use and diltiazem/verapamil use are highly statistically significant predictors of dizziness ($p<0.0001$) and ranolazine use is also a highly statistically significant predictor of asthenia, but the interactions between ranolazine and diltiazem/verapamil are not statistically significant. (Please note that I have included these p values and ones below at the request of the Division Director as measures of unlikeliness; they do not have the usual interpretation of that for a pre-specified primary hypothesis.)

Rates of SAEs (Table 7), withdrawals for AEs (Table 8), and in-hospital (Table 9) and post-hospital (Table 10) deaths were higher with combined ranolazine and diltiazem or verapamil use.

Table 7: Patients with SAEs by Post-Hospital Diltiazem/Verapamil Use in CVT 3036

	diltiazem/verapamil	
	no	yes
placebo	33%	44%
ranolazine	32%	52%

Table 8: Withdrawals for AEs by Post-Hospital Diltiazem/Verapamil Use in CVT 3036

	diltiazem/verapamil	
	no	yes
placebo	7%	11%
ranolazine	13%	16%

Table 9: In-Hospital Deaths by In-Hospital Diltiazem/Verapamil Use in CVT 3036

	diltiazem/verapamil	
	no	yes
placebo	1.3%	1.3%
ranolazine	1.4%	2.3%

Table 10: Post-Hospital Deaths by Post-Hospital Diltiazem/Verapamil Use in CVT 3036

	diltiazem/verapamil	
	no	yes
placebo	4.2%	3.2%
ranolazine	3.7%	6.0%

Ranolazine use, diltiazem/verapamil use, and age are highly significant ($p<.0001$) predictors of withdrawal. Diltiazem/verapamil use ($p=0.001$) and age ($p<.0001$) are highly significant predictors of SAEs while ranolazine is not. The interaction term between ranolazine use and diltiazem/verapamil use is not significant. None of the treatments is a significant predictor of deaths, although age is.

I did not detect any patterns to either the SAEs or withdrawals for AEs with combined ranolazine and diltiazem or verapamil use. However, deaths for patients on diltiazem or verapamil show the patterns in Table 11 and Table 12.

Table 11: In-Hospital Death Causes for Patients on Diltiazem/Verapamil in CVT 3036

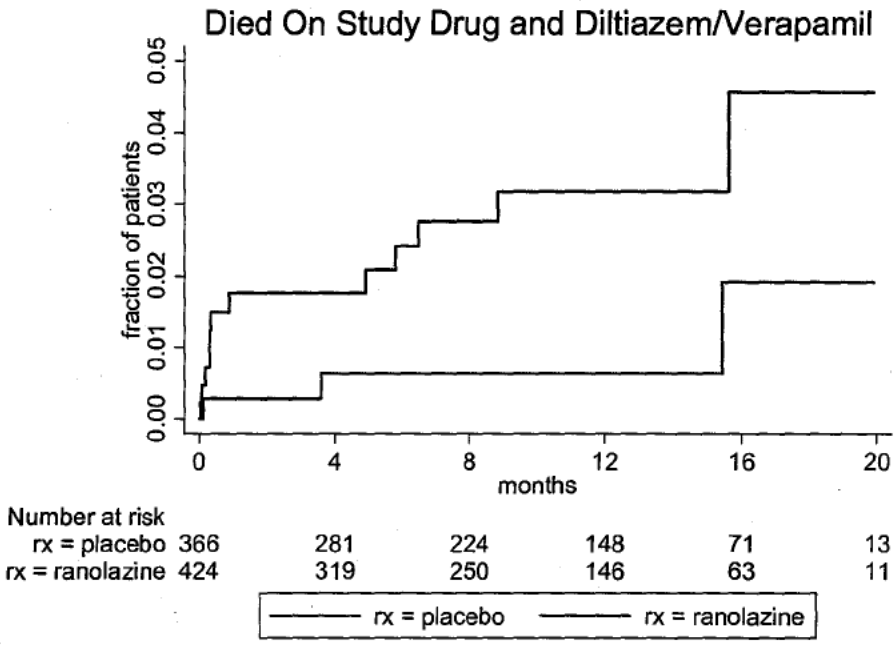
	Randomized arm		On study drug	
	placebo	ranolazine	placebo	ranolazine
acs	2	4	1	4
respiratory	1	0	0	0
sudden arrest	0	2	0	1
Total	3	6	1	5

Table 12: Post-Hospital Death Causes for Patients on Diltiazem/Verapamil in CVT 3036

	Randomized arm		On study drug	
	placebo	ranolazine	placebo	ranolazine
acs	2	3	1	2
bleed	0	1	0	0
hf	2	1	0	0
infection	1	1	0	0
other cardiac	0	1	0	0
sudden/arrest	1	6	1	5
unknown	1	1	0	1
Total	7	14	2	8

In Table 11 and Table 12 I show the deaths both by randomized arm regardless of whether the patient was on study treatment at the time of death and for those patients on study drug on the date of death. Twelve ranolazine but only three placebo patients treated with diltiazem or verapamil were on study drug within one day of their deaths ($p=0.04$ by Chi square). I show the Kaplan-Meier failure plot of deaths on study drug and verapamil or diltiazem, censoring patients who did not die on study drug at the time of study drug discontinuation, in Figure 6. The p value for the comparison of ranolazine to placebo for times to deaths on study drug is 0.035 by log rank analysis.

Figure 6: Kaplan-Meier Failure Plot of Patients Who Died on Study Drug and Diltiazem or Verapamil in CVT 3036



p = 0.035 by log rank

To determine whether there was an electrocardiographic pattern to the deaths and whether there were any premonitory drug effects such as PR prolongation or QRS widening, I examined ([redacted](b) (4)) the Holter records for 34 patients, including all who died in-hospital on diltiazem/verapamil (ranolazine and placebo) as well as selected other in-hospital deaths and survivors. Many of the deaths had a suggestive pattern of AV block, progressing from primary AV block through Mobitz 1 AV block to extreme bradycardia and asystole. Terminal events of block and asystole, rather than a tachyarrhythmia, were almost universal in the 19 patients I reviewed who died in hospital on Holter: Block was documented in 13 of the 15 ranolazine patients and all 4 placebo patients. Some atrial abnormality (bifid P, prolonged PR, bradycardia, atrial fibrillation) was present at baseline in most of these patients (about 72%) regardless of the use of diltiazem or verapamil.

I could not distinguish the ranolazine patients from the placebo patients using the Holter recordings. There were no premonitory changes in intervals, e.g., gradual PR lengthening or QRS widening, that we have seen with other IV antiarrhythmics. Changes in rhythm or intervals were frequently preceded by ST segment changes indicating ischemia. Patients also frequently showed signs of heart failure also temporally associated with the signs of ischemia. The Holter changes appeared to be the electrocardiographic manifestations of pump failure deaths with MIs rather than pharmacologic effects.

While I could not differentiate ranolazine and placebo based on the Holter recordings and the sponsor reported that overall bradycardia (heart rate < 40) on the Holters was less frequent with ranolazine (57%--including the ranolazine and diltiazem/verapamil patients who died) than with placebo (64%), I found that more ranolazine (57) than placebo (37, p=0.037) experienced bradycardia AEs during the first week despite the ranolazine and diltiazem/verapamil patient deaths not being reported as bradycardia AEs. Bradycardia AEs after the initial hospitalization were not increased with ranolazine except insignificantly in patients also on diltiazem/verapamil (6 vs. 3). More ranolazine (19) than placebo patients (8, p=0.034) also experienced AV block AEs during the first week but not post-hospital (and the ranolazine and diltiazem/verapamil deaths were not reported as AV block AEs).

The sponsor also submitted data on patients who took other CYP3A4 or Pgp inhibitors (based on a list defined by the sponsor) at some time during the study. The list has problems because it is undifferentiated as to the degree of CYP3A4 or Pgp inhibition and it includes topical formulations, e.g., Ketoderm, that do not produce systemic effects. For example, while ketoconazole use was rare, all of it was topical (and predominantly in placebo patients, 5 to 1). The one ranolazine case (61066075 at visit 5) coded by the sponsor as oral ketoconazole was actually a lansoprazole use. This case illustrates the problem of coding medications in international studies. The reported name of the drug (CMTRT) was "MEDEZOLI" (given orally, 30 mg). There is a Spanish tradename Medezol for ketoconazole gel but there is also a Georgian tradename Medezol for lansoprazole 30 mg capsules and this case is from Georgia. The sponsor coded the drug as "KETOCONAZOLE" (CMDECOD) and reported the use as a CYP3A4 inhibitor despite the Georgian tradename and the fact that the indication (CMINDC) for the use was "OTHER:Proton pump inhibitor" as it was for a lansoprazole (not reported as MEDEZOLI) use at visit 3. This case had proton pump inhibitor use in hospital (visit 2 recording) and at visits 3 and 5 but not at visit 4, suggesting that recording of medications was not complete at all visits.

There is another major limitation of post-hospital concomitant medication use recording: The CRFs capture neither start dates nor stop dates, so it is impossible to determine the start time or duration of treatment from the study data sets; one can usually determine drug usage from narratives or SAE reports for those patients having those documents, e.g. deaths. For in-hospital medications the CRFs captured the use of specific medications of interest at any time during the hospitalization by a checklist of generic names and drug classes. In addition to diltiazem and verapamil the only drug classes on the checklist showing CYP3A4 or Pgp inhibition are flouroquinolones, macrolides, and progesterone (but note that CYP3A4 inhibition may vary or be absent depending upon the specific drug). Progesterone use in hospital was rare (4 ranolazine cases) so I did not analyze these cases. Macrolide use in hospital was uncommon but more frequent in ranolazine (16) than placebo (10) patients. Deaths in hospital were similar in the macrolide

and no macrolide subgroups regardless of ranolazine use. Quinolone use was more frequent and balanced between the two groups (52 placebo, 56 ranolazine). In-hospital deaths were more frequent in patients randomized to ranolazine and receiving a quinolone at any time during the hospitalization as shown in Table 13.

Table 13: In-Hospital Deaths by In-Hospital Quinolone Use in CVT 3036

	quinolone	
	no	yes
placebo	1.3%	1.9%
ranolazine	1.3%	7.1%

However, deaths were few and in-hospital deaths on study drug were not differentiated by ranolazine (1 death each in patients taking a quinolone and ranolazine or placebo, with 3 other ranolazine patients dying 4-13 days after stopping study drug, 2 of infection). Hence the one other class of CYP3A4 drugs evaluable for in-hospital use in this study also shows a suggestion of increased mortality with combined ranolazine and quinolone use although the case specifics are not convincing that mortality is increased—but neither do these results establish that ranolazine has no interactions with other CYP3A4 inhibitors.

The FDA clinical pharmacology review recommended the following classification of CYP3A/Pgp inhibitors:

Strong: clarithromycin, telithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, indinavir, nelfinavir, ritonavir

Moderate: aprepitant, erythromycin, fluconazole, verapamil, diltiazem

He observed that the individual contributions of the CYP3A and Pgp inhibitory components of these drugs is not known.

Of these drugs, only clarithromycin, itraconazole, nefazodone, erythromycin, and fluconazole were given orally or parenterally to patients in CVT 3036, and usage was rare. Clarithromycin, the drug with the highest usage of these CYP3A4 inhibitors, was used in 14 placebo and 5 ranolazine patients, with fluconazole second at 5 and 3. Dizziness and asthenia were increased with clarithromycin use similarly in both ranolazine and placebo groups as were post-hospital deaths (3 and 2 respectively, so about 20% with clarithromycin use). All of these statistics do not consider whether the AE or death was associated temporally with the inhibitor use. The usage of other CYP3A4/Pgp inhibitors in CVT 3036 appears to be too infrequent to be able to draw any inferences regarding the effects of using ranolazine with them.

For comparison to a drug without CYP3A4 activity, I show selected corresponding results for concomitant amlodipine use in the following four tables.

Table 14: Patients with Dizziness AEs by Post-Hospital Amlodipine Use Post-Hospital in CVT 3036

	amlodipine	
	no	yes
placebo	7%	8%
ranolazine	13%	13%

Table 15: Withdrawals for AEs by Post-Hospital Amlodipine Use in CVT 3036

	amlodipine	
	no	yes
placebo	8%	7%
ranolazine	13%	15%

Table 16: In-Hospital Deaths by In-Hospital Amlodipine Use in CVT 3036

	amlodipine	
	no	yes
placebo	1.4%	1.1%
ranolazine	1.5%	1.0%

Table 17: Post-Hospital Deaths by Post-Hospital Amlodipine Use in CVT 3036

	amlodipine	
	no	yes
placebo	3.9%	4.8%
ranolazine	3.8%	4.2%

The amlodipine results in the above table do not suggest any interaction between ranolazine and amlodipine. Both sets of results (diltiazem/verapamil and amlodipine) are consistent with what is known about their potential for PK interaction with ranolazine.

I believe that the PK data showing roughly doubling of the exposure when ranolazine is combined with diltiazem or verapamil and the increases in typical and more serious adverse events and deaths argues that the dosage of ranolazine should be cut in half or more if diltiazem or verapamil are used concomitantly. The increases in deaths and particularly sudden deaths with combined ranolazine and diltiazem or verapamil use are concerning even though the numbers of deaths are small. On the other hand, the similarity of the Holter patterns in deaths on both ranolazine and placebo, the lack of pharmacologic effect in the Holters, and the overall neutral mortality in the study are reassuring that ranolazine is safe. I favor recommending that the ranolazine dosage be halved in all patients receiving a moderately strong CYP3A inhibitor and continuing the contraindication to concomitant strong CYP3A inhibitor use.

7.2.2.3. Interaction with simvastatin

While simvastatin (a weak inhibitor of CYP3A4 as well as a substrate for it) at 20 mg daily did not increase ranolazine levels in healthy subjects, the plasma levels of

simvastatin and its active metabolite are each increased about two-fold in healthy subjects receiving simvastatin 80 mg daily and ranolazine 1000 mg BID. Hence I examined adverse event and lab value profiles for simvastatin and other HMG-CoA reductase inhibitors ("statins").

Statin use was common in CVT 3036, with about 88% of patients taking a statin at some time. Among patients taking statins, simvastatin was the statin most frequently used (about 55%) followed by atorvastatin (about 44%). Use of lovastatin, the other statin with high CYP3A metabolism, was infrequent (about 1%)—for the following analyses I will include lovastatin with the simvastatin statistics because lovastatin should interact similarly to simvastatin. Please note that these use statistics are for any use and not continuous or exclusive use, e.g., about 18% of patients received more than one type of statin at some time (not concomitantly) during the study.

Rates of dizziness adverse events were increased with combined ranolazine and statin use as shown in Table 18.

Table 18: Patients with Dizziness AEs by Any Statin Use in CVT 3036

	placebo	simvastatin/ lovastatin	other statin	> 1 statin
placebo	3%	7%	8%	9%
ranolazine	5%	13%	14%	16%

All statins, e.g., simvastatin, atorvastatin, show the same pattern of dizziness AEs. Hence I would presume that the increased dizziness with combined ranolazine and statin use is the result of overlapping PD effects rather than a PK interaction.

Rates of myalgia AEs (Table 19) and hepatic AEs (Table 20) were higher with statin use but were not increased with combined statin and ranolazine use.

Table 19: Patients with Myalgia AEs by Any Statin Use in CVT 3036

	placebo	simvastatin/ lovastatin	other statin	> 1 statin
placebo	0.0%	0.7%	2.0%	1.6%
ranolazine	0.5%	0.9%	1.5%	1.0%

Table 20: Patients with Hepatic* AEs by Any Statin Use in CVT 3036

	placebo	simvastatin/ lovastatin	other statin	> 1 statin
placebo	0.0%	0.7%	2.0%	1.6%
ranolazine	0.5%	0.9%	1.5%	1.0%

*noninfectious hepatitis or hepatic insufficiency or steatosis

Withdrawals for AEs (Table 21) were more frequent with ranolazine use and were increased with concomitant statin and ranolazine use. However, they were more frequent with other statins than with simvastatin or lovastatin. Deaths (Table 22) were lower with any statin use and were very similar between ranolazine and

placebo. (The death rate was very low in the patients receiving more than one statin, but this may reflect the possibility that longer living patients are more likely to have opportunities for receiving more than one statin.)

Table 21: Patients with AEs Leading to Withdrawal by Any Statin Use in CVT 3036

	placebo	simvastatin/ lovastatin	other statin	> 1 statin
placebo	6%	7%	9%	9%
ranolazine	9%	13%	15%	15%

Table 22: Deaths by Any Statin Use in CVT 3036

	placebo	simvastatin/ lovastatin	other statin
placebo	10.2%	4.7%	4.6%
ranolazine	10.1%	4.5%	4.9%

The withdrawal AEs more frequent with ranolazine and statin use were the typical ranolazine AEs: dizziness, nausea, constipation, and asthenia.

Changes from baseline to last measurement in LDL were about the same with statins alone or statins combined with ranolazine as shown in Table 23. If anything, the LDL results suggest that ranolazine may increase LDL levels slightly.

Table 23: Changes from Baseline in LDL (mg/dL) by Any Statin Use in CVT 3036

	placebo	simvastatin/ lovastatin	other statin	> 1 statin
placebo	2	-15	-26	-19
ranolazine	7	-15	-21	-17

Changes from baseline to last measurement in ALT were small and similar regardless of statin or ranolazine use as shown in Table 24. Other statistics for ALT, e.g., maximum increase greater than threefold, were also indistinguishable by statin or ranolazine use.

Table 24: Changes from Baseline in ALT by Any Statin Use in CVT 3036

	placebo	simvastatin/ lovastatin	other statin	> 1 statin
placebo	-2	-4	-2	-4
ranolazine	-5	-6	-4	-7

These results do not suggest that there is a clinically important of ranolazine upon simvastatin or other statins. The results are slightly suggestive that statins may increase ranolazine levels.

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7.2.2.5. Cancer adverse events

Patients with a history of cancer were evenly distributed between ranolazine (135, 4.1%) and placebo (129, 3.9%). However, there were more newly diagnosed cancers in the ranolazine group compared to the placebo group as shown in Table 36.

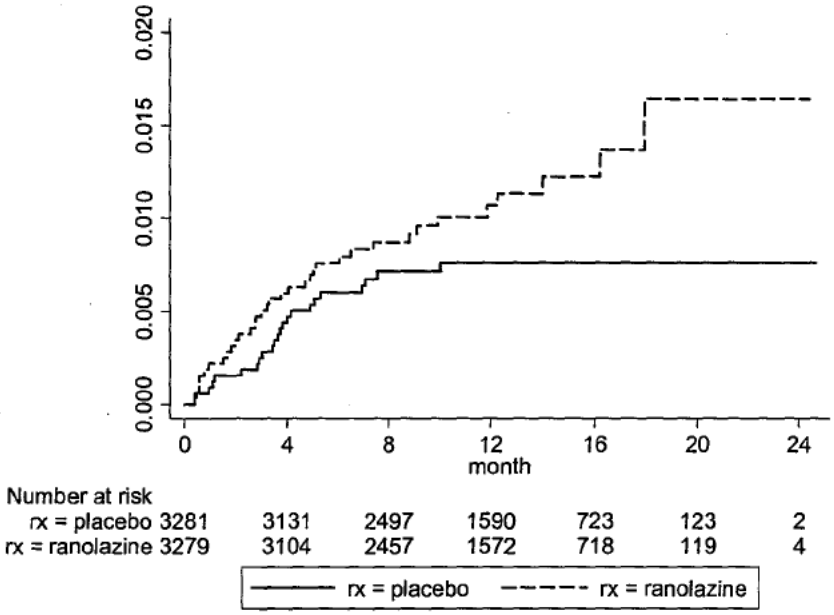
Table 36: Numbers of Newly Diagnosed Cancers (Excluding the First Week) in CVT 3036

	placebo	ranolazine
bladder	1	1
breast	3	1
colorectal	3	6
esophagus	0	1
head & neck	2	0

	placebo	ranolazine
kidney	0	3
leukemia	0	2
liver	1	0
lung	6	10
lymphoma	0	2
melanoma	2	0
mesothelioma	0	1
pancreas	1	1
prostate	2	2
sarcoma	0	1
small intestine	1	0
stomach	1	0
thymus	0	1
thyroid	0	1
unknown	0	1
uterus	0	1
total	23	35

Note that in Table 36 I have excluded cancers diagnosed within the first week—in these patients with ACS, cancer findings noted on admission were typically not worked up until after the ACS event subsided. There were four cancers in the ranolazine group diagnosed in the first two days compared to none in the placebo group—Hence not excluding cancers diagnosed in the first week makes the ranolazine numbers worse. The first newly diagnosed cancers after the first week were diagnosed starting at day 12. The Kaplan-Meier (K-M) incidence plot of cancers newly diagnosed after the first week is strange as shown Figure 7.

Figure 7: Kaplan-Meier Incidence Plot of Cancers Newly Diagnosed after 7 Days in CVT 3036



There is a moderate excess of cancers in the ranolazine group, largely colorectal, lung, and leukemia/lymphoma. The K-M incidence plot is difficult to interpret: It diverges early and the late separation of the curves is due to no cancers diagnosed in the placebo group after about 11 months. If the late divergence is real, it would be greatly concerning. A significant limitation for this analysis of cancer rates is a lack of power of CVT 3036 to detect or document a difference in cancer rates: The power to detect a 50% increase in all cancers is about 0.28; to have 0.80 power of detecting a 50% increase the study would have to be about four times as large. CVT 3036 doe not clearly document that ranolazine is carcinogenic but it does leave concerns about a carcinogenic potential.

The sponsor provided in Serial 043 a review of neoplasms in CVT 3036 that concludes that the tumor incidences in ranolazine-treated patients ere not different from placebo-treated patients nor were they different from those reported by the U.S. Cancer Statistics Working Group in the general population. The majority of the sponsor's analyses lump malignant tumors with benign disorders such as goiter and prostatic hypertrophy. The one analysis specifically addressing malignancies notes that 6 colorectal cancers were reported in ranolazine patients vs. 3 in placebo patients as I record in Table 36. The sponsor rejects this difference as suggestive of tumor promotion because of the short latency period and the lack of a history of polyps or adenomas in these patients. The sponsor's analyses do not contradict or negate my analyses—I still conclude that CVT 3036 does not eliminate concerns about a carcinogenic potential for ranolazine.

7.2.2.6. Renin-angiotensin system inhibitor-like adverse events

Surprisingly, ranolazine shows a pattern of AEs suggestive that it may be a renin-angiotensin system (RAS) inhibitor or that it potentiates the effects of other RAS inhibitors. I show the relevant AEs in Table 37 **and relevant lab values in**

Table 38. For lab values I excluded values (other than baseline values) within the first 14 days after the event because of instability and possible effects from other interventions during that time.

Table 37: Numbers of Patients with AEs Relevant to RAS Inhibition in CVT 3036

	placebo	ranolazine
patients	3281	3279
angioedema	0	6*
cough (dry/no URI)	82	120
cough due to ACEI	9	7
cough leading to d/c	1	5
hyperkalemia	20	19
hypokalemia	30	22
creatinine increased	37	60
renal impairment	67	97
hypertension	165	138

hypotension	148	228

*all angioedema cases were discontinued

Table 38: Lab Values Relevant to RAS Inhibition in CVT 3036

	placebo	ranolazine
potassium baseline meq/L	4.23	4.22
potassium mean meq/L	4.40	4.44
potassium max meq/L	4.64	4.68
potassium max > 5.5, n	110	132
potassium min < 3.5, n	117	88
creatinine baseline mg/dL	1.04	1.04
creatinine mean mg/dL	1.06	1.13
creatinine max mg/dL	1.15	1.24
creatinine max >1.5x cr base, n	484	616
hemoglobin base	13.8	13.8
hemoglobin change to last	0.08	-0.16

The increase in dry coughs suggested to me that ranolazine might have ACEI activity or potentiate ACEIs. In this ACS population concomitant ACEI use was common (about 71% in each group post-hospital) and concomitant ARB use was less common but not infrequent (about 13% in each group post-hospital.) Post-hospital use of either RAS inhibitor was about 78%. I show the rates for AEs relevant to RAS inhibition by both ranolazine and ACEI/ARB use in Table 39 and the relevant lab values in Table 40.

Table 39: Numbers of Patients with AEs Relevant to RAS Inhibition in CVT 3036 by Ranolazine and ACEI/ARB Use in CVT 3036

	placebo		ranolazine	
	no ACEI/ARB	ACEI/ARB	no ACEI/ARB	ACEI/ARB
patients	681	2557	753	2479
angioedema	0.00%	0.00%	0.00%	0.24%
cough (dry/no URI)	1.6%	2.8%	1.6%	4.4%
hyperkalemia	0.3%	0.7%	0.4%	0.6%
hypokalemia	0.4%	1.1%	0.4%	0.8%
creatinine increased	1.1%	1.1%	1.3%	1.9%
renal impairment	1.2%	2.3%	1.8%	3.3%
renal SAE	0.4%	0.7%	0.5%	1.3%

	placebo		ranolazine	
	no ACEI/ARB	ACEI/ARB	no ACEI/ARB	ACEI/ARB
hypertension	2.8%	5.7%	1.5%	5.1%
hypotension	4.7%	4.5%	6.1%	7.2%
anemia	3.5%	3.8%	3.7%	4.5%

Table 40: Lab Values Relevant to RAS Inhibition in CVT 3036 by Ranolazine and ACEI/ARB Use in CVT 3036

	placebo		ranolazine	
	no ACEI/ARB	ACEI/ARB	no ACEI/ARB	ACEI/ARB
potassium baseline meq/L	4.22	4.23	4.18	4.23
potassium mean meq/L	4.34	4.41	4.39	4.45
potassium max meq/L	4.58	4.66	4.62	4.71
potassium max > 5.5, %	2.7%	4.1%	2.6%	5.2%
potassium min < 3.5, %	3.7%	4.1%	2.6%	3.2%
creatinine baseline mg/dL	1.01	1.04	1.02	1.05
creatinine mean mg/dL	1.02	1.07	1.09	1.14
creatinine max mg/dL	1.11	1.17	1.18	1.25
creatinine max >1.5x base, %	14%	14%	17%	18%
hemoglobin base	13.9	13.7	14.0	13.8
hemoglobin change to last	.22	.05	-.05	-.20

Dry cough was only increased in the ACEI/ARB subgroups and it was only increased in the patients also taking ACEIs, not ARBs (analysis not shown). Note that it was substantially increased in ranolazine patients who at some time received an ACEI. I also analyzed these statistics by specific ACEIs and (analyses not shown) I did not find any differences in patterns of AEs for specific ACEIs.

For renal impairment AEs and renal SAEs, the rates are higher with ranolazine than placebo and even higher with combined ranolazine and ACEI/ARB use. The apparent increases in hypokalemia with ACEI/ARB use are likely spurious because ACEI/ARBs are used to treat hypertension and HF, diseases for which diuretics are also commonly prescribed. Similar confounding is likely operational for the increased rates of hypertension for ACEI/ARBs, but note the lower rate of hypertension for ranolazine alone and the higher rates of hypotension for ranolazine and ranolazine combined with ACEI/ARBS.

While anemia is not ordinarily considered an AE relevant to RAS inhibition, I have observed the association in other large outcome studies, e.g., the LIFE study with losartan in which hospitalizations for anemia were increased in the losartan group. In CVT 3036 rates of anemia are slightly increased with ACEI/ARB or ranolazine use and increased more with combined ACEI/ARB and ranolazine use.

There are some limitations to these analyses: ACEI/ARB use was not randomly assigned and I analyzed only any use of the ACEI/ARBs at hospital discharge or later and did not determine the timing of administration relative to the AE. Other confounding based on indications, in addition to hypertension and HF mentioned

above, is possible, e.g., a diabetic with declining renal function could have been started on the ACEI/ARB as treatment rather than the ACEI/ARB contributing to the renal impairment.

Despite these limitations, I still interpret these findings as suggestive that ranolazine potentiates RAAS inhibition and cannot rule out that ranolazine is a RAAS inhibitor. The increase in renal SAEs is worrisome, and I discuss it further below. There is a possible mechanism for how ranolazine might potentiate RAAS inhibition: One study demonstrated that ranolazine may interfere with tubular secretion of creatinine. Many of the ACEIs are renally excreted. So ranolazine might interfere with the renal excretion of ACEIs. However, its interference with creatinine secretion is presumed to be based on inhibition of organic cation transport (OCT), while ACEIs are anions and are handled by organic anion transport proteins (OATP), as are some ARBs. Ranolazine has both anion and cation metabolites. Regardless, a clinical PK and PD interaction study with an ACEI and an ARB is needed based on the clinical findings in CVT 3036.

7.2.2.7. Cytopenias

While the hemoglobin reductions are slight and almost universal, a few patients experienced rare events of cytopenias as shown in Table 41.

Table 41: Cytopenia Adverse Events in CVT 3036

	placebo	ranolazine
leucopenia	0	5
pancytopenia	0	3
thrombocytopenia	7	15
leuco/thrombo/pancytopenia	7	22

Note that there is only one case that overlaps among the cases of leucopenia, thrombocytopenia, and pancytopenia, so the difference between ranolazine and placebo in numbers of patients having any one of these three AEs is substantial. Regarding severity, one placebo patient with thrombocytopenia died of ACS and one ranolazine patient with pancytopenia died of infection. The latter patient, an 85 year-old male, developed pancytopenia and urosepsis about six months after starting treatment with ranolazine. He was discharged improved with the pancytopenia attributed to sepsis but also started on captopril. He continued to have recurrent infections and ranolazine was discontinued after eight months. He died of sepsis at about 12 months still taking captopril. While I did not include cytopenias in the previous section because the presumed mechanism is not ACE inhibition, leucopenia/agranulocytosis is a labeled concern of ACEIs, particularly captopril.

7.2.2.8. Serum creatinine increases and acute renal failure

As shown in Table 39, renal impairment AEs were more frequent with ranolazine than placebo, particularly with ACEI use. Ignoring ACEIs and other drugs, the

overall rates of such AEs were about 2% in placebo patients and 3% in ranolazine patients, with numbers of patients as shown in Table 37. Renal impairment AEs that were serious or led to withdrawal occurred in 0.7% of placebo patients and 1.3% of ranolazine patients, but deaths were more common among the placebo patients with these AEs than the ranolazine patients (19% vs. 12% of patients with renal impairment AEs, death counts one higher with placebo, 13 vs. 12). However, three times as many ranolazine as placebo patients with these AEs withdrew consent (22 vs. 7). About a third of the ranolazine AEs occurred within the first five days. During the first five days any renal impairment AEs were more frequent with ranolazine (32 vs. 14) as well as serious AEs or withdrawals (10 vs. 3).

Most risk factors for a renal impairment AE are not surprising as shown by the logistic regression in Table 42.

Table 42: Logistic Regression of Renal Impairment AEs by Baseline Risk Factors and Treatment in CVT 3036

```
Logistic regression                               Number of obs   =       6560
                                                  LR chi2(6)      =     210.64
                                                  Prob > chi2     =     0.0000
Log likelihood = -661.59008                       Pseudo R2       =     0.1373

------------------------------------------------------------------------------
   renimpair | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  ranolazine |   1.454996    .242088     2.25   0.024     1.050112    2.015989
         age |   1.060572   .0092079     6.77   0.000     1.042677    1.078773
        male |   1.617747   .2941507     2.65   0.008     1.132762    2.310374
  hx ren imp |   7.681227   1.561653    10.03   0.000     5.156735    11.44159
hypertension |   2.384353   .6489722     3.19   0.001     1.398592    4.064904
    diabetes |   1.506333   .2513178     2.46   0.014      1.08619    2.088989
------------------------------------------------------------------------------
```

That older age and histories of renal impairment, hypertension, or diabetes are risk factors are not surprising. That males are at greater risk than females may not have been predictable in advance but also is not surprising. Ranolazine remains a significant risk factor. However, there is one additional relevant subgroup analysis: For US patients there was minimal difference in renal impairment AEs between the two treatment groups overall.

Because of a lack of a substantial impact upon mortality and the neutral results in the US, these renal impairment AEs do not appear to be a serious problem. I hypothesize that they are related to the documented slight increases in creatinine with ranolazine and its RAS inhibitor-like effects discussed previously. The concern I have about drawing firm conclusions regarding renal safety for ranolazine relates to the questions about the completeness of the data and follow-up.

7.2.2.9. Miscellaneous adverse events

Two other adverse events appear to be more frequent with ranolazine than placebo as shown in Table 43.

Table 43: Miscellaneous Adverse Events in CVT 3036

	placebo	ranolazine
pulmonary fibrosis	4	8
without history	3	6
influenza	33	52

None of the pulmonary fibrosis cases received amiodarone. Four of the ranolazine and none of the placebo cases withdrew for AEs; one of the AE withdrawals also withdrew consent for follow-up. One case without a history withdrew for an AE of severe "IDIOPATHIC PULMONARY FIBROSIS" starting on the first day. Two of the ranolazine cases died: One death was in an 82 year-old white female without a prior history in whom "DIFFUSE PNEUMOSCLEROSIS" was noted on day 9; the other was in a 64 year-old white male with a prior history of pulmonary fibrosis. Pulmonary fibrosis must be mentioned in the label.

Regarding influenza, other infections appear to be evenly distributed between ranolazine and placebo. None of the influenza events were reported to have led to withdrawal. I suspect the difference in influenza rates may be related to other ranolazine toxicity such as nausea, vomiting, or dizziness.

8. Advisory Committee Meeting

We are not submitting this supplemental submission to an advisory committee.

9. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

10. Financial Disclosure

The sponsor submitted financial disclosures for CVT 3036 and CVT 3023 as agreed upon with the Division at pre-NDA meetings. The primary clinical reviewer reviewed these disclosures and, in a separate memo dated June 6, 2008, concluded that there was no unusual activity.

11. Labeling

My recommendations for labeling are the following:

- (b) (4) (b) (4)
- I recommend approval of the indication for the treatment of chronic angina but with the labeling changes itemized below.

- The current contraindication for moderately potent CYP3A inhibitors should be removed and replaced with a recommendation to halve the dosage in patients receiving concomitant CYP3A inhibitors.

- [redacted] (b) (4)

- The findings of increased deaths with concomitant diltiazem or verapamil use should be described in the clinical trials section.

- The occurrence of leucopenia and pancytopenia, including one death, should be described briefly in adverse reactions.

- Angioedema, pulmonary fibrosis, thrombocytopenia, leucopenia and pancytopenia should be added to the list of other adverse reactions that have been noted to occur rarely.

[redacted] (b) (4)

12. DSI Audits

Because the major study failed on its primary efficacy endpoint we elected not to perform DSI audits.

13. Conclusions and Recommendations

13.1. Recommended regulatory action

I recommend approval of ranolazine for the treatment of chronic angina. The major study submitted, CVT 3036, provides reassurance that ranolazine is safe at the marketed dosage in high risk ACS patients without potential drug interactions. The results in the subgroup treated with ranolazine and diltiazem or verapamil do not confirm that ranolazine at full dosage is safe in this subgroup, one with a known yet moderate drug interaction. I recommend that ranolazine dosage be cut in half for patients taking diltiazem, verapamil, or other moderately strong CYP3A4 or Pgp inhibitors. Ranolazine appears to have the potential for many drug interactions that are not well characterized but also, except for the interaction with diltiazem and verapamil, do not appear dangerous. I also recommend postmarketing safety studies as outline below under Postmarketing studies.

(b) (4)

[redacted]

13.2. Safety concerns to be followed postmarketing

I recommend that the safety concerns regarding potential drug interactions be addressed by specific postmarketing studies as discussed under Postmarketing studies. In addition, I note one other safety concern that is not a drug interaction: The analysis of cancer deaths does not rule out an effect upon cancers. The clinical data alone are slightly suspicious but would not raise any undue concerns if the pre-clinical data were completely negative. While I judge that the current pre-clinical and clinical findings are not sufficiently suspicious to justify mandating a cancer outcome study, I favor following the post-marketing safety reports for any hint of a problem with carcinogenesis.

13.3. Risk Minimization Plan

I do not recommend a risk minimization plan. While there are unanswered questions regarding the potential for ranolazine to interact with other drugs by several different mechanisms (see Postmarketing studies), I believe that these potential interactions can be

sufficiently addressed in the labeling. I also find it reassuring that the large CVT 3036 outcome trial did not find a difference in total mortality compared to placebo and the Holter recordings during IV administration did not show an increased risk of arrhythmias or premonitory interval changes other than QTc prolongation.

13.4. Postmarketing studies

I recommend that the sponsor perform the following postmarketing studies:

(b) (4)

- *In vitro* studies of ACE inhibition and angiotensin II receptor blockade and a clinical drug interaction study with placebo, ACEI, ARB, combined ACEI and ranolazine, and combined ranolazine and ARB arms or crossover periods with measurements of drug levels for all drugs, BP, and renin-angiotensin system pharmacodynamics

(b) (4)

13.5. Comments to be conveyed to the applicant

The proposed labeling changes and postmarketing studies will be discussed with the sponsor during label negotiations.

References

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/s/

Thomas Marciniak
10/23/2008 11:28:15 AM
MEDICAL OFFICER

NDA# 21526
Submission dated 8-26-08

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

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

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

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

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

Concomitant drug use patterns

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

The summary of death by treatment groups are shown below.

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

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

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/s/

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

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

Conclusion

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

Background

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

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

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

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

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

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Maryann Gordon
9/26/2008 10:31:07 AM
MEDICAL OFFICER

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

Conclusion

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

Background

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

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

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

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

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

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

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

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

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

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

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

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

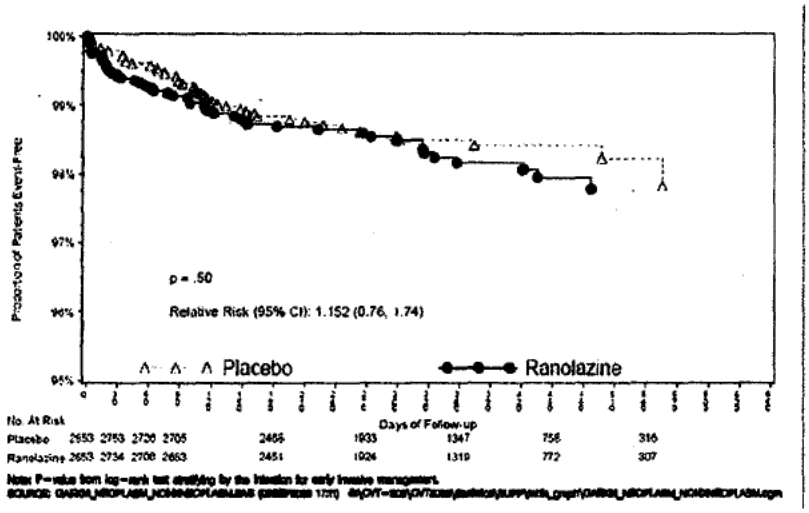
Cancer reports of any type by age group were as follows:
Less than 65 years: 21 (1%) placebo, 31 (2%) ranolazine
Between 65 and 74 years: 18 (2%) placebo, 22 (2%) ranolazine
Greater than 75 years: 15 (3%) placebo, 10 (2%) ranolazine.

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

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

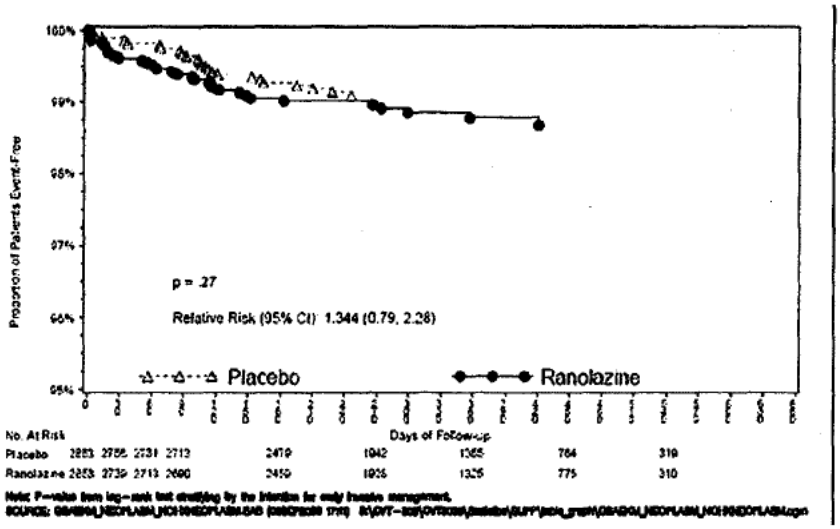
For those without a prior history of cancer, the time to reporting a cancer was greater for subjects who had been in the trial 180 days or less, regardless of treatment group, compared to those reporting cancer who were in the trial more than 180 days.

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



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

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



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Maryann Gordon
10/20/2008 09:14:12 AM
MEDICAL OFFICER

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

Conclusions

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

Background

Corrections to Arrhythmia Data for Study CVT 3036

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

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

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

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

Cross-Discipline Team Leader Review Memo

Date	July 22, 2008
From	Thomas A. Marciniak, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supp #	NDA 21,526 S-004 (b) (4)
Proprietary / Established (USAN) names	Ranexa® / ranolazine
Dosage forms / strength	extended release tablets / 500 and 1000 mg
Proposed Indication	1. Primary use for the treatment of chronic angina (S-004) (b) (4)
Recommended:	1. Approval for the treatment of chronic angina (but with many labeling cautions) (S-004) (b) (4)

1. Introduction to Review

Ranexa (ranolazine) is an oral drug approved on January 27, 2006, for the treatment of chronic angina in patients who have not achieved an adequate response with other antianginal drugs. We specified the secondary use because of concerns about QTc prolongation. While its mechanism of action in angina is not known, ranolazine does affect various cardiac ion currents, including inhibition of the late I_{Na} and I_{Kr}. We believe the QTc prolongation is related to the I_{Kr} inhibition, and other drugs that inhibit I_{Kr} produce both QTc prolongation and torsades de pointes (TdP). The sponsor argues that, despite the I_{Kr} inhibition and QTc prolongation, ranolazine should not cause TdP because of its effects upon other cardiac ion currents. The effect upon QTc is moderate. With repeat dosing, the mean effect on QTc of ranolazine 1000 mg BID at T_{max}, is about 6 msec. In 5% of the population the prolongation of QTc is 15 msec. TdP was not a problem in the clinical trials involving 2,018 patients treated for angina for the original approval.

To secure a first line indication, the sponsor proposed doing a large outcome study (CVT 3036 or MERLIN or TIMI-36) in patients with non-ST segment elevation acute coronary syndrome (ACS). While improvement in the primary efficacy endpoint for this study (the combined endpoint of cardiovascular (CV) death, myocardial infarction (MI), and recurrent ischemia) was not statistically significant, we agreed in a special protocol assessment prior to initiation of the trial that, regardless of winning on the primary efficacy endpoint, no adverse trend in death and arrhythmia would be assuring and could support approval of ranolazine as first-line therapy for long-term treatment of chronic angina. This submission provides the CVT 3036 trial results to support the primary use indication. It also summarizes the results of six other smaller studies to support primary use. (b) (4)

Because the limiting factor for primary use for this drug is safety and because the large outcome trial in this submission provides an unusual opportunity to dissect the safety of a drug, I summarize the primary clinical and statistical reviewers' conclusions regarding the primary endpoint, and I also discuss briefly the primary clinical reviewer's presentation of the (b) (4) I address in detail in this review safety findings. These safety findings include ones suggested by pre-clinical and prior clinical studies as well as new ones suggested by the CVT 3036 results.

The safety issues suggested by prior studies, in addition to the presumed potential for TdP, are the following:

- Ranolazine is metabolized mainly by CYP3A and to a lesser extent by CYP2D6. Plasma levels are increased about 2-fold by the moderate CYP3A4 inhibitors diltiazem and verapamil, drugs sometimes used to treat angina. I analyzed the adverse effects by diltiazem and verapamil use to ascertain whether there is any interaction.

- One preclinical study performed by an investigator independent from the sponsor suggests that ranolazine may be carcinogenic: Ranolazine promoted the development of intestinal tumors in APC(Min/+) mice. (Suckow, Gutierrez et al. 2004) Because of these preclinical findings I examined cancer rates in CVT 3036.

- Ranolazine increased serum creatinine by about 0.1 mg/dL in angina patients in the earlier clinical trials. A special study did not confirm decreases in glomerular filtration rate despite the increased creatinines, so the current label concludes that the increased serum creatinine is due to a blockage of creatinine's tubular secretion by ranolazine or one of its metabolites. However, as the IND reviewer, I received many serious adverse event reports of acute renal failure (ARF) from CVT 3036. Because of these reports I scrutinized creatinine changes and renal adverse events in CVT 3036. (b) (4)

In addition, the pre-NDA presentations raised an issue relevant to confidence in any safety (or efficacy) findings:

- The pre-NDA meeting materials suggested that there were problems with complete treatment and follow-up, i.e., about 15% of ranolazine and 13% of placebo patients withdrew consent to treatment and about 5% in each group also withdrew consent to follow-up. These withdrawals are high compared to other ACS studies. Our pre-NDA meeting preliminary responses cautioned as follows: "The apparent impediment to interpretation of CVT 3036 is the high rate of early terminations for withdrawal of consent. We would appreciate hearing a brief discussion of why withdrawals of consent, including in the placebo group, were high. In your submission you should document well the circumstances and statuses of all patients terminating early for withdrawal of consent. We note that about 5% of patients lacked follow-up due to withdrawal of consent. If any options are available for securing vital status on these

patients, e.g., investigator queries, national registries or death indexes, you should use them and provide the follow-up data in the NDA submission." Hence I scrutinized completeness of all aspects of the data collection. I believe that if there is any significant problem with completeness of the data collection, then we can not assume safety for ranolazine and we should not approve the primary use indication.

There are other safety signals that I detected only after analyzing the trial data. I discuss them under Safety below.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

As discussed in the Introduction to Review, we agreed in a special protocol assessment prior to initiation of the CVT 3036 trial that, regardless of winning on the primary efficacy endpoint, no adverse trend in death and arrhythmia would be assuring and could support approval of ranolazine as first-line therapy for long-term treatment of chronic angina. We also noted in the pre-NDA submission discussions that completeness of follow-up was an issue for this trial.

3. CMC/Microbiology/Device

There are no outstanding CMC issues for this approved product and the product is an oral drug not requiring special microbiological evaluation. The only CMC document for this submission is an environmental assessment. Please see the FDA chemist's review of that document.

4. Nonclinical Pharmacology/Toxicology

4.1. General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

The general unanswered pharmacologic property for this drug is its mechanism of action in angina.

4.2. Carcinogenicity

As mentioned in the Introduction to Review, ranolazine promoted the development of intestinal tumors in a knockout mouse strain, although it is not mutagenic and was not carcinogenic in mouse and rat long-term carcinogenicity studies. Because of the positive preclinical cancer promoter study, I examined cancer rates in CVT 3036.

4.3. Reproductive toxicology

Ranolazine is pregnancy category C. There are no adequate pre-clinical or clinical studies regarding effects upon fertility, reproductive capacity, fetal development, or pregnancy. However, chronic angina due to atherosclerotic heart disease is a rare disorder in women of child-bearing potential.

4.4. Other notable issues

There are no other notable nonclinical pharmacology or toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

5.1. General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

The general unanswered pharmacologic property for this drug is its mechanism of action in angina.

5.2. Drug-drug interactions

Because of its CYP metabolism and Pgp substrate status, ranolazine interacts with various drugs affecting these pathways. The most relevant question regarding known ranolazine-drug interactions is regarding safety in patients taking the moderate CYP3A4 inhibitors used in angina patients, diltiazem and verapamil. Ranolazine appears to be a CYP3A inhibitor and, at the 1000 mg BID dosage, increases levels of simvastatin (a CYP3A4 substrate) 80 mg about twofold. (b) (4)

5.3. Pathway of elimination

Ranolazine is eliminated partly by CYP3A and CYP2D6 as well as excreted in the urine. Its metabolism is relevant to drug-drug interactions mentioned above. Its excretion in the urine is relevant to the issue of acute renal failure. I show the proposed metabolic pathways of ranolazine in Figure 1. I also show, for comparison, the structures of creatinine in Figure 2 and a typical ACE inhibitor (captopril) in Figure 3—I discuss the relevance of these latter structures under Safety below.

Figure 1: Ranolazine Metabolism

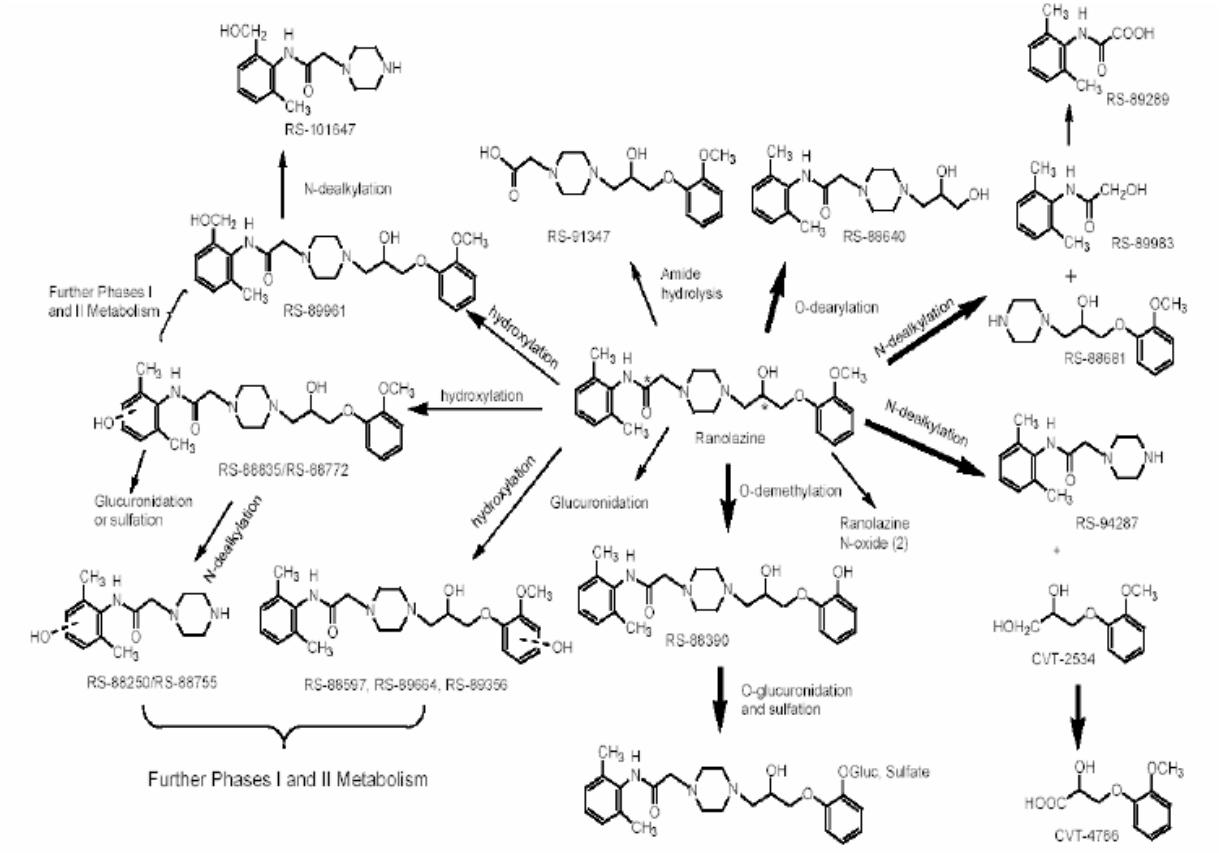


Figure 2: Chemical Structure of Creatinine

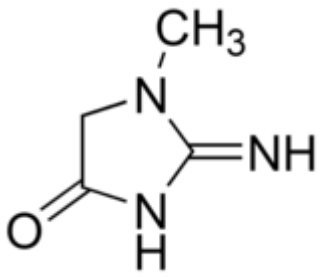
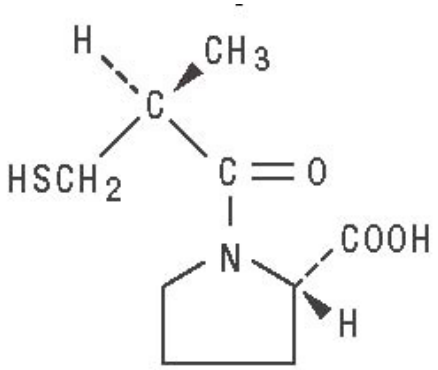


Figure 3: Chemical Structure of Captopril



5.4. Demographic interactions/special populations

Effects on angina frequency and exercise tolerance were considerably smaller in women than in men in the ranolazine angina studies. Because the major trial CVT 3036 for this submission failed for its primary efficacy endpoint, it may not be useful for discerning differential efficacy effects by sex.

5.5. Thorough QT study or other QT assessment

Ranolazine prolongs the QTc interval but has not led to TdP in earlier, smaller clinical studies. CVT 3036 (the large, longer-term clinical trial in this submission) provides the higher exposures needed to document a lack of torsadagenic potential as well as an initial Holter monitoring phase to explore all possible arrhythmogenic effects.

5.6. Other notable issues

There are no other notable clinical pharmacology or biopharmaceutics issues

6. Clinical Microbiology

Ranolazine is an oral non-antimicrobial drug for which there are no clinical microbiology concerns.

7. Clinical/Statistical

7.1. Efficacy

7.1.1. Primary clinical and statistical reviewers' findings and conclusions

7.1.1.1. First line treatment of chronic angina

The primary efficacy endpoint for CVT 3036, a trial in a new population for this drug of non-ST segment elevation acute coronary syndromes (ACS), was a combined endpoint of CV mortality, MI, and recurrent ischemia. The primary clinical and statistical reviewers, as well as the sponsor, agree that this trial failed on this primary endpoint: There were slightly fewer primary endpoint events in the ranolazine group (695 vs. 753), a relative risk of about 0.92 with an insignificant p value of 0.11 by pre-specified time-to-event analysis. Of the components, there were slightly more CV deaths with ranolazine (87 to 78) but less recurrent ischemia (400 vs. 465). Because there is no disagreement that this study failed on its primary endpoint and because the results do not suggest any additional efficacy or safety issues, I will not discuss the primary endpoint or the secondary efficacy endpoints further.

7.1.3. Pediatric use

Stable angina is extremely rare in children, so I am recommending a waiver of pediatric studies.

7.2. Safety

7.2.1. Primary clinical reviewer's findings and conclusions

The primary clinical reviewer makes the following pertinent observations about safety:

- All cause mortality was virtually identical in both treatment groups (5.3%).
- Sudden death rates were also similar (1.7% for ranolazine and 2% for placebo.)
- Rates of symptomatic documented arrhythmias were similar (3.1% and 3.0%).

- Dizziness, constipation, nausea, asthenia, and hypotension were AEs more frequent than 3% and occurring more frequently with ranolazine than placebo.

- Serum creatinine increased slightly and hemoglobin decreased slightly with ranolazine.

- Renal dysfunction (defined as renal failure, renal failure acute, renal impairment, renal failure chronic) was higher with ranolazine (3% vs. 2%).

- In the high dose tolerability study CVT 3023, many subjects were unable to tolerate doses 1500 mg bid and above. Dose limiting adverse events included syncope, nausea, dizziness, and vomiting (25%).

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

7.2.2. Discussion of notable safety issues

The major issue regarding the interpretation of this study is data completeness. I discuss it first below, followed by other safety issues that deserve additional comment. They include the ones raised by previous studies and mentioned in the Introduction to Review above. There were also some surprising findings.

7.2.2.1. Data completeness and quality

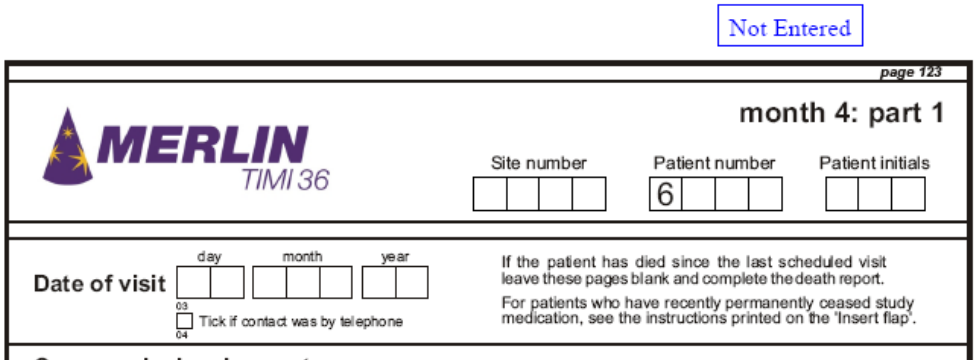
The editorial in JAMA on the CVT 3036 primary results article described the study as a "well-designed and rigorously conducted clinical trial." (Newby and Peterson 2007) The design is appropriate and most aspects of trial conduct appear good, e.g., the SAE reports are consistent between the IND and the NDA, the case report forms are reasonably detailed and accurate, and the CRFs, SAS data sets, and reports are consistent. However, there is one significant limitation of the data collection in CVT 3036: a substantial number of patients are reported as withdrew consent to treatment (ranolazine 14%, placebo 12%) and a smaller but still not inconsequential number are reported as withdrew consent to follow-up (about 5% in each group). The JAMA article reported the numbers of patients that withdrew consent to treatment in the patient flow diagram but listed only 7 ranolazine and 2 placebo patients as lost to follow-up. (Morrow, Scirica et al. 2007)

The follow-up in CVT 3036 was far less complete than 9 patients lost-to-follow-up would suggest. This latter number ignores those patients who withdrew consent to follow-up and other patients for whom follow-up was incomplete. CVT 3036 was an event-driven trial. The study report notes that the pre-specified number of events was reached and final visits for patients were scheduled starting September 25,

2006. Hence the most relevant follow-up statistic (particularly for more complex determinations such as adverse event evaluations) is the percentage of patients who are not known to be dead and who did not have a follow-up visit on or after September 25, 2006.

There is one major complication for determining site staff-patient, face-to-face visits: The CRF has 116 different forms with some forms completed at multiple visits. There are a vast number of fields, the majority of which the sponsor entered into the study data sets. Two critical fields that the sponsor reports not to have entered are the dates of the visits and whether the contact was by phone. I have show an excerpt from a typical visit form from the sponsor's annotated blank CRFs in Figure 4.

Figure 4 : Typical Visit CRF Header from the Sponsor's Annotated Blank CRFs for CVT 3036



The sponsor provided this surrogate for documentation of a visit: "a study visit was defined by evaluable (non-missing) data from at least one test or procedure that required the patient to be present at the study site or at a hospital. A test or procedure could include physical examination, vital signs, 12-lead ECG, Holter monitor, laboratory test, exercise tolerance test, quality-of-life questionnaire, hospitalization, angiogram, or a revascularization procedure. A test or procedure with partial dates was not considered as a "known" visit." I calculated that 14% of ranolazine and 13% of placebo patients had incomplete follow-up using the sponsor's dates for a last visit by this surrogate, counting patients not known to be dead as having incomplete follow-up if their last visits were prior to September 25, 2006.

The subgroups with complete and incomplete follow-up differ substantially: The mean duration of follow-up patients with incomplete follow-up was about 4.1 months compared to 11.6 months for patients with complete follow-up in both treatment groups. The patients with incomplete follow-up were similar in age but included more women (40% vs. 35%). Rates of AEs leading to withdrawals were substantially different among the subgroups as shown in Table 1 as were rates of SAEs as shown in Table 2.

Table 1: Rates of AEs Leading to Withdrawals by Treatment and Follow-up Status in CVT 3036

	follow-up	
	incomplete	complete
placebo	20%	9%
ranolazine	27%	14%

Table 2: Rates of SAEs by Treatment and Follow-up Status in CVT 3036

	follow-up	
	incomplete	complete
placebo	32%	38%
ranolazine	26%	39%

While it is slightly reassuring that the percentage in each group is about the same, 17% incomplete follow-up could obscure many problems—it is substantially greater than the absolute rates of some the serious AEs identified below (angioedema, leucopenia) and greater than the differences in most serious AEs (e.g., cancer). The differences sex and particularly the differences in AE withdrawals and SAE rates confirm that the incomplete follow-up subjects can not be considered missing completely at random. Any observed differences in AEs must be interpreted in view of the possibilities that the differences are underestimated and that AE problems have been obscured completely.

Completeness of follow-up is not the only data quality issue for CVT 3036. I requested lot numbers of drugs with the intention of checking whether any variations in AE rates could be related to specific lot numbers. However patients in CVT 3036 were not dispensed consistent lot numbers even at the same visit. I show the distributions of lot numbers for the oral study drugs in Table 3.

Table 3: Distributions of Oral Study Drug Lot Numbers Dispensed at One Visit in CVT 3036

	placebo		ranolazine	
	n	%	n	%
2H2794, 3E2720	37	0.2%		
A01548, A01645	202	1.1%		
2H2795	237	1.3%		
2H2795, 3E2718	616	3.3%		
A09761, A09762, A09763, A09765	1410	7.5%		
3I2776, 3I2778, 3I2779, A01550	5609	29.7%		
3I2773, 3I2774, A01548	476	2.5%	2	0.01%
A01549, A01701, A02041, A02289, A03295	10276	54.5%	8	0.04%
2I2799			51	0.3%
3E2724			203	1.1%
A13942			389	2.1%
3E2724, 3E2725			612	3.3%
A10395, A10397			768	4.2%
3H3023, 3H3024, 3K3050			936	5.1%
A02036, A02037, A02038			4745	25.9%

	placebo		ranolazine	
	n	%	n	%
A10381, A10382, A1039			5013	27.3%
3H3026, 3K3043, 3K3044, 3K3045	3	0.02%	5619	30.6%

Note that five (for placebo) and four (for ranolazine) lot numbers were the modes of lot numbers dispensed at one visit. Visits were typically every four months, so the mode of four for ranolazine appears to be explained by dispensing four bottles. However, the wide variation in lot numbers dispensed makes it virtually impossible to correlate lot numbers with AEs. Conversely, while the lot numbers appear randomly assigned, the lot number groupings appear less random.

There are also problems with the Holter recordings. I asked the sponsor to submit files regarding the durations of the Holter recordings for each patient, reasons for discontinuations, etc. The Holter stop times and durations the sponsor submitted in the MERLIN04.XPT dataset in Serial 023 appear to be unreliable. I found the following problems:

- Virtually all durations are an integer number of hours. The sponsor described getting the start times from the CRFs but deriving the durations from the Holter recordings themselves and calculating the end time as the start time plus the duration. The Holter devices with which I am familiar record time much more precisely, e.g., minute or second. Furthermore, 1,825 (28%) of the recordings are exactly 168 hours (i.e., 7 days). While this might represent rounding, one of the following two outlier examples suggests not.

- I examined Holter durations for patients who died in-hospital. Among them, the following two patients died the day of admission. I verified the Holter start time (hstart) and death time (dthtime) against the CRFs.

Table 4: Outliers for Holter Recordings Continuing After Death in CVT 3036

usubjid	(b) (6)
CVT3036_86076032	
CVT3036_94096001	

Note that the Holter durations exceed the times between Holter start and death by 6 days and 5 hours respectively. The first patient is among those with a complete Holter recording of 168 hours (and the only one in this category among the patients who died prior to 168 hours). The sponsor reported that the first case was a technician error and, for the second case, the Holter showed ECG activity for the duration of 18 hours. The sponsor also reported that rounding was done to the hour and that the Holters were set to record only for 168 hours. After considering these two extreme examples and the sponsor's explanations suggesting serious quality problems, I have concluded that the Holter durations are unreliable.

The Holter duration data are unacceptable. The sponsor will need to verify and resubmit these data, and those in the related MERLIN03.XPT from Serial 026, before they can be reviewed and the Holter data relied upon to substantiate the safety of ranolazine. In the resubmission the sponsor must provide durations to the precision of time recordings in the Holter.

7.2.2.2. Interaction with diltiazem and verapamil

About 8% of patients took diltiazem or verapamil in-hospital and 7% took diltiazem or verapamil post-hospital, slightly higher in ranolazine patients. The sponsor alleges that AEs were slightly higher in the patients taking diltiazem or verapamil and that the AEs had similar patterns with the exception of substantially more dizziness in the ranolazine patients also taking diltiazem or verapamil. I note that other common ranolazine adverse reactions, such as asthenia, were also increased by this combination, and I show my analyses for dizziness in Table 5 and asthenia in Table 6.

Please note: I present here the results only for combined diltiazem or verapamil use. The results for diltiazem or verapamil analyzed separately are similar, although the verapamil results show more variability because of the smaller number of patients on verapamil.

Table 5: Patients with Dizziness AEs by Post-Hospital Diltiazem/Verapamil Use Post-Hospital in CVT 3036

	diltiazem/verapamil	
	no	yes
placebo	7%	10%
ranolazine	12%	22%

Table 6: Patients with Asthenia AEs by Post-Hospital Diltiazem/Verapamil Use in CVT 3036

	diltiazem/verapamil	
	no	yes
placebo	3%	3%
ranolazine	5%	8%

By logistic regression both ranolazine use and diltiazem/verapamil use are highly statistically significant predictors of dizziness ($p<0.0001$) and ranolazine use is also a highly statistically significant predictor of asthenia, but the interactions between ranolazine and diltiazem/verapamil are not statistically significant. (Please note that I have included these p values and ones below at the request of the Division Director as measures of unlikeliness; they do not have the usual interpretation of that for a pre-specified primary hypothesis.)

Rates of SAEs (Table 7), withdrawals for AEs (Table 8), in-hospital and post-hospital deaths (Table 10) were higher with combined ranolazine and diltiazem or verapamil use.

Table 7: Patients with SAEs by Post-Hospital Diltiazem/Verapamil Use in CVT 3036

	diltiazem/verapamil	
	no	yes
placebo	34%	44%
ranolazine	33%	53%

Table 8: Withdrawals for AEs by Post-Hospital Diltiazem/Verapamil Use in CVT 3036

	diltiazem/verapamil	
	no	yes
placebo	8%	10%
ranolazine	13%	16%

Table 9: In-Hospital Deaths by In-Hospital Diltiazem/Verapamil Use in CVT 3036

	diltiazem/verapamil	
	no	yes
placebo	1.3%	1.2%
ranolazine	1.4%	2.1%

Table 10: Post-Hospital Deaths by Post-Hospital Diltiazem/Verapamil Use in CVT 3036

	diltiazem/verapamil	
	no	yes
placebo	4.2%	3.2%
ranolazine	3.7%	6.1%

Ranolazine use, diltiazem/verapamil use, and age are highly significant ($p<.0001$) predictors of withdrawal. Diltiazem/verapamil use ($p=0.001$) and age ($p<.0001$) are highly significant predictors of SAEs while ranolazine is not. The interaction term between ranolazine use and diltiazem/verapamil use is not significant in these analyses. None of the treatments is a significant predictor of deaths, although age is.

I did not detect any patterns to either the SAEs or withdrawals for AEs with combined ranolazine and diltiazem or verapamil use. However, deaths for patients on diltiazem or verapamil show the patterns in Table 11 and Table 12.

Table 11: In-Hospital Death Causes for Patients on Diltiazem/Verapamil in CVT 3036

	Randomized arm		On study drug	
	placebo	ranolazine	placebo	ranolazine
acs	2	4	1	4
respiratory	1	0	0	0
sudden arrest	0	2	0	2
Total	3	6	1	6

Table 12: Post-Hospital Death Causes for Patients on Diltiazem/Verapamil in CVT 3036

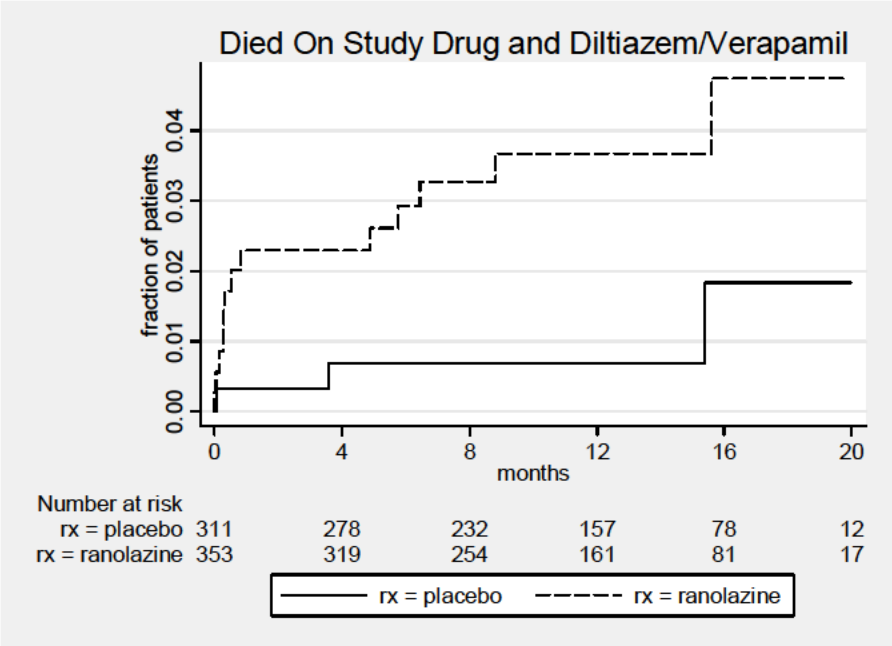
	Randomized arm		On study drug	
	placebo	ranolazine	placebo	ranolazine
acs	2	3	1	1
bleed	0	1	0	0
hf	2	2	0	1
infection	1	1	0	0
other cardiac	0	1	0	0
sudden/arrest	1	5	1	4
unknown	1	1	0	1
Total	7	14	2	7

In Table 11 and Table 12 I show the deaths both by randomized arm regardless of whether the patient was on study treatment at the time of death and for those patients on study drug on the date of death. Thirteen ranolazine but only three placebo patients treated with diltiazem or verapamil were on study drug on the date of their deaths (p=0.023 by Chi square). I show the Kaplan-Meier failure plot of deaths on study drug and verapamil or diltiazem, censoring patients who did not die on study drug at the time of study drug discontinuation, in Figure 5. The p value for the comparison of ranolazine to placebo for times to deaths on study drug is 0.023 by log rank analysis.

Because of these concerning results, we requested at a teleconference on July 8, 2008, that the sponsor provide their analyses regarding events in the subgroups of patients treated with diltiazem or verapamil as well as other CYP3A4 and Pgp inhibitors. The sponsor's encodings of diltiazem and verapamil use appear to be accurate and I have only one minor disagreement with them: Four patients (two in each of the treatment groups) did not have any concomitant medication records for diltiazem or verapamil but did have antianginal therapy intensification records listing diltiazem or verapamil. The sponsor counted these four patients as not taking diltiazem or verapamil while I counted them for all of my analyses above as taking diltiazem or verapamil. I counted, as the sponsor did, patients whose CRFs recorded use only for the two weeks preceding hospitalization as not taking diltiazem/verapamil. I also performed all of the above analyses using the sponsor's assignments and confirmed that, regardless of how these four cases are counted, the results remain the same. The sponsor also submitted data on 273 patients who took other CYP3A4 or Pgp inhibitors at some time during the study. Because of the late

and incomplete submission (e.g., drug identity and duration were not submitted), I did not review these data.

Figure 5: Kaplan-Meier Failure Plot of Patients Who Died on Study Drug and Diltiazem or Verapamil in CVT 3036



p = 0.023 by log rank

For comparison, I show selected corresponding results for concomitant amlodipine use (excluding any patients who received diltiazem or verapamil) in the following four tables.

Table 13: Patients with Dizziness AEs by Post-Hospital Amlodipine Use Post-Hospital in CVT 3036

	amlodipine	
	no	yes
placebo	7%	8%
ranolazine	12%	13%

Table 14: Withdrawals for AEs by Post-Hospital Amlodipine Use in CVT 3036

	amlodipine	
	no	yes
placebo	8%	7%
ranolazine	13%	15%

Table 15: In-Hospital Deaths by In-Hospital Amlodipine Use in CVT 3036

	amlodipine	
	no	yes
placebo	1.4%	1.1%
ranolazine	1.5%	1.0%

Table 16: Post-Hospital Deaths by Post-Hospital Amlodipine Use in CVT 3036

	amlodipine	
	no	yes
placebo	4.0%	4.7%
ranolazine	3.5%	4.5%

The amlodipine results in the above table do not suggest any interaction between ranolazine and amlodipine. Both sets of results (diltiazem/verapamil and amlodipine) are consistent with what is known about their potential for PK interaction with ranolazine.

I believe that the PK data showing roughly doubling of the exposure when ranolazine is combined with diltiazem or verapamil and the increases in typical and more serious adverse events and deaths argues that the dosage of ranolazine should be cut in half or more if diltiazem or verapamil are ever used concomitantly. The increases in deaths and particularly sudden deaths with combined ranolazine and diltiazem or verapamil use are very concerning even though the numbers of deaths are small. While in the entire study there appear to be no increase in sudden deaths and no problems with TdP (although note the data quality problems), the adverse events and deaths with combined ranolazine and diltiazem or verapamil use suggest that the therapeutic range for ranolazine beyond which AEs and mortality increase is very narrow. We don't know whether halving the dose is adequate in all patients taking a moderate CYP3A inhibitor. We need substantial evidence of safety to counter this suggestive evidence of a serious safety problem. Scrutinizing the in-hospital Holters should help us to understand the in-hospital deaths, but Holters are not available for the post-hospital deaths. I favor continuing to contraindicate all moderate to potent CYP3A inhibitor use with ranolazine unless the sponsor can provide substantial evidence of safety, i.e., an adequate and well-controlled clinical events interaction study with concomitant diltiazem use.

7.2.2.3. Interaction with simvastatin

While simvastatin (a weak inhibitor of CYP3A4 as well as a substrate for it) at 20 mg daily did not increase ranolazine levels in healthy subjects, the plasma levels of simvastatin and its active metabolite are each increased about two-fold in healthy subjects receiving simvastatin 80 mg daily and ranolazine 1000 mg BID. Hence I examined adverse event and lab value profiles for simvastatin and other HMG-CoA reductase inhibitors ("statins").

Statin use was common in CVT 3036, with about 88% of patients taking a statin at some time. Among patients taking statins, simvastatin was the statin most frequently used (about 55%) followed by atorvastatin (about 44%). Use of lovastatin, the other statin with high CYP3A metabolism, was infrequent (about 1%)—for the following analyses I will include lovastatin with the simvastatin statistics because lovastatin should interact similarly to simvastatin. Please note

that these use statistics are for any use and not continuous or exclusive use, e.g., about 18% of patients received more than one type of statin at some time (not concomitantly) during the study.

Rates of dizziness adverse events were increased with combined ranolazine and statin use as shown in Table 17.

Table 17: Patients with Dizziness AEs by Any Statin Use in CVT 3036

	placebo	simvastatin/ lovastatin	other statin	> 1 statin
placebo	3%	7%	8%	9%
ranolazine	5%	13%	14%	16%

All statins, e.g., simvastatin, atorvastatin, show the same pattern of dizziness AEs. Hence I would presume that the increased dizziness with combined ranolazine and statin use is the result of overlapping PD effects rather than a PK interaction.

Rates of myalgia AEs (Table 18) and hepatic AEs (Table 19) were higher with statin use but were not increased with combined statin and ranolazine use.

Table 18: Patients with Myalgia AEs by Any Statin Use in CVT 3036

	placebo	simvastatin/ lovastatin	other statin	> 1 statin
placebo	0.0%	0.7%	2.0%	1.6%
ranolazine	0.5%	0.9%	1.5%	1.0%

Table 19: Patients with Hepatic* AEs by Any Statin Use in CVT 3036

	placebo	simvastatin/ lovastatin	other statin	> 1 statin
placebo	0.0%	0.7%	2.0%	1.6%
ranolazine	0.5%	0.9%	1.5%	1.0%

*noninfectious hepatitis or hepatic insufficiency or steatosis

Withdrawals for AEs (Table 20) were more frequent with ranolazine use and were increased with concomitant statin and ranolazine use. However, they were more frequent with other statins than with simvastatin or lovastatin. Deaths (

Table 21) were lower with any statin use and were very similar between ranolazine and placebo. (The death rate was very low in the patients receiving more than one statin, but this may reflect the possibility that longer living patients are more likely to have opportunities for receiving more than one statin.)

Table 20: Patients with AEs Leading to Withdrawal by Any Statin Use in CVT 3036

	placebo	simvastatin/ lovastatin	other statin	> 1 statin
placebo	6%	7%	9%	9%
ranolazine	9%	13%	15%	15%

Table 21: Deaths by Any Statin Use in CVT 3036

	placebo	simvastatin/ lovastatin	other statin
placebo	10.2%	4.7%	4.6%
ranolazine	10.1%	4.5%	4.9%

The withdrawal AEs more frequent with ranolazine and statin use were the typical ranolazine AEs: dizziness, nausea, constipation, and asthenia.

Changes from baseline to last measurement in LDL were about the same with statins alone or statins combined with ranolazine as shown in Table 22. If anything, the LDL results suggest that ranolazine may increase LDL levels slightly.

Table 22: Changes from Baseline in LDL (mg/dL) by Any Statin Use in CVT 3036

	placebo	simvastatin/ lovastatin	other statin	> 1 statin
placebo	2	-15	-26	-19
ranolazine	7	-15	-21	-17

Changes from baseline to last measurement in ALT were small and similar regardless of statin or ranolazine use as shown in Table 23. Other statistics for ALT, e.g., maximum increase greater than threefold, were also indistinguishable by statin or ranolazine use.

Table 23: Changes from Baseline in ALT by Any Statin Use in CVT 3036

	placebo	simvastatin/ lovastatin	other statin	> 1 statin
placebo	-2	-4	-2	-4
ranolazine	-5	-6	-4	-7

These results do not suggest that there is a clinically important of ranolazine upon simvastatin or other statins. The results are slightly suggestive that statins may increase ranolazine levels.

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(b) (4)

7.2.2.5. Cancer adverse events

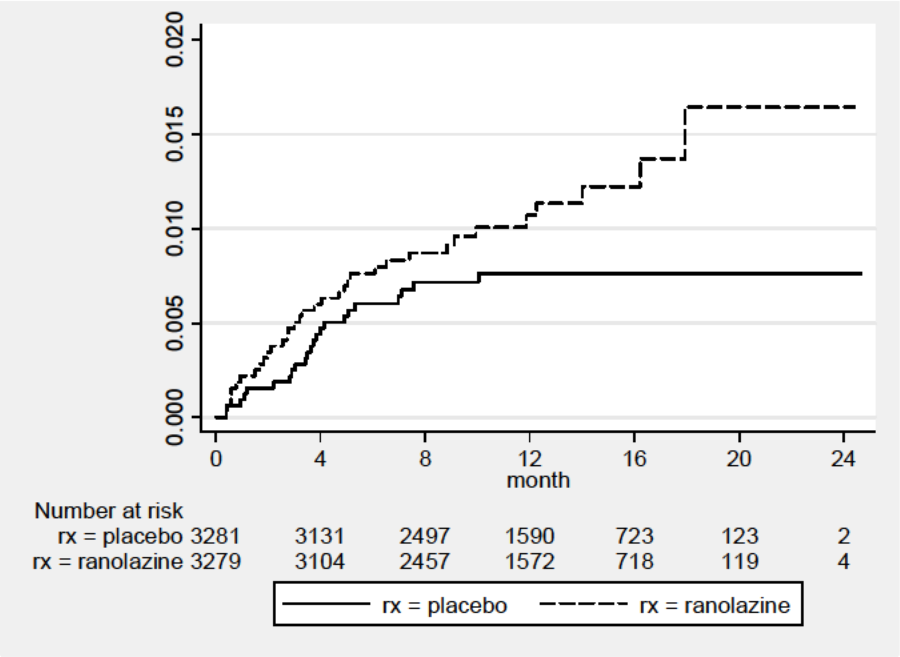
Patients with a history of cancer were evenly distributed between ranolazine (135, 4.1%) and placebo (129, 3.9%). However, there were more newly diagnosed cancers in the ranolazine group compared to the placebo group as shown in Table 32.

Table 32: Numbers of Newly Diagnosed Cancers (Excluding the First Week) in CVT 3036

	placebo	ranolazine
bladder	1	1
breast	3	1
colorectal	3	6
esophagus	0	1
head & neck	2	0
kidney	0	3
leukemia	0	2
liver	1	0
lung	6	10
lymphoma	0	2
melanoma	2	0
mesothelioma	0	1
pancreas	1	1
prostate	2	2
sarcoma	0	1
small intestine	1	0
stomach	1	0
thymus	0	1
thyroid	0	1
unknown	0	1
uterus	0	1
total	23	35

Note that in Table 32 I have excluded cancers diagnosed within the first week—in these patients with ACS, cancer findings noted on admission were typically not worked up until after the ACS event subsided. There were four cancers in the ranolazine group diagnosed in the first two days compared to none in the placebo group—Hence not excluding cancers diagnosed in the first week makes the ranolazine numbers worse. The first newly diagnosed cancers after the first week were diagnosed starting at day 12. The Kaplan-Meier (K-M) incidence plot of cancers newly diagnosed after the first week is strange as shown Figure 6.

Figure 6: Kaplan-Meier Incidence Plot of Cancers Newly Diagnosed after 7 Days in CVT 3036



There is a moderate excess of cancers in the ranolazine group, largely colorectal, lung, and leukemia/lymphoma. The K-M incidence plot is difficult to interpret: It diverges early and the late separation of the curves is due to no cancers diagnosed in the placebo group after about 11 months. If the late divergence is real, it would be greatly concerning. A significant limitation for this analysis of cancer rates is a lack of power of CVT 3036 to detect or document a difference in cancer rates: The power to detect a 50% increase in all cancers is about 0.28; to have 0.80 power of detecting a 50% increase the study would have to be about four times as large. CVT 3036 doe not clearly document that ranolazine is carcinogenic but it does leave concerns about a carcinogenic potential.

7.2.2.6. Renin-angiotensin system inhibitor-like adverse events

Surprisingly, ranolazine shows a pattern of AEs suggestive that it may be a renin-angiotensin system (RAS) inhibitor or that it potentiates the effects of other RAS inhibitors. I show the relevant AEs in Table 33 and relevant lab values in Table 34. For lab values I excluded values (other than baseline values) within the first 14 days after the event because of instability and possible effects from other interventions during that time.

Table 33: Numbers of Patients with AEs Relevant to RAS Inhibition in CVT 3036

	placebo	ranolazine
patients	3281	3279
angioedema	0	6*

cough (dry/no URI)	82	120
cough due to ACEI	9	7
cough leading to d/c	1	5
hyperkalemia	20	19
hypokalemia	30	22
creatinine increased	37	60
renal impairment	67	97
hypertension	165	138
hypotension	148	228

*all angioedema cases were discontinued

Table 34: Lab Values Relevant to RAS Inhibition in CVT 3036

	placebo	ranolazine
potassium baseline meq/L	4.23	4.22
potassium mean meq/L	4.40	4.44
potassium max meq/L	4.64	4.68
potassium max > 5.5, n	110	132
potassium min < 3.5, n	117	88
creatinine baseline mg/dL	1.04	1.04
creatinine mean mg/dL	1.06	1.13
creatinine max mg/dL	1.15	1.24
creatinine max >1.5x cr base, n	484	616
hemoglobin base	13.8	13.8
hemoglobin change to last	0.08	-0.16

The increase in dry coughs suggested to me that ranolazine might have ACEI activity or potentiate ACEIs. In this ACS population concomitant ACEI use was common (about 71% in each group post-hospital) and concomitant ARB use was less common but not infrequent (about 13% in each group post-hospital.) Post-hospital use of either RAS inhibitor was about 78%. I show the rates for AEs relevant to RAS inhibition by both ranolazine and ACEI/ARB use in Table 35 and the relevant lab values in Table 36.

Table 35: **Numbers of Patients with AEs Relevant to RAS Inhibition in CVT 3036 by Ranolazine and ACEI/ARB Use in CVT 3036**

	placebo		ranolazine	
	no ACEI/ARB	ACEI/ARB	no ACEI/ARB	ACEI/ARB
patients	681	2557	753	2479
angioedema	0.00%	0.00%	0.00%	0.24%
cough (dry/no URI)	1.6%	2.8%	1.6%	4.4%
hyperkalemia	0.3%	0.7%	0.4%	0.6%
hypokalemia	0.4%	1.1%	0.4%	0.8%
creatinine increased	1.1%	1.1%	1.3%	1.9%
renal impairment	1.2%	2.3%	1.8%	3.3%
renal SAE	0.4%	0.7%	0.5%	1.3%
hypertension	2.8%	5.7%	1.5%	5.1%
hypotension	4.7%	4.5%	6.1%	7.2%
anemia	3.5%	3.8%	3.7%	4.5%

Table 36: Lab Values Relevant to RAS Inhibition in CVT 3036 by Ranolazine and ACEI/ARB Use in CVT 3036

	placebo		ranolazine	
	no ACEI/ARB	ACEI/ARB	no ACEI/ARB	ACEI/ARB
potassium baseline meq/L	4.22	4.23	4.18	4.23
potassium mean meq/L	4.34	4.41	4.39	4.45
potassium max meq/L	4.58	4.66	4.62	4.71
potassium max > 5.5, %	2.7%	4.1%	2.6%	5.2%
potassium min < 3.5, %	3.7%	4.1%	2.6%	3.2%
creatinine baseline mg/dL	1.01	1.04	1.02	1.05
creatinine mean mg/dL	1.02	1.07	1.09	1.14
creatinine max mg/dL	1.11	1.17	1.18	1.25
creatinine max >1.5x base, %	14%	14%	17%	18%
hemoglobin base	13.9	13.7	14.0	13.8
hemoglobin change to last	.22	.05	-.05	-.20

Dry cough was only increased in the ACEI/ARB subgroups and it was only increased in the patients also taking ACEIs, not ARBs (analysis not shown). Note that it was substantially increased in ranolazine patients who at some time received an ACEI.

For renal impairment AEs and renal SAEs, the rates are higher with ranolazine than placebo and even higher with combined ranolazine and ACEI/ARB use. The apparent increases in hypokalemia with ACEI/ARB use are likely spurious because ACEI/ARBs are used to treat hypertension and HF, diseases for which diuretics are also commonly prescribed. Similar confounding is likely operational for the increased rates of hypertension for ACEI/ARBs, but note the lower rate of hypertension for ranolazine alone and the higher rates of hypotension for ranolazine and ranolazine combined with ACEI/ARBS.

While anemia is not ordinarily considered an AE relevant to RAS inhibition, I have observed the association in other large outcome studies, e.g., the LIFE study with losartan in which hospitalizations for anemia were increased in the losartan group. In CVT 3036 rates of anemia are slightly increased with ACEI/ARB or ranolazine use and increased more with combined ACEI/ARB and ranolazine use.

There are some limitations to these analyses: ACEI/ARB use was not randomly assigned and I analyzed only any use of the ACEI/ARBs at hospital discharge or later and did not determine the timing of administration relative to the AE. Other confounding based on indications, in addition to hypertension and HF mentioned above, is possible, e.g., a diabetic with declining renal function could have been started on the ACEI/ARB as treatment rather than the ACEI/ARB contributing to the renal impairment.

Despite these limitations, I still interpret these findings as suggestive that ranolazine potentiates RAAS inhibition and cannot rule out that ranolazine is a RAAS inhibitor. The increase in renal SAEs is worrisome, and I discuss it further

below. There is a possible mechanism for how ranolazine might potentiate RAAS inhibition: One study demonstrated that ranolazine may interfere with tubular secretion of creatinine. Many of the ACEIs are renally excreted. So ranolazine might interfere with the renal excretion of ACEIs. However, its interference with creatinine secretion is presumed to be based on inhibition of organic cation transport (OCT), while ACEIs are anions and are handled by organic anion transport proteins (OATP), as are some ARBs. Ranolazine has both anion and cation metabolites. Regardless, a clinical PK and PD interaction study with an ACEI and an ARB is needed based on the clinical findings in CVT 3036.

7.2.2.7. Cytopenias

While the hemoglobin reductions are slight and almost universal, a few patients experienced rare events of cytopenias as shown in Table 37.

Table 37: Cytopenia Adverse Events in CVT 3036

	placebo	ranolazine
leucopenia	0	5
pancytopenia	0	3
thrombocytopenia	7	15
leuco/thrombo/pancytopenia	7	22

Note that there is only one case that overlaps among the cases of leucopenia, thrombocytopenia, and pancytopenia, so the difference between ranolazine and placebo in numbers of patients having any one of these three AEs is substantial. Regarding severity, one placebo patient with thrombocytopenia died of ACS and one ranolazine patient with pancytopenia died of infection. The latter patient, an 85 year-old male, developed pancytopenia and urosepsis about six months after starting treatment with ranolazine. He was discharged improved with the pancytopenia attributed to sepsis but also started on captopril. He continued to have recurrent infections and ranolazine was discontinued after eight months. He died of sepsis at about 12 months still taking captopril. While I did not include cytopenias in the previous section because the presumed mechanism is not ACE inhibition, leucopenia/agranulocytosis is a labeled concern of ACEIs, particularly captopril.

7.2.2.8. Serum creatinine increases and acute renal failure

As shown in Table 35, renal impairment AEs were more frequent with ranolazine than placebo, particularly with ACEI use. Ignoring ACEIs and other drugs, the overall rates of such AEs were about 2% in placebo patients and 3% in ranolazine patients, with numbers of patients as shown in Table 33. Renal impairment AEs that were serious or led to withdrawal occurred in 0.7% of placebo patients and 1.3% of ranolazine patients, but deaths were more common among the placebo patients with these AEs than the ranolazine patients (19% vs. 12% of patients with renal impairment AEs, death counts one higher with placebo, 13 vs. 12). However, three times as many ranolazine as placebo patients with these AEs withdrew

consent (22 vs. 7). About a third of the ranolazine AEs occurred within the first five days. During the first five days any renal impairment AEs were more frequent with ranolazine (32 vs. 14) as well as serious AEs or withdrawals (10 vs. 3).

Most risk factors for a renal impairment AE are not surprising as shown by the logistic regression in Table 38.

Table 38: Logistic Regression of Renal Impairment AEs by Baseline Risk Factors and Treatment in CVT 3036

```
Logistic regression                                 Number of obs   =       6560
                                                    LR chi2(6)      =     210.64
                                                    Prob > chi2     =     0.0000
Log likelihood = -661.59008                         Pseudo R2       =     0.1373

------------------------------------------------------------------------------
   renimpair | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  ranolazine |   1.454996    .242088     2.25   0.024     1.050112    2.015989
         age |   1.060572   .0092079     6.77   0.000     1.042677    1.078773
        male |   1.617747   .2941507     2.65   0.008     1.132762    2.310374
  hx ren imp |   7.681227   1.561653    10.03   0.000     5.156735    11.44159
hypertension |   2.384353   .6489722     3.19   0.001     1.398592    4.064904
    diabetes |   1.506333   .2513178     2.46   0.014      1.08619    2.088989
------------------------------------------------------------------------------
```

That older age and histories of renal impairment, hypertension, or diabetes are risk factors are not surprising. That males are at greater risk than females may not have been predictable in advance but also is not surprising. Ranolazine remains a significant risk factor. However, there is one additional relevant subgroup analysis: For US patients there was minimal difference in renal impairment AEs between the two treatment groups overall.

Because of a lack of a substantial impact upon mortality and the neutral results in the US, these renal impairment AEs do not appear to be a serious problem. I hypothesize that they are related to the documented slight increases in creatinine with ranolazine and its RAS inhibitor-like effects discussed previously. The concern I have about drawing firm conclusions regarding renal safety for ranolazine relates to the questions about the completeness of the data and follow-up.

7.2.2.9. Miscellaneous adverse events

Two other adverse events appear to be more frequent with ranolazine than placebo as shown in Table 39.

Table 39: Miscellaneous Adverse Events in CVT 3036

	placebo	ranolazine
pulmonary fibrosis	4	8
without history	3	6
influenza	33	52

None of the pulmonary fibrosis cases received amiodarone. Four of the ranolazine and none of the placebo cases withdrew for AEs; one of the AE withdrawals also withdrew consent for follow-up. One case without a history withdrew for an AE of severe "IDIOPATHIC PULMONARY FIBROSIS" starting on the first day. Two of the ranolazine cases died: One death was in an 82 year-old white female without a prior history in whom "DIFFUSE PNEUMOSCLEROSIS" was noted on day 9; the other was in a 64 year-old white male with a prior history of pulmonary fibrosis. Pulmonary fibrosis must be mentioned in the label.

Regarding influenza, other infections appear to be evenly distributed between ranolazine and placebo. None of the influenza events were reported to have led to withdrawal. I suspect the difference in influenza rates may be related to other ranolazine toxicity such as nausea, vomiting, or dizziness.

8. Advisory Committee Meeting

We are not submitting this supplemental submission to an advisory committee.

9. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

10. Financial Disclosure

The sponsor submitted financial disclosures for CVT 3036 and CVT 3023 as agreed upon with the Division at pre-NDA meetings. The primary clinical reviewer reviewed these disclosures and, in a separate memo dated June 6, 2008, concluded that there was no unusual activity.

11. Labeling

My recommendations for labeling are the following:

- [redacted] (b) (4)

- I recommend approval of the indication for the treatment of chronic angina but with many labeling cautions as itemized below. The indication sections, including the highlights, should include the following text: "Limitation of use: Ranexa has many drug interactions, including ones mediated by CYP3A, Pgp, and organic ion transporters. The clinical effects of many of these interactions have not been well characterized. Consider all potential drug interactions when prescribing Ranexa."

- All currently labeled contraindications should remain. They are pre-existing QT prolongation, hepatic impairment, QT-prolonging drugs, and potent and moderately potent CYP3A inhibitors.

- The drug interactions sections, including the highlights, should be expanded to include all of the following:
    - Digoxin
    - Drugs metabolized by CYP2D6
    - (b) (4)
    - (b) (4)
    - (b) (4)
    - Other organic ion transport-mediated drugs

- The findings of increased deaths with concomitant diltiazem or verapamil use should be described or referenced in warnings, adverse reactions, and drug interactions.

- (b) (4)

- The occurrence of leucopenia and pancytopenia, including one death, should be described briefly in adverse reactions.

- Angioedema, pulmonary fibrosis, thrombocytopenia, leucopenia and pancytopenia should be added to the list of other adverse reactions that have been noted to occur rarely.

- (b) (4)

(b) (4)

12. DSI Audits

Because the major study failed on its primary efficacy endpoint we elected not to perform DSI audits.

13. Conclusions and Recommendations

13.1. Recommended regulatory action

I recommend approval of ranolazine for the treatment of chronic angina but with many labeling cautions. The major study submitted, CVT 3036, provides some reassurance that ranolazine is safe at the marketed dosage in high risk ACS patients without potential drug interactions. However, the reassurance of safety is limited by the incomplete follow-up in the study and the quality of the Holter recordings. The results in the subgroup treated with ranolazine and diltiazem or verapamil do not confirm that ranolazine is safe in this subgroup, one with a known yet moderate drug interaction. Ranolazine appears to have the potential for many drug interactions that are not well characterized but also, except for the interaction with diltiazem and verapamil, do not appear dangerous. The label must explicitly address all of the potential interactions. I also recommend required postmarketing safety studies as outline below under Postmarketing studies.

(b) (4)

13.2. Safety concerns to be followed postmarketing

I recommend that the safety concerns regarding potential drug interactions be addressed by specific postmarketing studies as discussed under Postmarketing studies. In addition, I note two other safety concerns that are not drug interactions:

- While the study overall is reassuring that arrhythmias and sudden death are not problematic, the subgroup analysis in patients receiving diltiazem or verapamil does not confirm that ranolazine is convincingly safe with regard to this safety

issue. Furthermore, the incomplete follow-up and quality problems with the Holter data make the overall study results less convincing. We will continue to scrutinize the post-marketing adverse event reports regarding arrhythmias and sudden deaths.

- The analysis of cancer deaths also does not rule out an effect upon cancers. The clinical data alone are slightly suspicious but would not raise any undue concerns if the pre-clinical data were completely negative. While I judge that the current pre-clinical and clinical findings are not sufficiently suspicious to justify mandating a cancer outcome study, I favor following the post-marketing safety reports for any hint of a problem with carcinogenesis.

13.3. Risk Minimization Plan

I do not recommend a risk minimization plan. While there are unanswered questions regarding the potential for ranolazine to interact with other drugs by several different mechanisms (see Postmarketing studies), I believe that these potential interactions can be sufficiently addressed in the labeling. I also find it slightly reassuring that the large CVT 3036 outcome trial did not find a difference in total mortality compared to placebo. I would have found it more reassuring if follow-up in that study had been more complete.

13.4. Postmarketing studies

I recommend the following postmarketing safety studies be required:

- [redacted] (b) (4)

- *In vitro* studies of ACE inhibition and angiotensin II receptor blockade and a clinical drug interaction study with placebo, ACEI, ARB, combined ACEI and ranolazine, and combined ranolazine and ARB arms or crossover periods with measurements of drug levels for all drugs, BP, and renin-angiotensin system pharmacodynamics

The results of the above studies may suggest other clinical studies to be required. In addition, to remove the contraindication with moderately potent CYP3A inhibitors, the sponsor must do the following:

- Submit for review Holter recordings for patients who were administered diltiazem or verapamil and who died, experienced an arrhythmia related SAE, withdrew, or had a dose reduction and for other patients specified by the Division.

- If the Holter recordings do not convincingly confirm or refute a problem with arrhythmias or deaths for patients taking ranolazine and diltiazem or verapamil, the sponsor must conduct and submit a successful double-blind, placebo-controlled trial of ranolazine or placebo added to diltiazem or verapamil.

13.5. Comments to be conveyed to the applicant

The proposed labeling changes and postmarketing studies will be discussed with the sponsor during label negotiations.

References

Morrow, D. A., B. M. Scirica, et al. (2007). "Effects of Ranolazine on Recurrent Cardiovascular Events in Patients With Non-ST-Elevation Acute Coronary Syndromes: The MERLIN-TIMI 36 Randomized Trial." JAMA **297**(16): 1775-1783.

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