Cardiovascular and Renal Drugs Advisory Committee

Briefing Document

Ranexa™
(ranolazine)
Extended Release Tablets

NDA 21-526

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LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AP	action potential
APD	action potential duration
AUC	area under the curve
AV	atrioventricular
b.i.d.	twice daily
BP	blood pressure
BUN	blood urea nitrogen
CAD	coronary artery disease
CARISA	Combination Assessment of Ranolazine In Stable Angina (Study CVT 3033)
CHF	congestive heart failure
C_{max}	observed maximum plasma concentration
DTS	Duke treadmill score
EAD	early afterdepolarization
ECG	electrocardiogram
ETT	exercise treadmill test
GTN	glyceryl trinitrate
HbA_{1c}	glycosylated hemoglobin A_{1c}
HMG CoA	hydroxymethyl glutaryl coenzyme A
HR	heart rate
IR	immediate-release
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	intent-to-treat
iv	intravenous(ly)
JT	QT interval minus the QRS duration
LOCF	last observation carried forward
LS	least squares
LV	left ventricular
MARISA	Monotherapy Assessment of Ranolazine In Stable Angina (Study CVT 3031)
MI	myocardial infarction
mmHg	millimeters of mercury

msec	millisecond(s)
NA	not applicable or not available
NS	not statistically significant
NYHA	New York Heart Association
P-gp	P-glycoprotein
PK	pharmacokinetic
po	per os (orally)
PR	electrocardiographic interval from the onset of the P-wave to the onset of ventricular depolarization
PTCA	percutaneous transluminal coronary angioplasty
PVC	premature ventricular contraction
q.d.	once daily
QRS	electrocardiographic interval from the onset of ventricular depolarization through its conclusion
QT	electrocardiographic interval from beginning of QRS complex to end the of T-wave
QTc	QT interval corrected for heart rate
QTcB	QT interval using Bazett correction for heart rate ($QT/RR^{0.5}$)
QTcF	QT interval using Fridericia correction for heart rate ($QT/RR^{1/3}$)
QT_{max}	the longest QT/QTc from any lead of a 12-lead ECG
RAD	reactive airway disease
RAN	ranolazine
RPP	rate pressure product
RR	electrocardiographic interval from peak of one QRS complex to the next
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SR	sustained-release
ST segment	represents the early stages of ventricular repolarization
t.i.d.	three times daily
TdP	torsade de pointes
TDR	transmural dispersion of repolarization
VF	ventricular fibrillation
vs	versus
VT	ventricular tachycardia

1 OVERVIEW

Ranolazine represents the first new class of anti-anginal drugs since calcium channel blockers were introduced in the 1970s. The major rationale for the development of ranolazine is its non-hemodynamic pharmacodynamic profile, in contrast to the profiles of currently available anti-anginal drugs (nitrates, beta-blockers and calcium channel blockers). Ranolazine has been developed and is proposed for the treatment of chronic angina in patients with severe coronary disease, as defined by their ischemia-limited exercise performance. This document includes an assessment of the demonstrated anti-anginal benefits of ranolazine vs the theoretical risk associated with small, but dose-related increases in the QTc interval.

Despite modern interventional therapy and use of the older anti-anginal medications, there are still 6.6 million patients who currently suffer from chronic angina. Such a large disease burden represents an unmet need and reflects many limitations of current therapy, including the morbidity and mortality of invasive procedures, and adverse events associated with current anti-anginal medications. For example, despite enormous growth in myocardial revascularization procedures, performed largely to prevent angina attacks,[1] approximately 60 to 80% of patients continue to require anti-anginal drugs. Even with both optimal revascularization and pharmacotherapy, up to 26% (or 1.7 million patients) still suffer angina attacks.[2-3]

Today's classes of drugs have similar depressive effects on blood pressure, heart rate, contractile function, and/or AV nodal conduction; as a result, when angina cannot be eliminated by combinations of beta-blockers, calcium channel blockers and nitrates, it is often these drugs' hemodynamic consequences that limit further dose escalation and thus preclude complete symptom relief. Furthermore, modern interventions have resulted in a precipitous drop in post-infarct mortality, resulting in a population of angina patients with more complex cardiac disease than before. These patients often require two or more classes of anti-anginal drugs to control their symptoms, but often cannot tolerate the

overlapping hemodynamic side effects of these therapies. Therefore, a drug that provides an anti-anginal and anti-ischemic benefit in the absence of deleterious effects on hemodynamic parameters could be especially useful in modern angina patients with complex cardiac disease.

The anti-anginal and anti-ischemic benefits of ranolazine have been clearly demonstrated across a broadly representative population of chronic angina patients in two Phase 3 studies and three supporting Phase 2 clinical trials. Importantly, it was learned early in the development program that ranolazine significantly increased exercise performance in patients judged by their physicians to be optimally treated with either atenolol or diltiazem yet continuing to have angina. In one of these trials, the increase in symptom-limited exercise duration was significantly greater on ranolazine than on atenolol 100 mg q.d.; furthermore, heart rate and blood pressure remained unchanged on ranolazine, compared to reductions of 29 bpm and 18 mmHg, respectively, on atenolol.

In a randomized, double-blind, placebo-controlled Phase 3 study of ranolazine as anti-anginal monotherapy (Study CVT 3031 or MARISA), statistically significant, dose-related increases in treadmill exercise parameters were demonstrated, at both trough and peak plasma ranolazine concentrations. In the second Phase 3 trial (Study CVT 3033 or CARISA), when given over a background of the most commonly prescribed doses of atenolol, diltiazem or amlodipine, ranolazine again significantly increased treadmill exercise times. In addition, ranolazine significantly reduced angina frequency and nitroglycerin use in a dose-related fashion. In each of these studies, the anti-anginal and anti-ischemic effects of ranolazine were demonstrated not to depend upon reductions in blood pressure or heart rate, nor was prolongation of the PR interval observed. Thus, the pharmacodynamic profile of ranolazine addresses an unmet need for a non-hemodynamic anti-anginal agent to complement the currently available agents.

Ranolazine is generally safe and well tolerated. The most common (≥ 2%) adverse events in Phase 3 controlled angina studies with an apparent dose

relationship to ranolazine were dizziness, constipation, nausea, and asthenia. In general, these events are mild to moderate in severity, occur soon after the initiation of therapy, and respond promptly to a reduction in dose or discontinuation of treatment. In clinical trials, AEs that resulted in discontinuation more frequently on ranolazine than on placebo were dizziness and nausea. Patient acceptance of ranolazine appears to be good, with 85% of patients electing to continue on open-label treatment after completing MARISA, and 82% after CARISA. Serious adverse events were sporadic, with no apparent pattern or dose relationship.

The demonstrated benefits of ranolazine must be weighed against the theoretical risk associated with the small, dose-related increases in the QTc interval, which average 2 to 5 msec at peak over the dose range 500–1000 mg b.i.d. Under maximum CYP3A4 inhibition by ketoconazole, the average QTc increase was 20 msec for subjects on 1000 mg b.i.d. While the degree of risk associated with QTc prolongation due to ranolazine is not precisely defined, there has never been a report of torsade de pointes in 2783 subjects/patients treated with ranolazine (1714 subject/patient years of exposure). In chronic angina patients whose mean Duke score was –14, first-year mortality during long-term treatment with ranolazine was 2.0%; i.e., not higher than the 5% annual mortality expected in this high-risk population of patients.[4]

An extensive program of nonclinical studies in multiple model systems, from single cells to whole animals, demonstrates that the cellular electrophysiologic profile underlying the QTc effect of ranolazine is fundamentally different from that of drugs known to cause torsade de pointes. Ranolazine neither provokes early afterdepolarizations nor increases the dispersion of repolarization, factors known to contribute to the genesis of torsade de pointes. Moreover, ranolazine has been shown to prevent the development of — and to even actively reverse — these pro-arrhythmic signals when other drugs known to cause torsades have induced them. These findings can only diminish the perceived risk due to QT prolongation by ranolazine.

Finally, patients who might benefit from the non-hemodynamic profile of ranolazine are easily identified. In contrast to the theoretical risk of the small QTc prolongation due to ranolazine, physicians can determine which of their patients benefit from ranolazine by directly observing a reduction in their angina symptoms. Those patients who do not respond to ranolazine with a decrease in angina symptoms need not be continued on the drug. For those whose angina symptoms are decreased by ranolazine, the benefit may outweigh the risk, if any, of the small QT effect.

In summary, ranolazine offers anti-anginal and anti-ischemic efficacy that does not depend upon decreases in blood pressure or heart rate, a novel pharmacodynamic profile clearly distinct from those of the current, hemodynamically acting anti-anginal drugs. Its efficacy, safety and tolerability have been demonstrated across a broadly representative population of patients with chronic angina, including 2783 subjects and patients, with a total duration of exposure exceeding 1700 subject/patient years. A small, dose-related increase in the QTc interval has been thoroughly clinically characterized; furthermore, an extensive program of nonclinical studies has demonstrated that the cellular electrophysiology of ranolazine is fundamentally different from that of drugs that prolong the QTc and are known to cause torsade de pointes, and similar to that of drugs that prolong the QTc but do not cause torsades. There has never been a reported case of torsade de pointes on ranolazine, and the first-year mortality of 2% on ranolazine is not higher than what has been reported for similarly characterized populations with high-risk coronary artery disease. Ranolazine will provide a valuable new therapeutic tool to the cardiac specialists who care for the 6.6 million patients in the United States who currently suffer from chronic angina.

2 INTRODUCTION

2.1 Chronic Angina

Approximately 6.6 million patients currently suffer from chronic angina in the United States, with about 400,000 new cases diagnosed each year.[5] These patients are typically elderly with an average age of 69 years.[6] The majority take two or more anti-anginal drugs in an attempt to control their debilitating symptoms.[7] Despite treatment, at least half of chronic angina patients endure two or more attacks per week and nearly half (47%) experience angina at rest, resulting in a profoundly diminished perception of their health and their ability to lead an active life.[6] The decrease in quality of life between patients who suffer attacks as seldom as monthly is greater than the decrement from monthly to weekly or from weekly to daily angina.[8] Although revascularization procedures reduce symptoms for many chronic angina patients, one year later, about a quarter of those considered to have been optimally revascularized continue to suffer from angina and 60–80% require anti-anginal medications.[2,3,9]

For patients, the relationship between angina episodes and their underlying ischemic heart disease has been likened to the acute phases of other chronic diseases such as asthma or multiple sclerosis (MS). Angina, asthma attacks, and exacerbations of MS all have a severe impact on the patient's quality of life, raise anxiety about future health, and cause an avoidance of particular activities in an effort to avoid these episodes.[10] In a study of 439 diabetic patients and 1666 angina patients, Wandell and colleagues found that the impact of angina on quality of life was equal to or greater than that of type 2 diabetes.[11] Green and coworkers report results from a 271-patient study that show that physical limitation and angina frequency are the most important determinants of quality of life after percutaneous coronary intervention.[8] Thus, reducing the symptoms of angina is a critical factor in maximizing patients' quality of life.

2.2 Limitations of Current Therapy

When angina cannot be controlled by combinations of beta-blockers, calcium channel blockers and nitrates, it is often their depressive effects on blood

pressure, heart rate, contractile function and/or atrioventricular (AV) nodal conduction, as well as other dose-related side effects, which limit further dose escalation and preclude relief from angina. Co-morbidities such as reactive airway disease, congestive heart failure (CHF), and diabetes complicate treatment with existing anti-anginal drugs because these conditions cause patients to be more vulnerable to known side effects of currently-approved therapies. For many chronic angina patients with these diseases, maximally tolerated anti-anginal therapy may not reach the maximum dose recommended in product labeling, may include only two of the three currently available drug classes, and may provide incomplete relief.

Beta-blockers are used only with caution, if at all, in patients with reactive airway disease, in whom even $beta_1$-selective drugs may precipitate bronchospasm. This is a major factor in the treatment of the 10–15% of the chronic angina population that also has co-existing chronic obstructive pulmonary disease. Beta-blockers can also worsen claudication in patients with angina who have significant peripheral vascular disease (approximately 10–15% of the chronic angina population) and can mask the symptoms of hypoglycemia in patients with both angina and diabetes (approximately 20–25% of the chronic angina population).[6]

Patients with CHF comprise approximately 25% of chronic angina patients. Although beta-blockers are indicated as a treatment for CHF, they must be initiated and titrated with caution in order to avoid precipitating more severe heart failure; consequently, a complete anti-anginal effect cannot be achieved with beta-blockers in some CHF patients. Furthermore, co-administration of beta-blockers with digoxin may additively slow AV nodal conduction.

All of these potential untoward effects of beta-blockers have resulted in warnings or precautions in the product labeling.

The calcium channel blockers diltiazem and verapamil should be used with caution in patients with CHF, as they may precipitate worsening failure, particularly when combined with a beta-blocker. These drugs also prolong AV nodal conduction and may cause second or third degree AV block. The combination of calcium channel blockers with beta-blockers or digoxin may result in additive prolongation effects at the AV node.

In the Multicenter Diltiazem Postinfarction Trial (MDPIT), patients without pulmonary congestion showed a reduced number of cardiac events on diltiazem vs placebo, while patients with pulmonary congestion had an increased number of events due to diltiazem.[12] A similar pattern was observed with respect to deaths from cardiac causes. In a further analysis of the MDPIT data,[13] diltiazem increased late-onset CHF in patients who demonstrated an early post-infarction reduction of ejection fraction, a group predisposed to CHF.

Many dihydropyridine calcium channel blockers should also be used with caution in patients with CHF because of the risk of worsening failure. In view of these and other similar data, most calcium channel blockers carry warnings or precautions against their use in patients with CHF.

Finally, while long-acting nitrates are used to treat angina, tolerance to nitrates develops rapidly, so they cannot provide continuous anti-anginal prophylaxis.

Thus, the treatment of angina is suboptimal in many patients because they cannot tolerate the currently available agents at doses sufficient to treat their symptoms either because of their concomitant diseases, or because of the adverse effects intrinsic to the drugs themselves. Clearly, a well tolerated anti-anginal drug, which provides continuous efficacy in addition to that provided by existing agents, without further reducing blood pressure, heart rate and/or contractile function, would be a useful new tool to alleviate the burden of chronic angina. Such a drug would provide physicians an additional option to treat patients who remain symptomatic with angina but cannot tolerate reductions in

blood pressure, heart rate, contractile performance or AV nodal conduction from initiation and/or upward titration of beta-blockers, calcium channel blockers, or long-acting nitrates.

2.3 Summary of the Ranolazine Clinical Development Program

2.3.1 History

The clinical development of ranolazine was initially undertaken by Syntex Inc., with the first study conducted in 1985. From that date until 1994, a total of 61 studies (designated by the prefix RAN) were conducted by Syntex. Initial pharmacology studies were carried out using an IV formulation. These were followed by a series of Phase 2 studies in patients with chronic angina utilizing an immediate-release (IR) formulation of ranolazine (dihydrochloride salt). However, during the IR development program, it was observed that ranolazine IR ≤ 120 mg did not result in therapeutic plasma concentrations. Doses ≥ 240 mg were effective at peak concentration, but failed to maintain an adequate plasma concentration throughout the dosing interval. Therefore, a sustained-release (SR) formulation of ranolazine (free base) was developed to maintain plasma ranolazine concentrations in the range demonstrated to be therapeutic in earlier IR studies.

Syntex-sponsored clinical trials with ranolazine SR were initiated in the United Kingdom in 1991. Phase 1 and clinical pharmacology studies confirmed that ranolazine plasma levels attained with the IR formulation and associated with improved exercise performance could be achieved and maintained by ranolazine SR. In September 1994, Roche Holding, Ltd., acquired Syntex.

In March 1996, CV Therapeutics, Inc., acquired the license for ranolazine from Roche, and initiated a clinical development program with ranolazine SR for the treatment of chronic angina. All ranolazine clinical trials sponsored by CV Therapeutics are identified with the code “CVT” in the study number (e.g., CVT 3011).

2.3.2 Exposure

Ranolazine has been studied in 3021 subjects/patients, 2783 of whom received ranolazine, with 1714 subject/patient years of exposure to any formulation of ranolazine. The number exposed to ranolazine SR was 1460. The mean duration of exposure of angina patients to ranolazine SR was 495 days; 867 chronic angina patients have been exposed to ranolazine SR doses ≥ 500 mg b.i.d. for at least 28 days, with 502 and 259 patients exposed for over 1 or 2 years, respectively. The majority of the long-term experience with ranolazine is derived from two open-label studies (CVT 3032 and CVT 3034), which followed patients after their completion of one of the two Phase 3 studies (CVT 3031 and CVT 3033) described below, with some patients now under treatment for over 5 years. Ranolazine has been studied in a chronic angina population representing a broad range of demographics and concurrent diseases. It has been studied both in the presence and absence of other common cardiovascular drugs, including other anti-anginals (beta-blockers, calcium channel blockers, long-acting nitrates), diuretics, and ACE inhibitors.

2.3.3 Overview of the Design of Key Clinical Studies

The critical design features of the Phase 3 ranolazine efficacy studies, CVT 3031 (or MARISA, for Monotherapy Assessment of Ranolazine In Stable Angina) and CVT 3033 (or CARISA, for Combination Assessment of Ranolazine In Stable Angina), were based on draft FDA guidelines for evaluating anti-anginal drugs and were similar to those used for previously approved anti-anginal drugs. The ranolazine program used the same primary endpoint (symptom-limited exercise duration at trough drug levels) as these approved products. A modified Bruce protocol for an exercise treadmill test (ETT) was used to determine this endpoint.

The Phase 3 studies evaluated safety and efficacy throughout the dosing interval with twice daily (b.i.d.) dosing. MARISA was a 4-week, randomized, double-blind, placebo-controlled, crossover design, dose-definition study intended to evaluate the anti-anginal effect of ranolazine SR as monotherapy in patients with chronic angina. Patients received double-blind placebo and ranolazine SR at

doses of 500, 1000, and 1500 mg b.i.d. for treatment periods of 1 week each in random order. CARISA was designed to determine the anti-anginal efficacy and tolerability of 12 weeks of treatment with ranolazine SR at a dose of 750 or 1000 mg b.i.d. in chronic angina patients receiving anti-anginal medication (atenolol, diltiazem CD, or amlodipine). CARISA was a randomized, 3-arm, 3-strata, parallel group, double-blind, placebo-controlled study.

Peak concentrations for the SR tablet are typically observed 4–6 hours after dose intake. Therefore, in the Phase 3 studies, which employed twice daily dosing, treadmill parameters, ECG recordings, and ranolazine plasma concentrations were collected 4 and 12 hours after dose intake at steady-state, corresponding to approximate peak and trough plasma concentrations, respectively. Based on the plasma concentrations observed in the previous IR studies that achieved therapeutic efficacy, it was determined that effective concentrations should exceed approximately 800 ng/mL. When MARISA was designed, the SR dose 500 mg b.i.d. was predicted to achieve this level at peak, but not at trough, and would therefore help define the minimally effective dose. The highest dose in MARISA was set at 1500 mg b.i.d. to adequately investigate dose response for safety and efficacy parameters over a 3-fold dose range, and a 9- to 10-fold concentration range between the lowest trough and highest peak. It was anticipated that 1500 mg b.i.d. might result in an unacceptable patient tolerability profile.

The ranolazine SR clinical program includes studies that evaluated pharmacokinetic parameters using plasma concentration-time profiles after both single and multiple dosing and explored the between-subject variability in these parameters. In addition, factors that affect the distribution of the parameters in the population were identified and quantified. This information forms the basis for dosing recommendations in subpopulations with altered ranolazine pharmacokinetics, as well as in the presence of drugs affecting ranolazine plasma concentrations.

The relationship between ranolazine exposure and effects on cardiac repolarization was extensively evaluated in Study CVT 3111 and in an integrated population analysis of the concentration-response relationship for QTc across studies on angina patients and healthy volunteers. The aim was to quantify the magnitude of the effect on the QT interval and to identify any contributing factors. Because ranolazine, as compared with other anti-anginal drugs, has a mechanism of action that does not depend upon changes in heart rate and blood pressure, hemodynamic effects were monitored in all clinical studies to document the absence of a relationship between efficacy and changes in blood pressure and heart rate.

The safety and efficacy of ranolazine have been evaluated across a broadly representative chronic angina population. A number of relevant patient subgroups have been investigated, including patients with CHF, reactive airway disease, diabetes, and those with low blood pressures, slow heart rates, and long PR intervals. In addition, ranolazine has been studied both as monotherapy and when given over a background of beta-blockers or calcium channel blockers.

3 NONCLINICAL PHARMACOLOGY, CLINICAL PHARMACOKINETICS, AND METABOLISM

3.1 Introduction

Ranolazine has been shown to have a number of pharmacologic actions. This section summarizes the nonclinical pharmacology underlying the novel pharmacodynamic profile of ranolazine.

3.2 Mechanism of Anti-anginal and Anti-ischemic Action

3.2.1 Summary of Pharmacologic Effects

The mechanism of action of ranolazine has not been fully elucidated. However, unlike beta-blockers, calcium channel blockers and long acting nitrates, the anti-anginal and anti-ischemic effects of ranolazine do not depend upon reductions in heart rate or blood pressure, or upon vasodilation.

In nonclinical models, ranolazine can partially inhibit fatty acid oxidation (pFOX inhibition) and can stimulate glucose oxidation. Shifting the increase in fatty acid oxidation that occurs during myocardial ischemia toward glucose oxidation results in more oxygen-efficient production of adenosine triphosphate (ATP), because less oxygen is required to yield a given amount of ATP during glucose oxidation. The relative increase in glucose oxidation is believed to improve cardiac efficiency and to reduce ischemia-induced increases in lactic acid and cellular acidosis. This metabolic activity has been proposed to contribute to the anti-ischemic effect of ranolazine.

Ranolazine exhibits an energy-dependent binding to mitochondria with an apparent affinity of 2 μM, and binds to $\alpha_{1a,b}$ and $\beta_{1,2}$-adrenergic receptors with affinities (K_i values) in the range of 5 to 21 μM, and to serotonin $5HT_{1A}$ receptors with an affinity of 2 μM. Ranolazine does not specifically bind to the opioid receptors or to L-type calcium channels. Ranolazine attenuates α_1- and β_1-adrenergic receptor-mediated responses, and has $5HT_{1A}$ receptor agonist activity. Ranolazine also inhibits a number of specific ion currents, including the late sodium current (late I_{Na}) with a potency (IC_{50}) as low as 5 μM, and ranolazine weakly inhibits the late L-type calcium current (late $I_{Ca,L}$) with an IC_{50} of 50 μM. It

is unknown whether any of these other possible sites of action contribute the anti-anginal and anti-ischemic effects of ranolazine.

3.2.2 Nonclinical Pharmacology

Ranolazine was shown to exhibit energy-dependent binding to isolated mitochondria with an apparent dissociation affinity of 2 μM, and to inhibit palmitoyl-CoA oxidation in isolated mitochondria (IC_{50} = 1.4 mM). In isolated hearts, ranolazine (≥ 10 μM) has been shown to stimulate glucose oxidation and improve post-ischemic mechanical function. In isolated skeletal muscle, ranolazine (10 μM) inhibited fatty acid oxidation and stimulated glucose oxidation.

In addition, the binding of ranolazine to a wide spectrum of cell surface receptors (e.g., adrenergic, dopaminergic, histaminergic, etc.) and ion channels (e.g., Ca^{2+}, K^{+}, etc.) was determined. At relevant concentrations (i.e., ≤ 10 μM which is approximately 2-fold the mean peak steady-state plasma concentration associated with the ranolazine dose of 1000 mg b.i.d.), ranolazine was found to specifically bind only to α_1- and β_1-adrenergic receptors, and to serotonin $5HT_{1A}$ receptors (Table 3-1). At higher concentrations, ranolazine also specifically bound to the β_2-adrenergic receptor. Ranolazine did not bind to opioid receptors, to serotonin $5HT_{2A}$ or $5HT_{2B}$ receptors, or to L-type calcium channels (i.e., benzothiazepine, dihydropyridine, phenylalkylamine subtypes).

Additional studies were carried out to determine the functional significance of the radioliogand binding data. In functional assays, ranolazine (≤ 10 μM) inhibited α_1- and β_1-adrenergic receptor-mediated responses, and was found to have agonist activity at the $5HT_{1A}$ receptor (Table 3-1). At concentrations higher than 10 μM, ranolazine also inhibited β_2-adrenergic receptor-mediated responses. Ranolazine, at concentrations up to 20 μM, was without effect on L-type calcium channel-mediated contractility in rat left atria.

Table 3-1 Pharmacologic Receptor Activity of Ranolazine

Receptor	Binding (μM)	Function	
		Activity (μM)	Assay System
α_1-adrenergic	K_i = 5–21 (α_{1a} and α_{1b})	IC_{50} = 26	Inhibition of phenylephrine-induced contractility in rabbit aorta
		K_B = 4	Inhibition of phenylephrine-induced increase in blood pressure in awake rats
β_1-adrenergic	K_i = 5–9	IC_{50} = 2	Inhibition of isoproterenol-induced increase in contractility in rat left atria
		K_B = 10	Inhibition of isoproterenol-induced increase in cAMP in rat C6 glioma cells
		K_B = 5	Inhibition of isoproterenol-induced increase in heart rate in awake rats
β_2-adrenergic	K_i = 15	K_B = 12	Inhibition of isoproterenol-induced increase in cAMP in DDT1 MF-2 cells
$5HT_{1A}$	K_i = 2	EC_{50} = 5	Inhibition of neurogenic twitch in guinea pig ileum (agonism)

cAMP = cyclic adenosine monophosphate

EC_{50} = concentration of a drug that produces half of the maximal response

IC_{50} = concentration of an inhibitor that produces 50% inhibition of a response

K_B = equilibrium dissociation constant of the antagonist-receptor complex

K_i = equilibrium dissociation constant of a competitor drug

The R- and S-enantiomers of ranolazine were tested in the same assays described for racemic ranolazine. The S-enantiomer was found to have somewhat higher binding affinity and functional potency than the R-enantiomer at the α_1-, β_1- and β_2-adrenergic receptors. The R-enantiomer was essentially inactive in β_1- and β_2-adrenergic receptor binding and functional assays. The two enantiomers were approximately equipotent agonists at the $5HT_{1A}$ receptor.

The eleven most abundant metabolites of ranolazine (present above 1% relative to ranolazine in human plasma) were also evaluated for binding and functional receptor activity. Three of the metabolites exhibited activity at α_1-, β_1- and β_2-adrenergic receptors, and at the $5HT_{1A}$ receptor, with potencies similar to or less than those of ranolazine. Only one of these metabolites has the potential to have even weak activity at these receptors with the plasma concentrations achieved

clinically. In addition, although two metabolites were shown to bind to the opioid receptor, they would not achieve sufficient plasma concentrations to contribute to the clinical pharmacology of ranolazine.

Ranolazine has also been shown to affect several cardiac ion currents which may be relevant to the pharmacological actions (therapeutic and non-therapeutic) of the drug. In canine left ventricular (LV) myocytes, ranolazine inhibited late I_{Na} with IC_{50} values ranging from 5 to 21 μM, depending on the voltage-clamp test potential and frequency (basic cycle length or BCL) of depolarization. Although ranolazine only weakly inhibited late $I_{Ca,L}$ (IC_{50} = 50 μM), the slope of the concentration-response curve was shallow, and a ranolazine concentration of 5 μM inhibited this current by 25–30%.

The pharmacology of ranolazine observed *in vivo* suggests that its anti-anginal and anti-ischemic effects derive from a different mechanism than that for existing anti-anginal medications. In whole animals, the anti-ischemic effects of ranolazine (at concentrations as low as 150 ng/mL) were not associated with significant changes in blood pressure or heart rate. For example, in awake dogs, ranolazine (at steady-state concentrations in the range of 1–14 μM) did not cause significant (< 5%) slowing of heart rate or lowering of arterial blood pressure, and did not affect coronary blood flow, coronary vascular resistance or LV contractility. These findings suggest a lack of significant inhibition by ranolazine of α_1- or β_1-adrenergic-mediated responses at steady-state *in vivo*, or L-type calcium channel currents and dependent responses.

Presently, two hypotheses have been proposed to explain the anti-ischemic and anti-anginal effects of ranolazine without concomitant effects on heart rate, arterial blood pressure, LV contractility, or peripheral vasodilation. They include a metabolic effect on energy substrate utilization (inhibition of fatty acid oxidation), and a selective inhibition of late I_{Na}, which would act to decrease cellular Ca^{2+} overload during ischemia by reducing Ca^{2+} entry through the reverse mode of the Na-Ca exchanger.[14,15] The contribution of the α_1- and β_1-

adrenergic receptor blockade effects to therapeutic efficacy, if any, remains to be established. Effects on these receptors may explain infrequent observations of postural changes in blood pressure and syncope.

3.3 Clinical Pharmacokinetics

The pharmacokinetics of ranolazine in humans have been documented after intravenous (iv) administration and after oral (po) administration of an immediate-release (IR) capsule or tablet or a sustained-release (SR) tablet, the intended commercial formulation.

Virtually all of the clinical studies in the ranolazine development program provide ranolazine plasma concentration data after single and/or multiple doses of either the IR or SR formulation. In studies in angina patients, PK sampling was performed on only a few occasions per patient, which is insufficient for modeling of the individual concentration-time profile. Therefore, a population-based approach was used for the SR formulation, which merged data from studies with frequent and sparse sampling. This approach also allowed determination of the distribution of PK parameters in the angina population.

3.3.1 Bioavailability

Ranolazine is well-absorbed after oral administration with an average of 73% of the administered dose excreted in urine (Study CVT 3019). Unchanged ranolazine accounted for < 5% of radioactivity in both urine and feces, indicating that both absorption and metabolism of ranolazine are extensive after oral administration. The absolute bioavailability of the IR formulation was 35–50% (Studies RAN009 and RAN019). The relative bioavailability of the SR tablet compared to the IR capsule in development studies was in the range of 90–97% (Studies RAN067 and RAN0102).

Food intake has no effect on the rate or extent of absorption of the SR tablet as determined by C_{max} and AUC (Studies CVT 3014 and RAN0113).

3.3.2 Dose Proportionality

Overall, pharmacokinetic studies of IR capsules and SR tablets at steady-state show a modest departure from dose proportionality with C_{max} and AUC increasing more than proportionally to dose over the dose range 500–1500 mg b.i.d. Exposures relative to the 500 mg b.i.d. dose are 100, 250, and 400%, on average, for the dose levels 500, 1000, and 1500 mg b.i.d., respectively; although the 1500 mg b.i.d. dose is not recommended for clinical use. A partial autoinhibition of the drug metabolic enzyme CYP2D6 caused by ranolazine and/or metabolites explains the decrease in ranolazine clearance with dose.

Study CVT 3111, which used an iv infusion to reach high ranolazine concentrations, showed evidence of two parallel elimination pathways, of which one becomes partly saturated at plasma concentrations typically seen within the clinical dose range. A dose-dependent decrease in formation rate of two of the primary metabolites is compatible with the more than dose proportional increase in ranolazine plasma concentrations observed in this study.

3.3.3 Pharmacokinetic Information

3.3.3.1 Immediate-Release and Intravenous Formulations

Ranolazine is rapidly absorbed after oral intake of an aqueous solution or an IR capsule, with maximum plasma concentrations observed after an average of 0.6 or 1.0 hours, respectively. A two-compartment model with a short initial distribution phase best describes the disposition after iv administration. After oral administration, the distribution phase cannot be discerned; therefore, a one-compartment model is more relevant for this route of administration.

The average terminal elimination half-life after intake of the IR capsule ranged from 1.4 to 1.9 hours across studies, both after single oral doses over the dose range 120–400 mg and after multiple doses over the dose range 240–400 mg t.i.d. Elimination half-lives of the same magnitude have been documented after iv administration that achieved plasma concentrations corresponding to those for the proposed clinical dose range. At higher concentrations, a prolongation of the elimination half-life (to approximately 3 hours) has been observed. The

peak/trough difference with three times daily (t.i.d.) dosing of the IR capsule is more than 10-fold.

3.3.3.2 Sustained-Release Tablet

The absorption phase is prolonged for the SR tablet with maximum plasma concentrations typically seen 4–6 hours after dose intake. Absorption is indicated to be ongoing beyond 12 hours after dose intake. The effective terminal elimination half-life is 4 to 5 hours, on average, after a single dose and 7 hours after multiple dosing to steady-state. Steady-state is typically achieved within 3 days of multiple dosing, but may occasionally take longer. According to a population PK evaluation, the peak/trough difference at steady-state is 1.6-fold, on average, at dosing within the range 500–1000 mg b.i.d.

3.4 Metabolic Information

Following oral administration of a radiolabeled ranolazine solution (Study CVT 3019), peak concentrations of ranolazine and most of the primary metabolites were reached within 1 hour after dosing. Approximately 73% of the dose was recovered in urine. Only 4.5% of the radioactivity recovered, or 3% of the dose, was excreted in urine as unchanged ranolazine. Eleven ranolazine metabolites are present above 1% relative to ranolazine in human plasma. After multiple dosing to steady-state with 500 mg b.i.d. in healthy volunteers, four metabolites achieved plasma concentrations exceeding 10% of the levels of the parent compound. These results indicate that ranolazine is rapidly and extensively absorbed and that the major route of elimination is via metabolism followed by urinary excretion.

Patients with moderate hepatic impairment showed a decrease in the relative exposure to all metabolites as compared to healthy controls (Study CVT 3018). This is compatible with a reduction in hepatic functional mass.

Ketoconazole and paroxetine caused a decrease in the steady-state concentrations of some ranolazine metabolites (Studies CVT 301-10 and CVT 301-13, respectively). The metabolites affected and the degree of change

reflect the dependency on CYP3A4 and CYP2D6 for the different metabolic pathways.

3.5 Drug-Drug Interactions

In man, ranolazine is almost completely metabolized before excretion and the enzyme CYP3A4 has been identified to catalyze the quantitatively most important pathways (70–75% on average). Pathways predominantly catalyzed by CYP2D6 contribute to a lesser extent to the metabolism of ranolazine (20% on average). Other routes of elimination including glucuronidation, direct excretion of unchanged ranolazine and possibly other CYP enzymes account for, on average, < 10% of the total clearance. Accordingly, drug interaction studies have been carried out with the potent CYP3A4 inhibitor ketoconazole, the moderate inhibitor diltiazem at different doses, and the weak inhibitor simvastatin.

Substrates for CYP3A4 are commonly also substrates for P-glycoprotein (P-gp). The effect of P-gp inhibition by verapamil on ranolazine pharmacokinetics have been evaluated. Ranolazine effects on digoxin pharmacokinetics have also been evaluated in several studies, where the assumed mechanism of the interaction is inhibition of P-gp by ranolazine with respect to digoxin. To complete a comprehensive evaluation of ranolazine metabolism, an interaction study with the potent CYP2D6 inhibitor, paroxetine, has been conducted in which phenotyping for this enzyme using dextromethorphan was performed at baseline and at steady-state levels of ranolazine.

Potent inhibition of CYP3A4 by ketoconazole (200 mg b.i.d.) increases ranolazine exposure at steady-state 3- to 4-fold (Study CVT 301-10). The observation that potent inhibition of CYP3A4 by ketoconazole increases ranolazine concentrations by, on average, 3- to 4-fold and not to a larger extent confirms that ranolazine has alternative pathways for its elimination. The moderate CYP3A4 inhibitor diltiazem causes a less pronounced and dose dependent interaction with mean increases in ranolazine average steady-state

plasma concentrations of 1.5- to 2.4-fold over the diltiazem total daily dose range (180–360 mg) (Studies CVT 3012, RAN0121, and RAN068).

CYP2D6 contributes to ranolazine clearance, but to a lesser degree than CYP3A4. The potent CYP2D6 inhibitor paroxetine (20 mg q.d.) increases ranolazine concentrations approximately 1.2-fold at steady-state (Study CVT 301-13).

Verapamil (120 mg t.i.d.) increases ranolazine average plasma concentrations 2.3-fold at steady-state. The primary cause of this effect is likely inhibition of P-gp in the gut, increasing the bioavailability of ranolazine.

Ranolazine increases digoxin concentrations 1.4- to 1.6-fold at clinically relevant doses, which is likely to be a result of inhibition of P-gp. It is suggested that this occurs both at the level of intestinal absorption and at the level of renal tubular excretion of digoxin.

The drug-drug interaction program also confirmed that ranolazine and its metabolites are weak inhibitors of several CYP450 enzymes. These results are described below.

Ranolazine 1000 mg b.i.d. at steady-state caused a less than 2-fold increase in simvastatin exposure dosed at 80 mg q.d. (Study CVT 3017). The effects on active simvastatin metabolites, as well as on the HMG-CoA reductase inhibitory activity, were of the same magnitude as for the simvastatin parent compound. Simvastatin is predominantly metabolized by CYP3A4 and potent CYP3A4 inhibitors such as itraconazole or grapefruit juice increase simvastatin concentrations more than 10-fold. This confirms that ranolazine has minor inhibitory effects on CYP3A4 *in vivo*.

The inhibitory effects of ranolazine on CYP2D6 have been evaluated through phenotyping with dextromethorphan before and after dosing with ranolazine 1000 mg b.i.d. to steady-state (Study CVT 301-13). The results demonstrate that

ranolazine and/or metabolites cause a partial inhibition of CYP2D6, but not to the extent that a metabolic shift is generally seen.

Ranolazine has no significant effects on the kinetics of the R- and S-enantiomers of warfarin and does not modify the effect of warfarin on indices of prothrombin time to a clinically meaningful degree (Study RAN0110). The metabolic pathways for the enantiomers of warfarin involve CYP2C9, CYP1A2, and CYP3A4. The results suggest a lack of major inhibitory effects of ranolazine on these three enzymes.

3.6 Special Population Studies

Renal impairment is associated with a decrease in ranolazine clearance that is linearly correlated with the degree of impairment. For a decrease in creatinine clearance from 100 to 30 mL/min, the increase in ranolazine exposure is 1.8-fold.

Mild hepatic impairment has no effect on ranolazine pharmacokinetics as compared with matched healthy controls, whereas moderate impairment was associated with a 1.8-fold increase in ranolazine exposure (Study CVT 3018).

According to a population PK evaluation, gender, diabetes, and CHF (NYHA Class I–IV) status, have no statistically significant effect on the pharmacokinetics of ranolazine.

3.7 Summary of Pharmacologic Effects, Clinical Pharmacokinetics, and Metabolism

Ranolazine has a number of pharmacologic properties. The relative contribution of each of these activities to the anti-ischemic and anti-anginal effects of ranolazine has not been fully elucidated. However, in animal and human studies, the anti-anginal and anti-ischemic effects of ranolazine can be demonstrated in the absence of, and therefore do not depend on, reductions in heart rate and blood pressure; both partial inhibition of fatty acid oxidation and selective inhibition of late I_{Na} by ranolazine are consistent with this non-hemodynamic profile.

The pharmacokinetics of ranolazine are well understood. The SR tablet formulation provides adequate plasma levels over the twice daily dosing interval. Ranolazine is almost completely metabolized before excretion and the enzyme CYP3A4 has been identified to catalyze the quantitatively most important pathways. Pathways predominantly catalyzed by CYP2D6 contribute to a lesser extent to the metabolism of ranolazine. Drug-drug interactions have been well characterized and corroborate the finding that CYP3A4 is a major determinant for ranolazine clearance. Gender, diabetes, and CHF status have no significant effect on the pharmacokinetics of ranolazine. However, renal impairment is associated with a decrease in ranolazine clearance that is linearly correlated with the degree of impairment, and moderate hepatic impairment is associated with a 1.8-fold increase in ranolazine exposure.

4 CONTROLLED STUDIES PROVIDING THE BASIS FOR EFFICACY

4.1 Introduction

The anti-anginal and anti-ischemic efficacy of ranolazine is based on a novel pharmacodynamic profile and is not dependent on effects on heart rate (HR) or blood pressure (BP). These benefits have been demonstrated prospectively in two Phase 3 and three supportive randomized, double-blind, placebo-controlled trials, which included a total of 1596 patients (see Table 4-1).

These key efficacy studies demonstrated that:

- The therapeutic effects of ranolazine are dose- and concentration-dependent.
- The anti-anginal and anti-ischemic efficacy of ranolazine is consistent throughout a broad population of chronic angina patients.
- The therapeutic benefit of ranolazine can be demonstrated without reductions in BP and HR, neither at rest nor during exercise, a fundamentally different pharmacodynamic profile than that of other currently available anti-anginal drugs.
- Ranolazine is effective as a monotherapy.
- Ranolazine is effective in addition to beta-blocker therapy or calcium channel blocker background therapy, in patients assessed by their physicians to be optimally treated with a beta-blocker or diltiazem, and under conditions approximating the maximal anti-anginal effect of atenolol.
- The effects of ranolazine on exercise duration in one study were statistically significantly greater than those of atenolol 100 mg q.d.
- Efficacy appears to persist without tachyphylaxis for as long as plasma concentrations are maintained in the therapeutic range.
- Abrupt withdrawal of ranolazine treatment is not associated with rebound increases in angina.

The key efficacy studies (two Phase 3 ranolazine SR studies [MARISA (CVT 3031) and CARISA (CVT 3033)] and three Phase 2 ranolazine IR studies [RAN080, RAN072, and RAN1514]), included the same exercise variables (exercise duration, time to onset of angina, and time to 1-mm ST-segment depression). Table 4-1 summarizes the major features of these studies providing the evidence for the efficacy of ranolazine. Pivotal support for the use of

ranolazine in chronic angina is based on the results of MARISA and CARISA. Both were conducted using the SR formulation proposed for marketing.

Table 4-1 Summary of Controlled Studies Providing the Basis for Efficacy

Study	Purpose, Population, and Design	Control	Treatments	Treatment Duration	Number of Patients Randomized	Primary Efficacy Endpoint
MARISA (CVT 3031)	Study the effect of multiple doses of ranolazine monotherapy in patients with chronic angina MC, 4-period cross-over, DB, randomized	Placebo	Ranolazine 500 mg b.i.d. (N = 181), 1000 mg b.i.d. (N = 180), 1500 mg b.i.d. (N = 187); Placebo b.i.d. (N = 179)	SB, placebo qualifying phase, 1-wk per treatment period	191	Exercise duration at trough (12 h post-dose)
CARISA (CVT 3033)	Study the effect of ranolazine on ETT duration at trough in patients with chronic angina also receiving a stable dose of diltiazem 180 mg q.d., atenolol 50 mg q.d., or amlodipine 5 mg q.d. MC, stratified, parallel, DB, randomized Study conducted in 3 phases: (1) SB, placebo, qualifying phase (2) DB, treatment phase (3) DB, rebound assessment phase	Placebo	Ranolazine 750 mg b.i.d. (N = 279), 1000 mg b.i.d. (N = 275); Placebo b.i.d. (N = 269)	1-2 wk qualifying phase, 12-wk treatment , 2-day, rebound assessment	823	Exercise duration at trough (12 h post-dose)

Table 4-1 Summary of Controlled Studies Providing the Basis for Efficacy (Cont'd)

Study	Purpose, Population, and Design	Control	Treatments	Treatment Duration	Number of Patients Randomized	Primary Efficacy Endpoint
RAN080	Assess anti-anginal efficacy and safety of ranolazine IR 400 mg t.i.d. in chronic angina patients MC, 3-way cross-over, DB, randomized, with preceding single-blind placebo washout period	Atenolol, Placebo	Ranolazine IR 400 mg t.i.d. (N = 155); Atenolol 100 mg q.d. (N = 154); Placebo t.i.d. (N = 154)	1-wk per treatment period	158	Exercise duration to time to onset of angina at peak (1.0 h post-dose)
RAN072	Evaluate safety, efficacy, and tolerability of 4 different doses of ranolazine IR in patients with severe symptomatic CAD despite treatment with approved doses of diltiazem or beta-blocker (atenolol or metoprolol): MC, single-dose, 2-period cross-over, DB, randomized	Placebo	Ranolazine IR 10 mg (N = 24), 60 mg (N = 26), 120 mg (N = 29), 240 mg (N = 27); Placebo (N = 106)	2–7 day washout between periods	106	Exercise duration at peak (2.5 to 3.0 h post-dose)
RAN1514	Assess anti-anginal efficacy in chronic angina patients in 2 phases: (1) SB, placebo, qualifying phase (2) DB, treatment phase with 4 treatment sequences, 4 treatments, and 5 DB periods: 3 dosing regimens of IR ranolazine vs placebo MC, extended-period, Latin square design, randomized	Placebo	Ranolazine IR 267 mg t.i.d. (N = 305), 400 mg t.i.d., (N = 309), 400 mg b.i.d. (N = 306); Placebo t.i.d. (N = 310)	1-wk per treatment period, with 1 treatment repeated in 5th period	318	Exercise duration to time to onset of angina at trough (8 h post-dose for t.i.d., 12 h post-dose for b.i.d.)

DB = double-blind; MC = multi-center; SB = single-blind.

Table 4-2 summarizes demographic and baseline characteristics for patients in the Phase 3 SR controlled angina studies, MARISA and CARISA. Overall, demographic and baseline characteristics were comparable between the ranolazine and placebo treatments. Cardiovascular events, other co-morbidities, and use of concomitant cardiovascular medications were generally similar between the two studies, and are typical of a chronic angina population.

Table 4-2 Demographic and Baseline Characteristics in Phase 3 Ranolazine SR Controlled Angina Studies MARISA and CARISA (All Patients Randomized)

Category	MARISA All Patients N = 191	CARISA All Patients N = 823	MARISA and CARISA Total N = 1014
	Number (%) of Patients		
Gender			
Male	140 (73.3)	638 (77.5)	778 (76.7)
Female	51 (26.7)	185 (22.5)	236 (23.3)
Age			
< 65 years	90 (47.1)	408 (49.6)	498 (49.1)
≥ 65 - < 75 years	75 (39.3)	326 (39.6)	401 (39.5)
≥ 75 years	26 (13.6)	89 (10.8)	115 (11.3)
Race			
Caucasian	174 (91.1)	803 (97.6)	977 (96.4)
Non-Caucasian	17 (8.9)	20 (2.4)	37 (3.6)
Underlying Disease			
Diabetes Mellitus	46 (24.1)	189 (23.0)	235 (23.2)
CHF	32 (16.8)	242 (29.4)	274 (27.0)
Prior Unstable Angina	37 (19.4)	177 (21.5)	214 (21.1)
Previous MI	100 (52.4)	474 (57.6)	574 (56.6)
Ventricular Arrhythmias	26 (13.6)	71 (8.6)	97 (9.6)
Valvular Heart Disease	3 (1.6)	54 (6.6)	57 (5.6)
Prior Cardiac Arrest	3 (1.6)	13 (1.6)	16 (1.6)
Hypertension	123 (64.4)	527 (64.0)	650 (64.1)
Prior Stroke	9 (4.7)	41 (5.0)	50 (4.9)
PTCA	62 (32.5)	152 (18.5)	214 (21.1)
CABG, TMR	53 (27.7)	145 (17.6)	198 (19.5)

Table 4-2 Demographic and Baseline Characteristics in Phase 3 Ranolazine SR Controlled Angina Studies MARISA and CARISA (All Patients Randomized) (Cont'd)

Category	MARISA All Patients N = 191	CARISA All Patients N = 823	MARISA and CARISA Total N = 1014
	Number (%) of Patients		
Concomitant Medications			
ACE Inhibitors	57 (29.8)	355 (43.1)	412 (40.6)
Alpha and Beta-Blockers	19 (9.9)	570 (69.3)	589 (58.1)
AT1 Angiotensin II Antagonists	14 (7.3)	18 (2.2)	32 (3.2)
Calcium Channel Blockers	5 (2.6)	527 (64.0)	532 (52.5)
Fibrates	10 (5.2)	46 (5.6)	56 (5.5)
HMG CoA Reductase Inhibitors	100 (52.4)	372 (45.2)	472 (46.5)
Platelet Aggregation Inhibitors	27 (14.1)	37 (4.5)	64 (6.3)

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; CHF = congestive heart failure; HMG CoA = hydroxymethyl glutaryl coenzyme A; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; TMR = transmyocardial revascularization.

4.2 Controlled Studies Providing the Basis for Anti-Anginal Efficacy of Ranolazine

4.2.1 MARISA: Anti-Anginal and Anti-Ischemic Efficacy of Ranolazine SR as Monotherapy in a Twice Daily Dosing Regimen

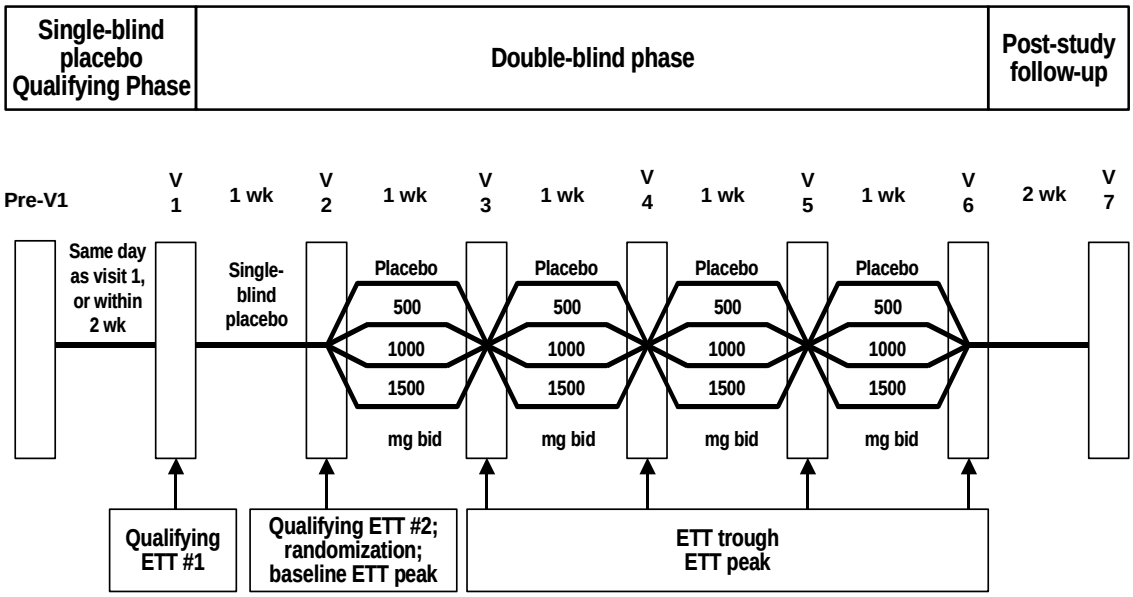
MARISA was a double-blind, randomized, placebo-controlled, multiple-dose, four-period cross-over, dose-definition study of ranolazine monotherapy in patients with chronic angina. The primary endpoint was the exercise treadmill test (ETT) duration at trough ranolazine plasma concentration (approximately 12 hours post-dose).

The study consisted of a 1-week, single-blind placebo qualifying phase and a 4-week, randomized placebo-controlled, double-blind treatment phase (1-week placebo, 3-week active treatment), followed by a follow-up visit 2 weeks after completion of the double-blind phase.

Patients were required to have discontinued all other anti-anginal medication (i.e., beta-blockers, calcium channel blockers, long-acting nitrates, and, in countries outside the United States, any other drug indicated for the treatment of chronic angina) prior to their first qualifying exercise test, and for the remainder of the study. Patients were eligible for study entry if during the single-blind qualifying phase they stopped exercising for angina and had a minimum ST-segment depression of 1 mm within 3–9 minutes on a modified Bruce ETT. The difference in exercise duration between the two qualifying tests could not exceed 20% of the longer test or 1 minute. This corresponds to a Duke Treadmill Exercise Score[16] of $\leq$ -10 (representing patients with severe coronary artery disease and at high risk).

A total of 191 patients were enrolled and randomized to 1 of 4 treatment sequences in the double-blind phase. During the double-blind phase, patients were treated for 1 week per treatment according to the sequences to which they were randomized. Patients had an ETT at trough and peak at the end of each treatment week. Figure 4-1 gives a schematic presentation of the MARISA study design.

Figure 4-1 MARISA Four-Period Cross-over Study Design



V = visit; ETT = exercise treadmill test.

The protocol-specified primary analysis of exercise duration at trough ranolazine plasma concentration (12 hours post-dose), used the population of all randomized patients who had evaluable efficacy measurements at baseline and at least 3 of the 4 double-blind periods (All/Near Completers Population, N = 175). The primary efficacy analysis was performed using an analysis of variance with effects for pooled site, patient within pooled site, period and treatment. A secondary analysis of this endpoint was performed using the "Intent-To-Treat" population (N = 185) of all patients with evaluable efficacy measurements at baseline and at least one post-baseline measurement, using a generalized estimating equations (GEE) model. Other key secondary treadmill efficacy outcomes included exercise duration at peak ranolazine plasma concentration (4 hours post-dose), time to onset of angina during exercise at trough and peak, and time to 1-mm ST-segment depression during exercise at trough and peak.

Adjustment for the multiple comparisons between doses in the primary efficacy analyses was addressed using a 3-stage step-down, closed testing procedure. As a first step, the average response of the 1500 mg and 1000 mg doses of ranolazine was compared to the placebo response. Conditionally on that test being significant at the 0.05 level, the 1500 mg and 1000 mg doses were compared individually to placebo at the 0.05 level. Conditionally on both of these being statistically significant, the 500 mg dose was compared to placebo. This procedure maintained the overall Type I error rate at 0.05.

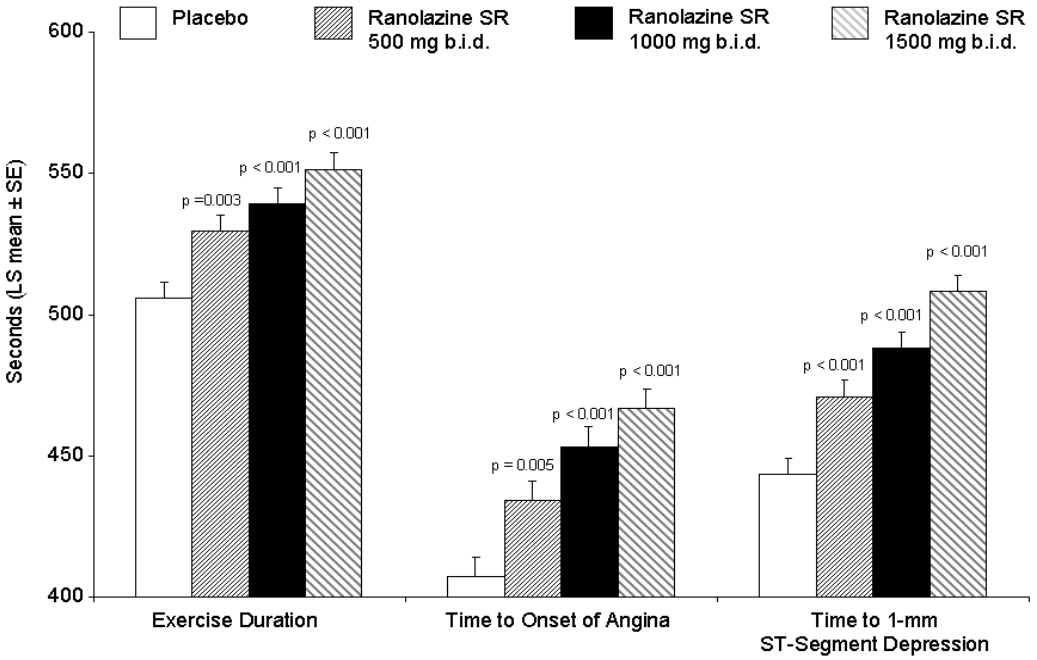
Efficacy Results

MARISA demonstrated that ranolazine SR administered in a twice daily dosing regimen provided a therapeutic benefit on the primary efficacy endpoint, exercise duration at trough (see Figure 4-2 and Table 4-3). The average effect of the 1000 mg and 1500 mg ranolazine SR doses was significantly different from placebo ($p < 0.001$), so the individual doses were compared to placebo. All three ranolazine SR doses significantly improved ETT duration at trough relative to placebo ($p \leq 0.003$). There was a clear dose-response relationship with respect to ETT duration, with an improvement at trough of 24, 34, and 46 seconds in patients treated with ranolazine 500 mg, 1000 mg, and 1500 mg, respectively, compared with placebo. ETT duration was also statistically significantly longer in all 3 doses at peak levels and increased monotonically with increasing dose, from 29 seconds in patients taking ranolazine 500 mg, to 50 seconds in those taking ranolazine 1000 mg, to 56 seconds in those taking ranolazine 1500 mg (see Figure 4-3 and Table 4-3). At each dose level, improvements at peak were greater than those at trough, further supporting a concentration response.

Analysis of the primary endpoint in the intent-to-treat population demonstrated similar results. Mean ($\pm$ SE) differences from placebo were 23, 35, and 46 seconds on ranolazine 500 mg, 1000 mg, and 1500 mg b.i.d., respectively (all $p \leq 0.007$).

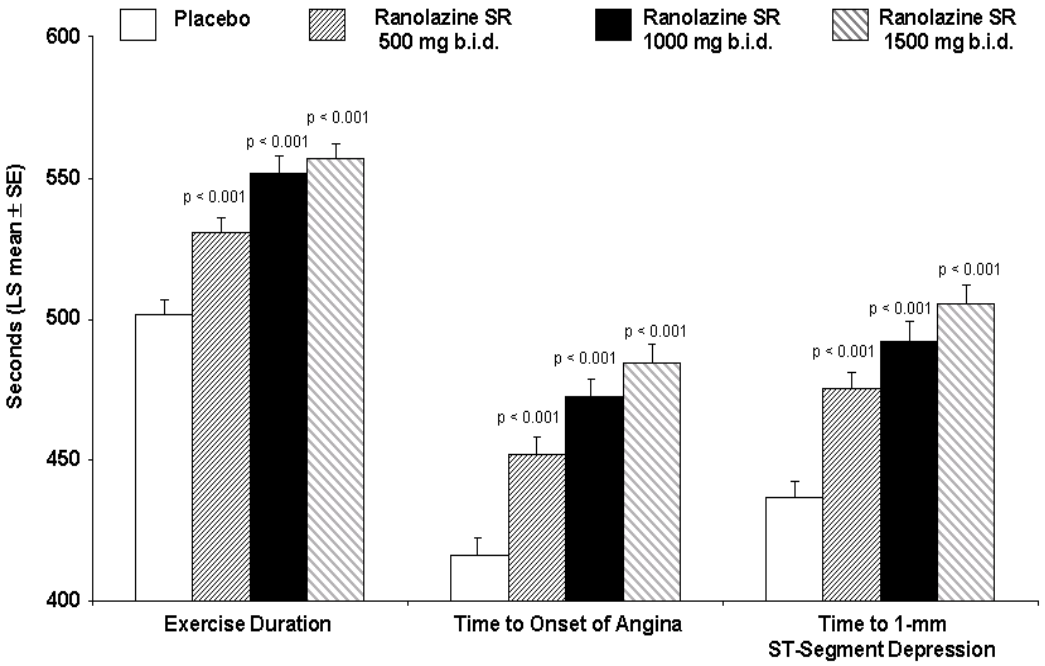
In addition to improving total exercise duration, all three ranolazine SR doses demonstrated statistically significant increases vs placebo in time to onset of angina and time to 1-mm ST-segment depression at both trough ($p \leq 0.005$) and peak ($p < 0.001$). A similar pattern of dose-concentration response was also seen for these secondary ETT parameters (see Table 4-3). The effective mean plasma ranolazine concentrations were ~ 850 ng/mL on 500 mg b.i.d. at trough to ~ 2500 ng/mL on 1000 mg b.i.d. at peak. On 1500 mg b.i.d. at peak, mean plasma ranolazine concentration was just under 4000 ng/mL.

Figure 4-2 Efficacy Endpoints at Trough in MARISA (All/Near Completers Population)



p-values for comparison of ranolazine SR vs placebo.
Note: LS means and p-values from ANOVA with effects for pooled site, patient within pooled site, period, and treatment.

Figure 4-3 Efficacy Endpoints at Peak in MARISA (All/Near Completers Population)



p-values for comparison of ranolazine SR vs placebo.
Note: LS means and p-values from ANOVA with effects for pooled site, patient within pooled site, period, and treatment.

Table 4-3 Results for Primary and Secondary Efficacy Variables in MARISA (All/Near Completers Population)

Variable	Placebo		Ranolazine SR					
			500 mg b.i.d.		1000 mg b.i.d.		1500 mg b.i.d.	
	Trough	Peak	Trough	Peak	Trough	Peak	Trough	Peak
Exercise Duration, sec								
	N = 174	**N = 172**	**N = 174**	**N = 174**	**N = 174**	**N = 174**	**N = 169**	**N = 167**
Least Squares Mean (SE)	505.7 (5.7)	501.7 (5.2)	529.4 (5.7)[a]	530.9 (5.2)	539.3 (5.7)[a]	551.8 (5.2)	551.6 (5.8)[a]	557.2 (5.3)
Mean Difference (SE)[b]	—	—	23.8 (7.9)[a]	29.3 (7.2)	33.7 (8.0)[a]	50.1 (7.2)	45.9 (8.0)[a]	55.5 (7.3)
p-value[b]	—	—	0.003[a]	< 0.001	< 0.001[a]	< 0.001	< 0.001[a]	< 0.001
Time to Onset of Angina, sec								
	N = 174	**N = 172**	**N = 174**	**N = 174**	**N = 174**	**N = 174**	**N = 169**	**N = 167**
Least Squares Mean (SE)	407.3 (6.8)	416.3 (6.1)	434.3 (6.8)	451.8 (6.1)	453.1 (6.8)	472.7 (6.1)	466.9 (7.0)	484.8 (6.3)
Mean Difference (SE)[b]	—	—	27.0 (9.5)	35.5 (8.5)	45.9 (9.5)	56.4 (8.5)	59.6 (9.6)	68.5 (8.6)
p-value[b]	—	—	0.005	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Time to 1-mm ST-Segment Depression, sec								
	N = 164	**N = 163**	**N = 162**	**N = 165**	**N = 161**	**N = 163**	**N = 153**	**N = 155**
Least Squares Mean (SE)	443.4 (5.7)	436.4 (5.9)	471.0 (5.8)	475.2 (5.9)	487.9 (5.8)	492.0 (5.9)	508.1 (6.0)	505.4 (6.1)
Mean Difference (SE)[b]	—	—	27.6 (8.1)	38.8 (8.2)	44.5 (8.1)	55.6 (8.2)	64.6 (8.2)	69.0 (8.4)
p-value[b]	—	—	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

[a] Primary efficacy variable
[b] Ranolazine SR vs placebo

Note: All/Near Completers population analyzed using ANOVA for cross-over study design with effects for pooled site, patient within pooled site, period, and treatment.

No clinically meaningful changes in rest or exercise HR or systolic BP (SBP) were observed in MARISA, although some small changes achieved statistical significance. Exercise HR was unaffected irrespective of dose or plasma ranolazine concentration, excluding a decrease in HR to account for the anti-ischemic effect. Ranolazine 500 mg b.i.d. had no effect on HR or SBP at rest or during exercise as compared to placebo (see Section 4.3 and Table 4-11 for further details).

The design of this study, in which each treatment preceded every other treatment exactly once, permitted testing for the possibility that exercise times were influenced by treatment in the immediately preceding period, that is "first order carryover effect", based on within-patient variability. This test is similar in power to the main test for treatment effect. There was no evidence of first order carryover effect in exercise duration ($p > 0.40$). In spite of this result, if an assumption was made that carryover effect was present, an analysis adjusting for carryover demonstrated results that were virtually identical to the primary efficacy analysis results. A more general test for treatment by period interaction showed no evidence that treatment effects differed significantly across periods ($p = 0.57$).

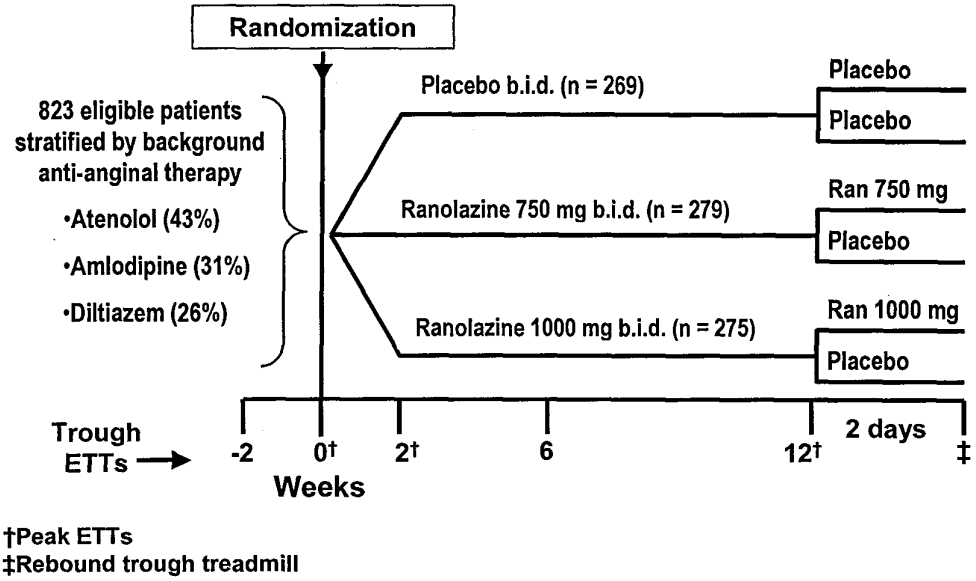
4.2.2 CARISA: Anti-Anginal and Anti-Ischemic Efficacy of Ranolazine SR in Combination With Background Therapy is Maintained Over 12 Weeks With No Rebound

CARISA was the second pivotal study conducted using the SR formulation. CARISA was a double-blind, randomized, stratified, placebo-controlled, parallel group, multiple-dose study of ranolazine 750 mg or 1000 mg b.i.d. used in combination with diltiazem 180 mg q.d., atenolol 50 mg q.d., or amlodipine 5 mg q.d., in patients with chronic angina. This study was designed to assess whether ranolazine is efficacious when given with the most commonly-prescribed, effective doses of other anti-anginal therapies.

The study was conducted in 3 phases: (1) a single-blind placebo qualifying phase lasting approximately 1 to 2 weeks, (2) a double-blind treatment phase lasting 12 weeks (ETTs were conducted at weeks 2, 6, and 12), and (3) a double-blind rebound assessment phase lasting 2 days. As in MARISA, a high-risk population with severe coronary disease was recruited based on a Duke Treadmill Exercise Score of ≤ -10. The entry criteria for CARISA were identical to MARISA with the exception that patients in CARISA were stabilized on one of the following three anti-anginal drug regimens prior to their first qualifying exercise test, and for the remainder of the study: atenolol 50 mg q.d., amlodipine 5 mg q.d., or diltiazem 180 mg in a formulation approved for once daily dosing.

A total of 823 patients were stratified according to background concomitant anti-anginal therapy and randomly assigned to receive either ranolazine 750 mg b.i.d., ranolazine 1000 mg b.i.d., or placebo b.i.d. At the end of the 12-week double-blind treatment phase, patients entered a 2-day rebound assessment phase, at which time they received, in a double-blind manner and in a 1:1 ratio, either the same treatment they had been given during the 12-week double-blind treatment phase or placebo. At the end of this 2-day rebound phase, patients had a final ETT at trough. Figure 4-4 gives a schematic presentation of the CARISA study design.

Figure 4-4 CARISA Study Design



The population used for the primary efficacy analysis included all patients who took at least one dose of double-blind drug and had at least one post-randomization ETT at trough and was designated as the “intent-to-treat” (ITT) population. All randomized patients took study drug. Thirty-two patients (3.9%) discontinued the study before performing an exercise test on double-blind study drug; 11/269 (4.1%) were on placebo, 7/279 (2.5%) on ranolazine 750 mg b.i.d., and 14/275 (5.1%) on ranolazine 1000 mg b.i.d. The remaining 791 (96.1%) patients comprise the ITT population.

For patients with missing data at Week 12, the last double-blind observation available was carried forward (LOCF) for the primary analysis. In the ITT population, 54 patients (6.8%) terminated the study without a Week 12 trough exercise test; 14/258 (5.4%) were on placebo, 18/272 (6.6%) on ranolazine 750 mg b.i.d., and 22/261 (8.4%) on ranolazine 1000 mg b.i.d. The last observation was at Week 6 for 24 patients and Week 2 for 30 patients.

The primary endpoint and all secondary endpoints in MARISA were also studied in CARISA, in which angina frequency and nitroglycerin consumption (collected

in angina diaries) were additional secondary endpoints. CARISA also evaluated the effect of withdrawing ranolazine after 12 weeks of treatment (rebound).

Adjustment for multiple comparisons (two doses of ranolazine vs placebo) in the primary efficacy analysis was addressed using a 2-stage step-down, closed testing procedure. As a first step, the average response of the two ranolazine groups was compared to placebo at the 0.05 level of significance. Conditionally on that test being significant, testing of each ranolazine dose group vs placebo was conducted at the 0.05 level. This procedure maintained the overall Type I error rate at 0.05.

Efficacy Results

This study demonstrated that ranolazine was effective at trough and peak when administered in combination with other anti-anginal drugs. The therapeutic benefit of ranolazine SR was maintained over 12 weeks of continuous dosing without the development of tolerance in patients also taking effective anti-anginal doses of amlodipine, diltiazem, or atenolol. In addition, abrupt withdrawal of ranolazine SR at the end of 12 weeks did not result in a rebound worsening of the patient's underlying angina.

Figure 4-5 and Table 4-4 summarize the results for the primary efficacy variable, symptom-limited exercise duration at trough. For the ITT population, mean changes from baseline at trough at Week 12, using LOCF, were statistically significant for both ranolazine SR doses (750 mg b.i.d. and 1000 mg b.i.d.) together ($p = 0.012$) and individually compared with placebo ($p \leq 0.030$), demonstrating the anti-anginal effect of ranolazine SR used in combination with effective doses of other anti-anginal drugs.

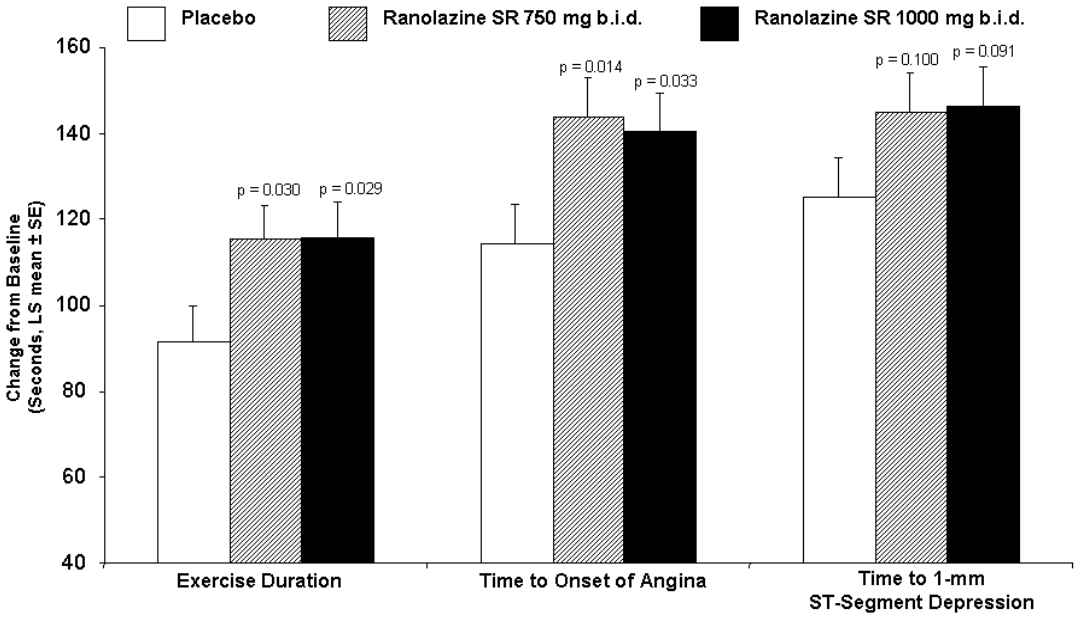
Other key secondary treadmill endpoints included exercise duration at peak, time to onset of angina, and time to 1-mm ST-segment depression at trough and peak. Patient reported frequency of angina episodes, patient-reported

nitroglycerin consumption during the 12 weeks of double-blind treatment, and assessments for the rebound phase were also key secondary efficacy endpoints.

As was observed in MARISA, the mean increases in exercise duration at peak in CARISA were also statistically significantly greater for patients treated with either dose of ranolazine SR than with placebo (see Figure 4-6). Although the changes from baseline in all three treatment groups were smaller at peak than at trough, the differences between active treatment and placebo were greater at peak than at trough. Mean change from baseline in time to onset of angina was significantly increased ($p \leq 0.033$) on ranolazine SR compared to placebo at trough and peak, demonstrating an anti-anginal effect of ranolazine SR. Mean change from baseline in time to 1-mm ST-segment depression at peak was significantly greater with either dose of ranolazine SR than with placebo (both $p \leq 0.004$) signifying an anti-ischemic effect of ranolazine SR and approached statistical significance at trough ($p = 0.100$ [ranolazine 750 mg b.i.d.] and $p = 0.091$ [ranolazine SR 1000 mg b.i.d.]). These clinically effective ranolazine concentrations (~ 1600 ng/mL on 750 mg b.i.d. at trough to ~ 2600 ng/mL on 1000 mg b.i.d. at peak) were in the range described for MARISA.

Figure 4-5, Figure 4-6, and Table 4-4 summarize exercise duration, time to onset of angina, and time to 1-mm ST-segment depression results.

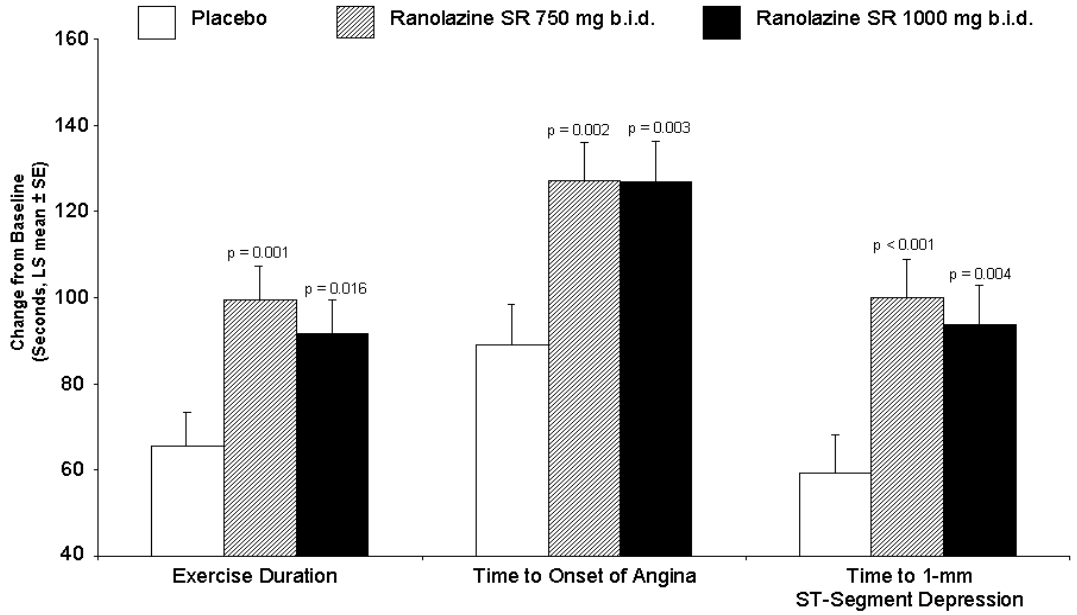
Figure 4-5 Trough Efficacy Endpoints at Week 12 Using LOCF in CARISA (ITT Population)



p-values for comparison of ranolazine SR vs placebo.

Note: LS means and p-values from ANCOVA model with effects for baseline covariate, treatment, pooled site, and background therapy.

Figure 4-6 Peak Efficacy Endpoints at Week 12 Using LOCF in CARISA (ITT Population)



p-values for comparison of ranolazine SR vs placebo.

Note: LS means and p-values from ANCOVA model with effects for baseline covariate, treatment, pooled site, and background therapy.

Table 4-4 Change from Baseline in Primary and Secondary Exercise Efficacy Variables at Week 12 Using LOCF in CARISA (ITT Population)

Variable	Placebo		Ranolazine SR			
			750 mg b.i.d.		1000 mg b.i.d.	
	Trough	Peak	Trough	Peak	Trough	Peak
Exercise Duration, sec						
	N = 258	**N = 256**	**N = 272**	**N = 270**	**N = 261**	**N = 255**
Least Squares Mean (SE)	91.7 (8.3)	65.4 (8.1)	115.4 (8.0)[a]	99.4 (7.8)	115.8 (8.2)[a]	91.5 (8.1)
Mean Difference (SE)[b]	—	—	23.7 (10.9)[a]	34.0 (10.7)	24.0 (11.0)[a]	26.1 (10.8)
p-value[b]	—	—	0.030[a]	0.001	0.029[a]	0.016
Time to Onset of Angina, sec						
	N = 258	**N = 256**	**N = 272**	**N = 270**	**N = 261**	**N = 255**
Least Squares Mean (SE)	114.3 (9.2)	88.9 (9.4)	144.0 (8.9)	126.9 (9.1)	140.3 (9.1)	126.8 (9.4)
Mean Difference (SE)[b]	—	—	29.71 (12.07)	38.02 (12.38)	26.01 (12.20)	37.88 (12.56)
p-value[b]	—	—	0.014	0.002	0.033	0.003
Time to 1-mm ST-Segment Depression, sec						
	N = 247	**N = 234**	**N = 260**	**N = 248**	**N = 244**	**N = 236**
Least Squares Mean (SE)	125.1 (9.2)	59.2 (9.0)	145.1 (9.0)	100.0 (8.7)	146.2 (9.3)	93.8 (8.9)
Mean Difference (SE)[b]	—	—	19.9 (12.2)	40.8 (11.8)	21.1 (12.4)	34.5 (11.9)
p-value[b]	—	—	NS	< 0.001	NS	0.004

[a] Primary efficacy variable

[b] Ranolazine SR vs placebo

Note: LS means and p-values from ANCOVA model with effects for baseline covariate, treatment, pooled site and background therapy.

The results of the patient-reported secondary variables are presented in Table 4-5. The > 4 mean angina attacks per week at baseline (compared to a reported average of 2 attacks per week in the general angina population)[6] reflect the severity of disease in the CARISA patient population. Ranolazine SR significantly ($p \leq 0.006$) reduced the mean frequency of angina in patients treated with ranolazine SR 750 mg b.i.d. or 1000 mg b.i.d. in a dose-dependent fashion compared to placebo. Mean nitroglycerin consumption was also significantly ($p \leq 0.016$) reduced in patients receiving ranolazine SR 750 mg b.i.d. or 1000 mg b.i.d., again in a dose-dependent fashion compared to placebo.

Table 4-5 Angina Diary Data from CARISA (ITT Population)

		Placebo	Ranolazine SR 750 mg b.i.d.	Ranolazine SR 1000 mg b.i.d.
Angina Frequency (attacks/week)		N = 258	N = 272	N = 261
	Mean at baseline	4.6	4.4	4.4
	Mean on treatment	3.31	2.47	2.13
	p-value vs placebo	–	*0.006*	*< 0.001*
Nitroglycerin Use (number/week)		N = 252	N = 262	N = 244
	Mean at baseline	4.1	4.0	3.7
	Mean on treatment	3.14	2.11	1.76
	p-value vs placebo	–	*0.016*	*< 0.001*

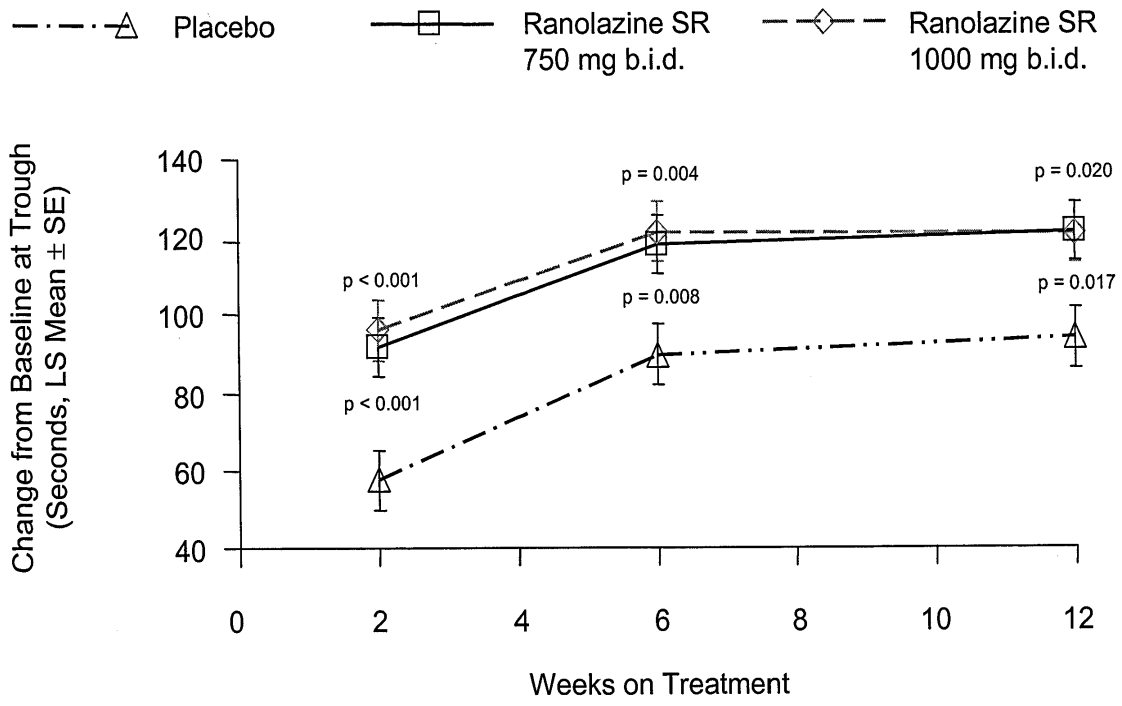
Note: p-values from ANCOVA model fitted to the ranked data with effects for treatment, baseline covariate, pooled site, and background therapy.

In contrast to MARISA, in which a clear dose-response for treadmill exercise performance was observed over a 3-fold range of doses, a dose-response for exercise performance was not evident over the 1.3-fold dose range studied in CARISA. The absence of an evident dose-response for exercise performance in CARISA may thus reflect the relatively narrow dose range studied. A dose-response was observed for angina frequency and for nitroglycerin consumption in CARISA.

Long-Term Effectiveness, Tolerance, and Withdrawal Effects

The magnitude of the increase in ETT duration was similar for 2, 6, and 12 weeks of ranolazine therapy, indicating that prolonged treatment does not result in loss of the ranolazine effect (see Figure 4-7).

Figure 4-7 Ranolazine's Effect on Exercise Duration Over 12 Weeks of Therapy in CARISA (ITT Population)



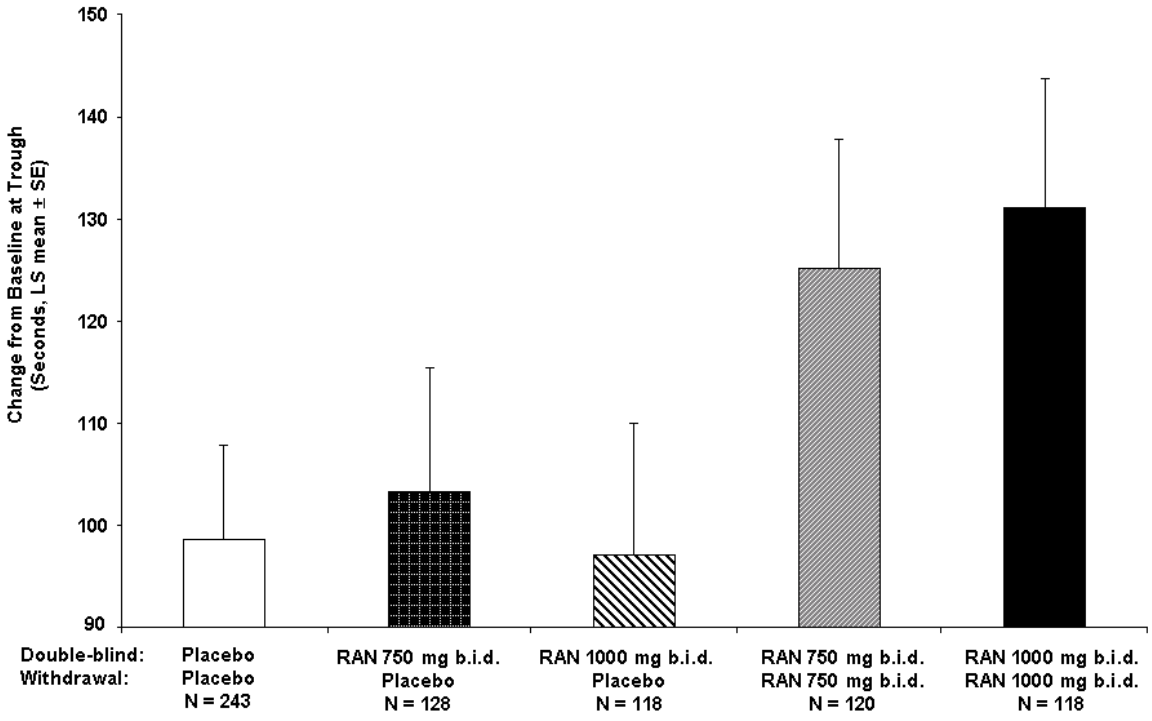
p-values for comparison of ranolazine SR vs placebo.

Note: LS means and p-values from ANCOVA model with effects for treatment, baseline covariate, pooled site, and background therapy.

There was no evidence of a rebound increase in angina for patients withdrawn from ranolazine during the rebound phase of the study. Change from baseline in ETT duration at the end of the rebound phase was compared for patients who received active treatment followed by placebo to those who received placebo throughout. No statistically significant differences were found, indicating that there is no evidence of a rebound effect.

In addition, it was noted that the therapeutic effect of ranolazine on exercise duration disappeared within 2 days after therapy was withdrawn. Exercise duration decreased by 22 seconds in patients withdrawn from 750 mg b.i.d. to placebo compared to those maintained on 750 mg b.i.d. In patients withdrawn from 1000 mg b.i.d., exercise duration decreased by 34 seconds compared to those who continued on 1000 mg b.i.d. These decreases in exercise duration after ranolazine withdrawal are similar in magnitude to the improvements seen with active treatment vs placebo during the 12-week, double-blind treatment phase (see Figure 4-8). Furthermore, withdrawal of the 1000 mg b.i.d. dose was followed by a larger decline in exercise performance than was observed upon withdrawal of the 750 mg b.i.d. dose.

Figure 4-8 Rebound Assessment: Change from Baseline in Exercise Treadmill Test Duration at Trough in CARISA (ITT Population)



Note: LS means and p-values from ANCOVA model with effects for treatment sequence, baseline covariate, pooled site, and background therapy.

As was observed in MARISA, there were no clinically meaningful changes in standing or exercise systolic BP or HR in CARISA (see Section 4.3 and Table 4-11 for further details).

4.2.3 RAN080: Efficacy of Ranolazine IR on Exercise Duration vs Atenolol 100 mg q.d.

While approval is sought only for the SR formulation of ranolazine, earlier studies using an IR formulation provide support for the efficacy of ranolazine. Study RAN080 provided the first clinical data to demonstrate anti-anginal and anti-ischemic efficacy of ranolazine with a unique pharmacodynamic profile. Study RAN080 remains notable because in this trial, the increase in exercise duration on ranolazine was greater than on atenolol 100 mg q.d. without statistically significant decreases in HR and SBP on ranolazine vs placebo but with a significant increase in end-exercise rate pressure product (RPP) on ranolazine compared to both placebo and atenolol (see Section 4.3 for further details).

Study RAN080 was a double-blind, randomized, placebo-controlled, three-period cross-over study. Patients received a 1-week treatment with 400 mg ranolazine IR t.i.d., 100 mg atenolol q.d., and matching double-dummy placebo in random order during three consecutive weeks. At the end of each of the randomized treatments, patients performed an exercise test at peak (~ 1 hour post-dose). Testing was done at the same time of day at each visit.

Male and female patients between 18 and 75 years of age with documented CAD who had previously shown improvement in symptoms and electrocardiographic signs of ischemia with medical therapy (beta-blockers, calcium channel blockers, or long-acting nitrates) were eligible for screening. Patients with ≥ 1-mm ST-segment depression in one lead within 3–9 minutes of beginning a screening exercise test qualified for randomization.

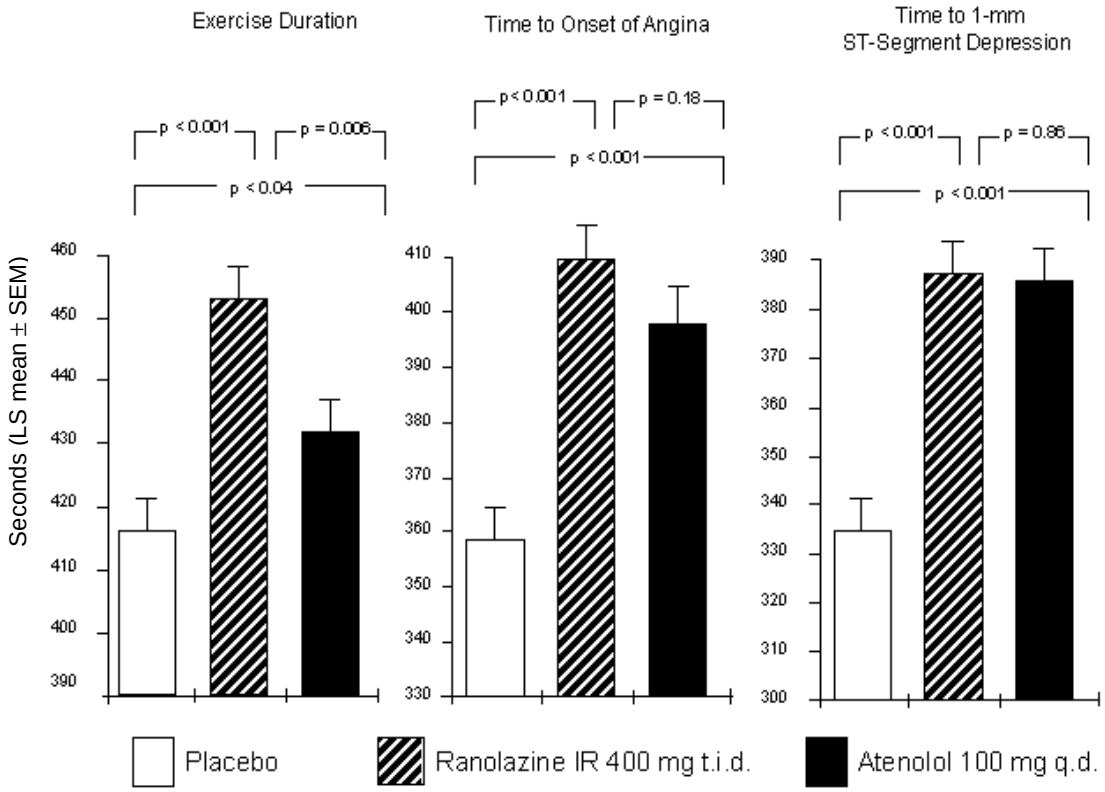
Diltiazem and dihydropyridine calcium channel blockers were permitted at screening. Patients who qualified for randomization while receiving a calcium

channel blocker (N = 85) continued that medication at the same dose throughout the double-blind phase of the study. Short-acting nitrates were permitted (except within 6 hours before exercise testing). Long-acting nitrates were allowed in the same fashion as calcium channel blockers. A total of 158 patients were randomized; 154 had at least one exercise test and were included in the "all-patients analysis".

Efficacy Results

Both atenolol and ranolazine resulted in statistically significant increases with respect to placebo in all three measured exercise parameters (see Figure 4-9 and Table 4-6). The effect of ranolazine on exercise duration was statistically significantly greater than that of atenolol 100 mg and numerically greater for time to angina and time to 1-mm ST-segment depression.

Figure 4-9 Exercise Test Parameters Demonstrating Anti-anginal and Anti-ischemic Effects of Ranolazine and Atenolol in Study RAN080 (All Patients Analysis)



Note: LS means and p-values from ANOVA model with effects for site, patient within site, period, treatment, and treatment by site interaction.

Table 4-6 Overall Summary of Key Efficacy Results in Ranolazine IR Study RAN080 (All Patients Analysis)

Variable	Placebo N = 152	Ranolazine IR 400 mg t.i.d. N = 153	Atenolol 100 mg q.d. N = 153
Exercise Duration, sec			
Least Squares Mean (SEM)	415.9 (5.4)	453.0 (5.4)	431.8 (5.4)
Mean Difference from placebo	—	37.1	16.0
Comparison to placebo	—	p < 0.001	p < 0.04
Comparison to atenolol	—	p = 0.006	—
Time to Onset of Angina, sec			
Least Squares Mean (SEM)	358.4 (6.1)	409.3 (6.1)	397.9 (6.0)
Mean Difference from placebo	—	51.0	39.5
Comparison to placebo	—	< 0.001	p < 0.001
Comparison to atenolol	—	p = 0.18	—
Time to 1-mm ST-Segment Depression, sec			
Least Squares Mean (SEM)	334.3 (6.5)	386.9 (6.5)	385.3 (6.4)
Mean Difference from placebo	—	52.6	51.0
Comparison to placebo	—	p < 0.001	p < 0.001
Comparison to atenolol	—	p = 0.86	—

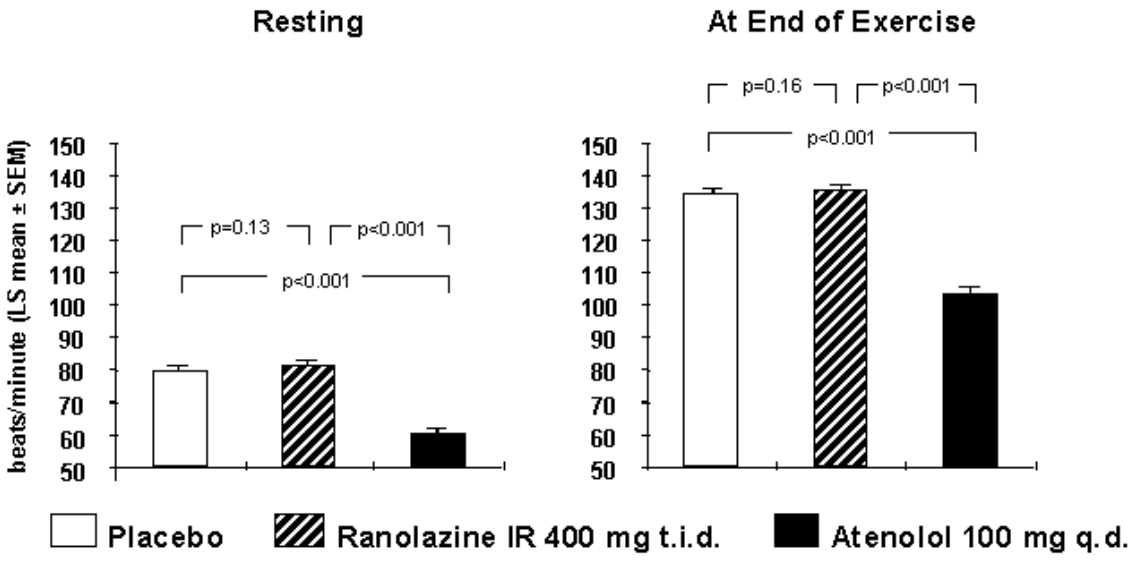
Note: LS means and p-values from ANOVA model with effects for site, patient within site, period, treatment and treatment by site interaction.

Increases in all exercise variables were greater with ranolazine than with atenolol; in particular, exercise duration increased statistically significantly more with ranolazine 400 mg t.i.d. (mean ranolazine level of 1741 ng/mL, in the range of 1578 ng/mL to 2031 ng/mL on 750 mg b.i.d. at trough and peak, respectively in CARISA) than with atenolol 100 mg q.d. Thus, in Study RAN080, a ranolazine concentration achievable with ranolazine SR 750 mg b.i.d. produced anti-anginal and anti-ischemic effects at least as great as those of atenolol 100 mg q.d.

The design of this study used all six possible sequences of the three treatments, so each treatment preceded every other treatment an equal number of times. This permitted testing for first order carryover effect using within patient variability and there was no evidence of carryover effect ($p > 0.6$).

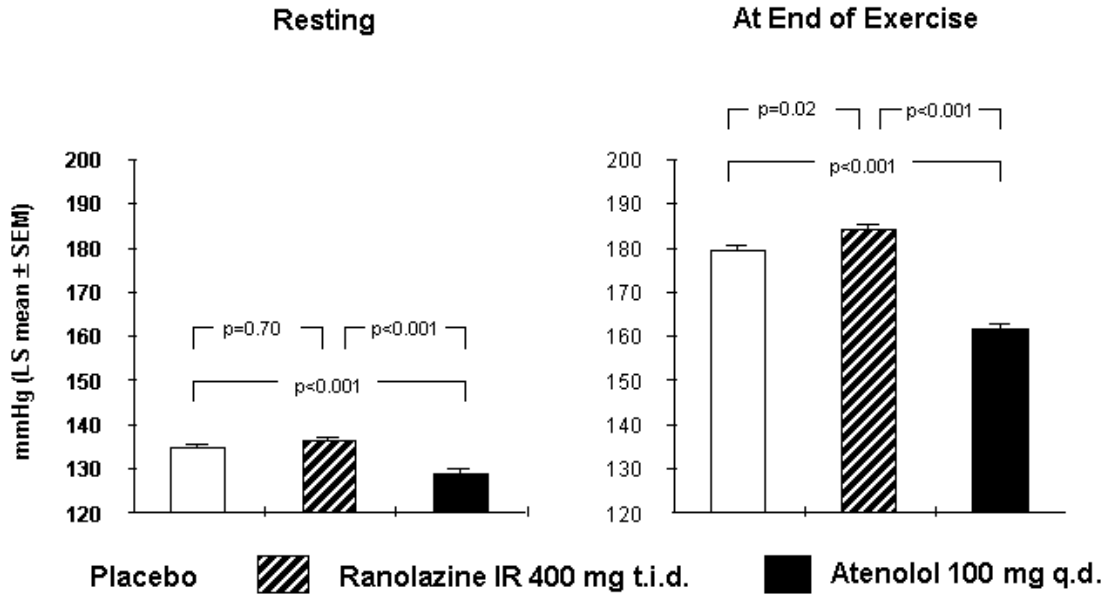
Ranolazine did not cause significant changes compared to placebo in HR; SBP increased a small but statistically significant amount relative to placebo (see Figure 4-10 and Figure 4-11, respectively). Both HR and SBP decreased significantly with atenolol treatment (see Section 4.3 for further detail). Thus, in Study RAN080, the increase in the ischemic threshold observed on ranolazine was achieved with a fundamentally different pharmacodynamic profile than that of atenolol.

Figure 4-10 Heart Rate in Study RAN080 (All Patients Analysis)



Note: LS means and p-values from ANOVA model with effects for site, patient within site, period, treatment and treatment by site interaction.

Figure 4-11 Systolic Blood Pressure in Study RAN080 (All Patients Analysis)



Note: LS means and p-values from ANOVA model with effects for site, patient within site, period, treatment and treatment by site interaction.

4.2.4 RAN072: Anti-Anginal and Anti-Ischemic Effects of Ranolazine IR Within 2.5 to 3 Hours Under Conditions of Maximal Effect of Atenolol

Study RAN072 was a study conducted with the IR formulation of ranolazine that demonstrated efficacy under conditions approximating the maximal or adequate treatment with either atenolol or diltiazem, respectively, in patients assessed by their physicians to be optimally treated with a beta-blocker or diltiazem.

Study RAN072 was a double-blind, randomized, placebo-controlled, single-dose, 2-period, cross-over study. Male and female patients between 18 and 75 years of age had severe CAD, ≥ 1-mm ST-segment depression in one lead (in the absence of other causes such as digitalis, left bundle branch block, or hypertrophy) according to their treadmill performance at entry, and were symptomatic despite therapy with an approved dose of diltiazem IR (≥ 60 mg t.i.d.) or a beta-blocker. The protocol required “patients entering the

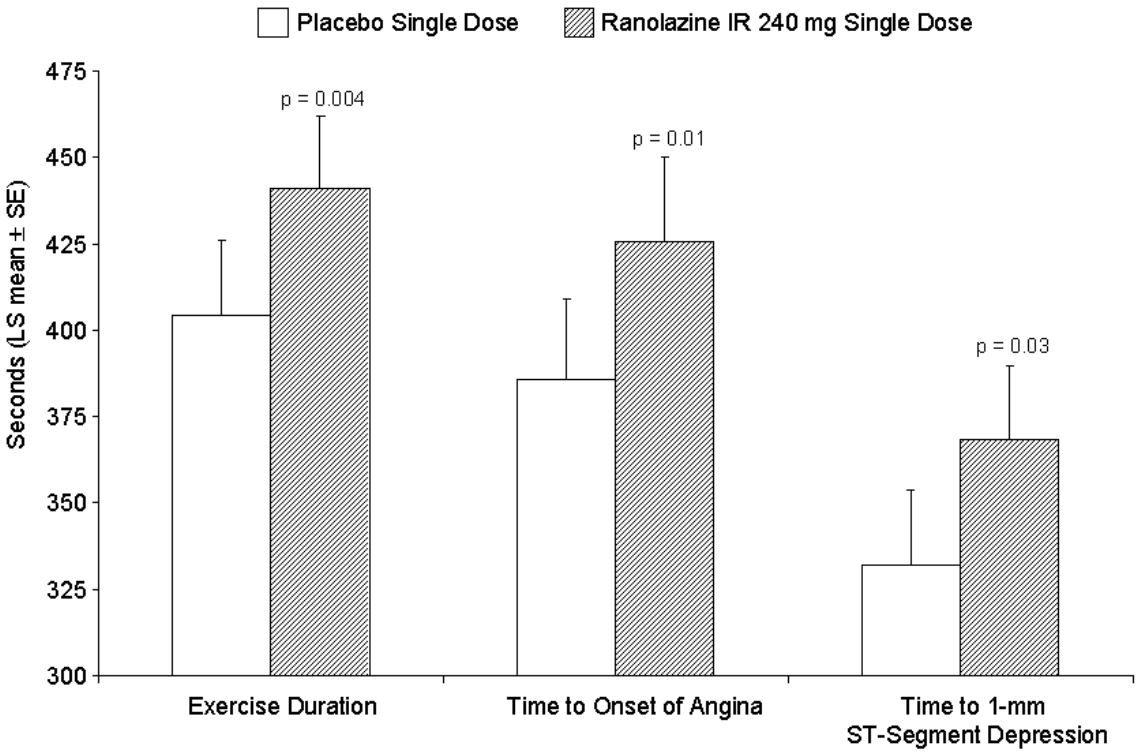
study to be receiving an optimal dose of the concomitant medication (beta-blocker or diltiazem) and be stabilized at this optimal regimen for at least 7 days". Study days (on which ranolazine or placebo was administered) were 2–7 days apart; exercise testing was performed at peak (2.5 to 3 hours after drug administration), at the same time of day for both treatments. Study treatment included, in random order, a single-dose of ranolazine IR at one of four dose levels (10, 60, 120, or 240 mg), and placebo.

One hundred and six patients were randomized. All received study drug and completed the study. Patients were divided into 2 groups: Group 1 comprised 62 patients treated with beta-blockers and Group 2 included 44 patients treated with diltiazem.

Efficacy Results

ETT duration, time to onset of angina, and time to 1-mm ST-segment depression increased significantly with respect to placebo within 2.5 to 3 hours after dosing only in the 25 patients treated with 240 mg ranolazine (mean plasma ranolazine concentration 880 ng/mL similar to that produced by 500 mg b.i.d. of the SR formulation at trough) (see Figure 4-12 and Table 4-7). These 25 patients received ranolazine over a background of maximally effective or adequate doses of atenolol or diltiazem, respectively (described later in this section). Doses of 10, 60, and 120 mg of ranolazine IR, which resulted in peak mean ranolazine plasma concentrations of $\leq$ 500 ng/mL, were not effective.

Figure 4-12 Overall Summary of Key Efficacy Results in Ranolazine IR Study RAN072 (All Patients Analysis)



p-values data for comparison of ranolazine IR vs placebo.

Note: LS means and p-values from ANOVA model fitted to the ranolazine – placebo differences with effects for background therapy, ranolazine dose, sequence, and all interactions among background therapy, dose and sequence.

Table 4-7 Overall Summary of Key Efficacy Results in Ranolazine IR Study RAN072 (All Patients Analysis)

Variable	Placebo 240 mg single dose N = 25	Ranolazine IR 240 mg single dose N = 25
Exercise Duration, sec		
Least Squares Mean (SE)	404.3 ± 21.5	440.9 ± 21.1
LS Mean Difference from Placebo (SE)	—	36.6 (12.5)
p-value	—	0.004
Time to Onset of Angina, sec		
Least Squares Mean (SE)	385.7 ± 23.3	425.4 ± 24.8
LS Mean Difference from Placebo (SE)	—	39.7 (15.1)
p-value	—	0.01
Time to 1-mm ST-Segment Depression, sec		
Least Squares Mean (SE)	331.9 ± 21.6	368.3 ± 21.4
LS Mean Difference from Placebo (SE)	—	36.5 (17.0)
p-value	—	0.03

p-values data for comparison of ranolazine IR vs placebo.

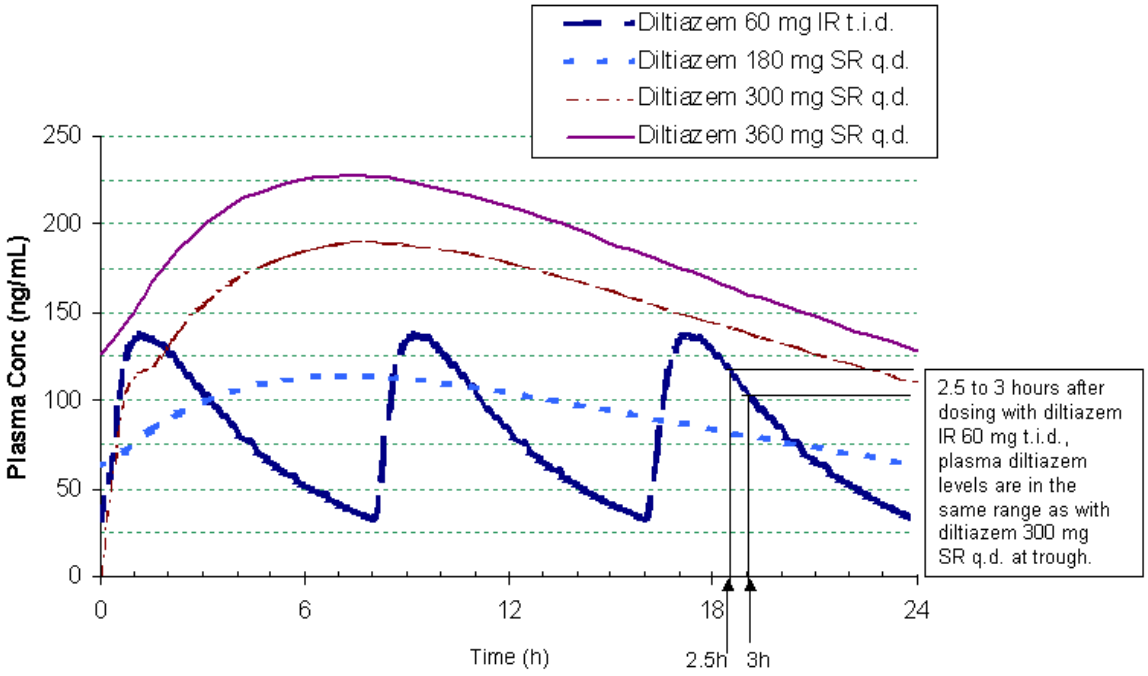
Note: LS means and p-values are from ANOVA model fitted to the ranolazine – placebo differences with effects for background therapy, ranolazine dose, sequence, and all interactions among background therapy, dose and sequence.

Pharmacokinetic/pharmacodynamic arguments can be made for conditions of maximal or near maximal anti-anginal and anti-ischemic effects of atenolol 100 mg q.d. in Study RAN072. The maximum early effect of atenolol on exercise tolerance in chronic angina patients is achieved 3 hours after steady-state dosing of 50 mg q.d.[17] Doses of 100 mg or 200 mg q.d. afford little further increase in exercise performance but maintain the effect for a longer period.[18]

Similarly, based on diltiazem PK modeling and the assumption that plasma diltiazem concentrations are generally dose-proportional, diltiazem IR 60 mg t.i.d. plasma levels at 2.5 to 3 hours after dosing are predicted to be near mean

steady-state trough levels of diltiazem CD 300 mg q.d. (see Figure 4-13). Trough efficacy plateaus with once daily diltiazem at doses ≥ 300–360 mg.

Figure 4-13 Projected Diltiazem Plasma Concentration Profiles (Diltiazem 60 mg IR t.i.d., 180 mg SR q.d., 300 mg SR q.d., 360 SR mg q.d.)



Source: Dilacor XR (Diltiazem sustained release) Capsules FDA Review Documents. NDA 20-092, 1991.[19]; Diltiazem Hydrochloride ER (extended release) Capsules FDA Review Documents. NDA 20-939, 1999.[20]

In Study RAN072, entry criteria specified that all patients were receiving an "optimal" dose of the concomitant medication (beta-blocker or calcium channel blocker). Under such conditions, reflecting maximal or adequate treatment with either atenolol or diltiazem, respectively, chronic angina patients experienced significant increases in their exercise performance after a single-dose of ranolazine IR 240 mg (N = 25) (see Table 4-8). All three major exercise parameters increased significantly on ranolazine compared to placebo for both atenolol and diltiazem strata combined, as well as within the atenolol stratum. Increases in exercise parameters did not achieve statistical significance within the smaller diltiazem stratum, which was not unexpected given the small sample

size; however, with the exception of time to 1-mm ST-segment depression, the increases within the diltiazem stratum were similar in magnitude to those observed overall (see Table 4-8). The average daily atenolol dose in 15 patients was 90.0 ± 21 mg and the median daily dose was 100 mg. The average daily diltiazem dose in 10 patients was 186.0 ± 19 mg and the median daily dose was 180 mg.

Table 4-8 Exercise Performance 2.5 to 3 Hours After a Single Dose of Ranolazine IR 240 mg in Study RAN072

	Atenolol Background N = 15		Diltiazem Background N = 10		Either Background N = 25	
	Placebo	**Ranolazine**	**Placebo**	**Ranolazine**	**Placebo**	**Ranolazine**
Exercise Duration, sec						
Least Squares Mean	398.5 ± 27.5	437.94 ± 27.0	410.0 ± 33.0	443.8 ± 32.4	404.3 ± 21.5	440.9 ± 21.1
Treatment Difference ± SE[a]	39.4 ± 16.0		33.8 ± 19.2		36.6 ± 12.5	
p-value	0.02		0.08		0.004	
Background-by-Treatment Interaction p-value[b] = 0.82						
Time to Onset of Angina, sec						
Least Squares Mean	375.1 ± 29.8	419.4 ± 31.8	396.3 ± 35.8	431.3 ± 38.1	385.7 ± 23.3	425.4 ± 24.8
Treatment Difference ± SE[a]	44.4 ± 19.4		35.0 ± 23.2		39.7 ± 15.1	
p-value	0.02		0.14		0.01	
Background-by-Treatment Interaction p-value[b] = 0.76						
Time to 1-mm ST-Segment Depression, sec						
Least Squares Mean	323.9 ± 27.7	376.4 ± 27.4	339.9 ± 33.2	360.3 ± 32.9	331.9 ± 21.6	368.3 ± 21.4
Treatment Difference ± SE[a]	52.5 ± 21.8		20.4 ± 26.1		36.5 ± 17.0	
p-value	0.02		0.43		0.03	
Background-by-Treatment Interaction p-value[b] = 0.35						

[a] Ranolazine vs placebo

[b] Test for interaction in the 240 mg dose group

Note: LS means and p-values from ANOVA applied to the ranolazine – placebo differences with effects for background therapy, ranolazine dose, sequence, and all interactions among background therapy, dose, and sequence.

Study RAN072 demonstrated additional anti-anginal and anti-ischemic effects of ranolazine at a mean plasma concentration produced at trough during steady-state dosing with ranolazine SR 500 mg b.i.d. over a background at or very near the maximal effect of either atenolol, or diltiazem at its maximum trough effect.

These observations support the utility of ranolazine in patients who remain symptomatic while receiving maximally or adequately effective doses of atenolol or diltiazem, respectively.

4.2.5 RAN1514: Anti-Anginal and Anti-Ischemic Effects of Ranolazine Over Background Therapy (Beta-Blocker or Calcium Channel Blocker) at Peak With 1 Week of Continuous Dosing

Study RAN1514 was a study conducted with the IR formulation of ranolazine that demonstrated efficacy in patients at ranolazine plasma levels achieved and maintained with the SR formulation.

Study RAN1514 was a double-blind, randomized, placebo-controlled, extended-period, Latin square study composed of two phases: a 2- to 7-week, single-blind placebo qualifying phase and a placebo-controlled, double-blind, cross-over treatment phase consisting of five 1-week periods. Male and female patients ≥ 21 years of age with angina who had previously shown improvement in symptoms and electrocardiographic signs of ischemia with medical therapy continued their normal anti-anginal and anti-ischemic medication upon entry into the qualifying phase of the study. While receiving this usual therapy, each patient had to experience the onset of angina within 3–13 minutes after beginning a baseline modified Bruce exercise test; at least 1-mm of ST-segment depression also had to be evident during that baseline test. Patients whose time to onset of angina and to 1-mm ST-segment depression were reduced by at least 1 minute during subsequent testing after withdrawal of one or more anti-anginal therapies were allowed to enter the double-blind phase of the study. Three hundred and eighteen patients were randomized in this study of which 315 took study drug. The 312 patients that had at least one ETT measurement were included in the “all patients analysis”.

Of the 318 patients enrolled, 77 were on a concomitant calcium channel blocker and 104 were on a concomitant beta-blocker, respectively, during the double-blind portion of Study RAN1514.

During the double-blind phase, three dosing regimens of ranolazine IR (267 mg t.i.d., 400 mg b.i.d., and 400 mg t.i.d.) and matching, double-dummy placebo were each administered for 1 week in random order during four 1-week treatment

periods, with the last treatment repeated during the fifth period. Trough (8 hours post-dose for the three times daily regimens and 12 hours post-dose for the twice daily regimen) and peak (1 hour post-dosing) treadmill tests were performed at the end of each 1-week double-blind treatment period.

Efficacy Results

Doses of 267 mg t.i.d., 400 mg b.i.d., and 400 mg t.i.d. at peak resulted in mean ranolazine plasma concentrations of ≥ 1346 ng/mL and statistically significantly increased mean times to angina and to 1-mm ST-segment depression compared to placebo at peak. In an analysis of all ranolazine regimens combined, ranolazine significantly increased all three exercise parameters vs placebo at peak (see Table 4-9). A test of first order carryover effect against within-patient variability showed no significant effect in any exercise parameter ($p > 0.7$).

The efficacy variables were also evaluated at trough (see Table 4-9). There were no statistically significant differences at trough between patients treated with any of the ranolazine IR doses and those treated with placebo, indicating that the ranolazine IR formulation was not sufficiently effective in maintaining anti-anginal and anti-ischemic ranolazine plasma levels throughout a twice daily or three times daily dosing interval. The SR formulation was developed because of this finding.

Table 4-9 Overall Summary of Key Efficacy Results in Ranolazine IR Study RAN1514 (All Patients Analysis)

Variable	Placebo		Ranolazine IR							
			267 mg t.i.d.		400 mg b.i.d.		400 mg t.i.d.		All Ranolazine Doses	
	Trough N = 306	Peak N = 306	Trough N = 299	Peak N = 296	Trough N = 300	Peak N = 299	Trough N = 304	Peak N = 303	Trough N = 312	Peak N = 312
Exercise Duration, sec										
Least Squares Mean (SE)	630.0 (NA)	640.2 (NA)	633.6 (NA)	652.2 (NA)	633.0 (NA)	649.8 (NA)	636.0 (NA)	650.4 (NA)	NA	NA
Mean Difference from Placebo (SE)	—	—	3.6 (5.4)	12.0 (5.4)	3.0 (5.4)	10.2 (5.4)	6.0 (5.4)	10.2 (5.4)	4.2 (4.2)	10.8 (4.2)
p-value	—	—	NS	NS	NS	NS	NS	NS	NS	0.013
Time to Onset of Angina, sec										
Least Squares Mean (SE)	514.8 (NA)	540.6 (NA)	526.8 (NA)	564.0 (NA)	526.2 (NA)	559.8 (NA)	519.0 (NA)	559.8 (NA)	NA	NA
Mean Difference from Placebo (SE)	—	—	11.4 (7.2)	23.4 (7.8)	10.8 (7.2)	19.2 (7.8)	4.2 (7.2)	19.2 (7.8)	9.0 (6.0)	20.4 (6.0)
p-value	—	—	NS	< 0.01	NS	0.013	NS	0.012	NS	< 0.01
Time to 1-mm ST-Segment Depression, sec										
Least Squares Mean (SE)	542.4 (NA)	574.8 (NA)	553.2 (NA)	599.4 (NA)	553.2 (NA)	591.6 (NA)	558.6 (NA)	596.4 (NA)	NA	NA
Mean Difference from Placebo (SE)	—	—	10.8 (7.8)	24.6 (7.2)	11.4 (7.8)	16.8 (7.2)	16.2 (7.8)	21.6 (7.2)	12.6 (6.0)	21.0 (6.0)
p-value	—	—	NS	< 0.01	NS	0.02	NS	< 0.01	0.047	< 0.01

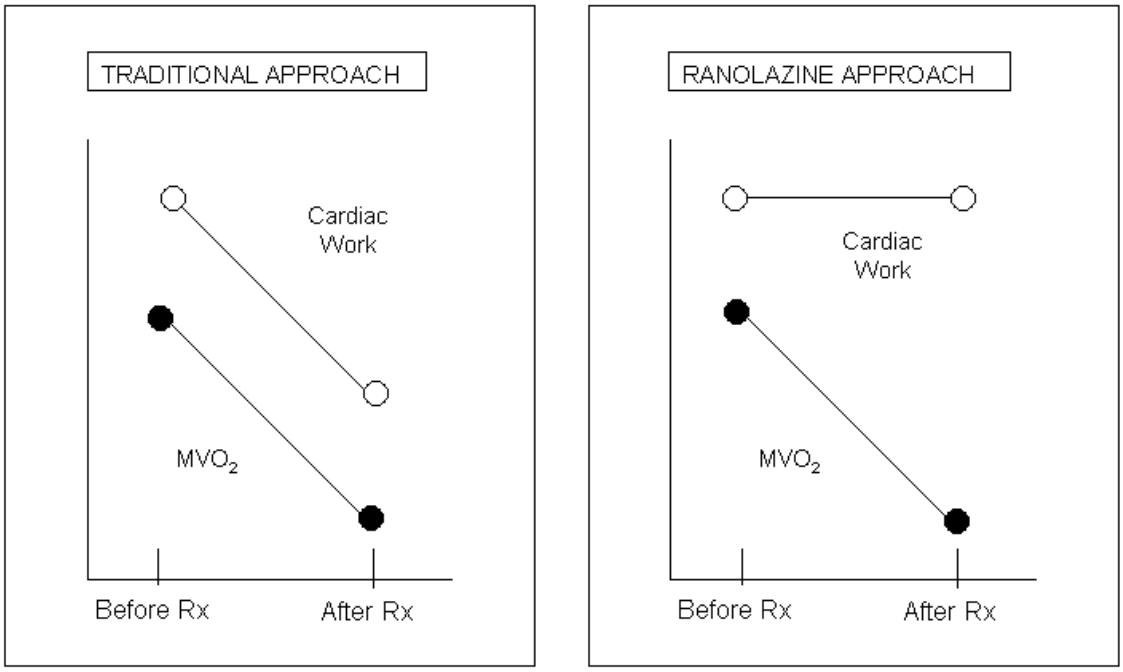
LS means and p-values from analysis of variance with effects for site, patient within site, period, treatment, previous treatment and interactions of site with treatment, and site with previous treatment.

4.3 Anti-Anginal and Anti-Ischemic Effects of Ranolazine: Lack of Dependence on Hemodynamic Effects

Myocardial ischemia occurs when myocardial oxygen demand (reflected by the myocardial oxygen consumption, or MVO_2), exceeds the available myocardial oxygen supply. In general, MVO_2 increases in parallel with cardiac work, as the heart needs more oxygen to oxidize more substrate to generate more ATP in order to support more mechanical work. Accordingly, although some currently available anti-anginal drugs increase myocardial oxygen supply via coronary vasodilatation, all of them attempt to prevent MVO_2 from exceeding the available myocardial oxygen supply by lowering one or more determinants of cardiac work (HR, BP, inotropic state, etc.). The reduction in cardiac work effects a parallel decrease in MVO_2, thus reducing the possibility that MVO_2 will exceed the diminished capacity for myocardial oxygen supply caused by coronary artery disease.

MVO_2 and cardiac work change in parallel only so long as the ratio between myocardial ATP production and MVO_2 is fixed. Ranolazine, however, may reduce the myocardial oxygen requirement needed to support a given level of cardiac mechanical work by shifting the myocardial fuel preference from fatty acid oxidation towards glucose oxidation, thus producing more ATP per mole of oxygen consumed.[21] Accordingly, treatment with ranolazine might alter the parallel relationship between cardiac work and MVO_2, such that more cardiac work could be supported by a given MVO_2 in the presence of ranolazine compared to its absence. This concept is illustrated in Figure 4-14.

Figure 4-14 Illustration of the Concept That Increased Efficiency of Oxygen Use Should Increase the Ratio of Cardiac Work to MVO_2



MVO_2 = myocardial oxygen demand.

Proof that ranolazine increases myocardial oxygen efficiency requires simultaneous measurements of cardiac work and MVO_2 during treatment with ranolazine compared to placebo. The product of HR and BP, or rate-pressure product (RPP), is an index of cardiac work that can be easily measured and reported in large, multi-center trials of anti-anginal drugs. Quantitative measurement of MVO_2 is not feasible in these trials; however, directional changes in MVO_2 can be inferred from changes in the ischemic threshold determined during exercise testing of patients with chronic angina.

As outlined above, myocardial ischemia occurs when oxygen demand, or MVO_2, exceeds supply. Accordingly, for an intervention to increase the ischemic threshold (i.e., to prolong treadmill exercise tolerance and delay the onset of exercise-induced myocardial ischemia), either myocardial oxygen supply must be increased, MVO_2 must be decreased, or both. Ranolazine does not affect coronary blood flow (i.e., myocardial oxygen supply)[22-25] (also Studies RAN014

and RAN070); therefore, an increase in the ischemic threshold associated with ranolazine must be due solely to a decrease in MVO_2. In turn, a decrease in MVO_2 can be caused only by a decrease in cardiac work, an increase in myocardial oxygen efficiency (i.e., the ratio of cardiac work to MVO_2), or some combination of the two.

4.3.1 RAN080: Effects of Ranolazine IR 400 mg t.i.d. vs Atenolol 100 mg q.d. on Rate Pressure Product During Exercise in Chronic Angina Patients

Study RAN080 was a randomized, double-blind, placebo-controlled trial designed to test prospectively the relative efficacy of ranolazine IR 400 mg t.i.d., atenolol 100 mg q.d., and placebo (described earlier in Section 4.2.3). RPP and exercise efficacy data from RAN080 are summarized in Table 4-10.

Table 4-10 Heart Rate, Blood Pressure, RPP, and Exercise Data at Peak in Study RAN080 (All Patients Analysis)

Variable	Least Squares Mean Difference from Placebo p-value	
	Ranolazine IR 400 mg t.i.d.[a]	Atenolol 100 mg q.d.[a]
Standing Pre-Exercise HR, bpm	1.5[b] NS	-19.2 < 0.001
Standing Pre-Exercise SBP, mmHg	-0.5[b] NS	-7.7 < 0.001
Standing, End-Exercise HR, bpm	2.0[b] NS	-28.7 0.001
Standing, End-Exercise SBP, mmHg	4.7[b] 0.02	-18.3 < 0.001
RPP at End-Exercise, bpm mmHg	1261[b] 0.005	-6797 < 0.001
Exercise Duration, sec	37.1[b] < 0.001	16.0 < 0.04
Time to Onset of Angina, sec	51.0 < 0.001	39.5 < 0.001
Time to 1-mm ST-Segment Depression, sec	52.6 < 0.001	51.0 < 0.001

[a] Study RAN080: Data presented are from the all patients analysis.

[b] The comparison for the difference between ranolazine and atenolol was significant, $p \leq 0.006$.

Atenolol significantly increased all three key exercise parameters with respect to placebo in association with a profound and statistically significant reduction in end-exercise RPP. Because atenolol does not increase coronary blood flow in patients with cardiac disease[26–28] nor do other selective $beta_1$-,[29,30] or non-selective $beta_1$/$beta_2$ adrenergic receptor antagonists,[29,31-33] the increase in the ischemic threshold observed with atenolol can be explained entirely by a reduction in MVO_2. Whether this reduction in MVO_2 occurred entirely due to the fall in RPP or if there was also some contribution from an increase in myocardial oxygen efficiency cannot be determined from these data.

Significant increases in all three key exercise parameters also were observed in Study RAN080 during treatment with ranolazine compared to placebo; indeed, exercise duration on ranolazine was also significantly longer than on atenolol. In contrast, however, to the significant decrease in end-exercise RPP observed with atenolol, end-exercise RPP increased significantly on ranolazine compared to both placebo and atenolol.

Thus, in Study RAN080, compared to placebo treatment, chronic angina patients on ranolazine (at a mean plasma ranolazine concentration similar to that produced by steady-state dosing with ranolazine SR 750 mg b.i.d.) could exercise significantly longer, and their hearts could do more mechanical work, before the symptoms and objective electrocardiographic evidence of myocardial ischemia supervened. A reduction in cardiac work due to ranolazine cannot have caused these effects, because cardiac work, reflected by RPP, increased on ranolazine. Because ranolazine does not affect coronary blood flow, an increase in myocardial oxygen delivery also cannot explain these findings. Therefore, ranolazine appears to have reduced MVO_2 by increasing the myocardial oxygen efficiency, consistent with its reported ability to switch myocardial ATP generation away from fatty acid oxidation towards glucose oxidation.[21]

4.3.2 Effects of Ranolazine on Rate Pressure Product in MARISA and CARISA

Exercise performance and RPP data from the two Phase 3 studies, MARISA and CARISA, are consistent with the increase in myocardial oxygen efficiency demonstrated in Study RAN080. In these two studies, ranolazine doses > 500 mg b.i.d. were sometimes associated with small but statistically significant decreases vs placebo in exercise RPP, in contrast to the increase in exercise RPP observed on ranolazine in Study RAN080. The exercise data from the two pivotal trials are presented together in Table 4-11.

Table 4-11 Heart Rate, Blood Pressure, RPP, and Exercise Data at Trough and Peak in MARISA and CARISA

	Least Squares Mean Difference from Placebo p-values ≤ 0.05									
	500 mg b.i.d.[a]		750 mg b.i.d.[b]		1000 mg b.i.d.[b]		1000 mg b.i.d.[a]		1500 mg b.i.d.[a]	
Ranolazine SR Dose	Trough	Peak	Trough	Peak	Trough	Peak	Trough	Peak	Trough	Peak
Standing Pre-Exercise HR, bpm	0.4 NS	0.3 NS	-1.5 NS	-1.4 NS	-1.5 NS	-1.3 NS	-1.5 0.043	-1.5 NS	-2.8 < 0.001	-2.6 0.001
Standing Pre-Exercise SBP, mmHg	-2.3 NS	-0.4 NS	-1.8 NS	-1.6 NS	-2.8 0.015	-2.8 0.018	-1.0 NS	-0.3 NS	-1.8 NS	-2.3 0.039
Standing End-Exercise HR, bpm	0.6 NS	1.7 NS	-3.1 p = 0.01	-2.3 NS	-2.8 p = 0.021	-2.1 NS	-1.7 NS	-0.4 NS	-1.5 NS	-1.5 NS
Standing End-Exercise SBP, mmHg	-1.7 NS	-2.2 NS	-1.8 NS	0.4 NS	-3.3 p = 0.035	0.1 NS	-3.6 p = 0.008	-3.5 p = 0.006	-5.4 p < 0.001	-6.5 p < 0.001
RPP at End-Exercise, bpm mmHg	-107.2 NS	43.3 NS	-617.9 p = 0.036	-258.3 NS	-822.1 p = 0.006	-315.5 NS	-737.8 p = 0.004	-512.5 p = 0.035	-929.0 p < 0.001	-1006.5 p < 0.001
Exercise Duration, sec	23.8 p = 0.003	29.3 p < 0.001	27.1 p = 0.017	34.2 p = 0.002	26.8 p = 0.020	24.3 p = 0.031	33.7 p < 0.001	50.1 p < 0.001	45.9 p < 0.001	55.5 p < 0.001
Time to Onset of Angina, sec	27.0 p = 0.005	35.5 p < 0.001	33.8 p = 0.007	38.4 p = 0.003	32.9 p = 0.010	37.6 p = 0.004	45.9 p < 0.001	56.4 p < 0.001	59.6 p < 0.001	68.5 p < 0.001
Time to 1-mm ST-Segment Depression, sec	27.6 p < 0.001	38.8 p < 0.001	20.8 NS	42.2 p < 0.001	27.9 p = 0.038	37.1 p = 0.003	44.5 p < 0.001	55.6 p < 0.001	64.6 p < 0.001	69.0 p < 0.001

[a] MARISA: Efficacy data presented are from the All/Near Completers population (N = 175); i.e., the primary efficacy analysis. HR/BP and RPP data are from all randomized patients with at least one measurement of end-exercise RPP (N = 179). Differences from placebo are from ANOVA model with effects for pooled site, patients within pooled site, period and treatment.

[b] CARISA: HR/BP and RPP data presented are from all randomized patients at Week 12 (N = 737). Note that the primary efficacy analysis was performed on Intent-to-Treat at Week 12 using LOCF (N = 791); an RPP analysis was not performed on this population. Differences from placebo are from an analysis of covariance (ANCOVA) model with effects for baseline, pooled site, background therapy and treatment.

There are at least two reasons why the clinically meaningful and statistically significant increases in exercise tolerance on ranolazine in MARISA and CARISA cannot be explained entirely by the small but statistically significant decreases in end-exercise RPP observed at some doses and time points.

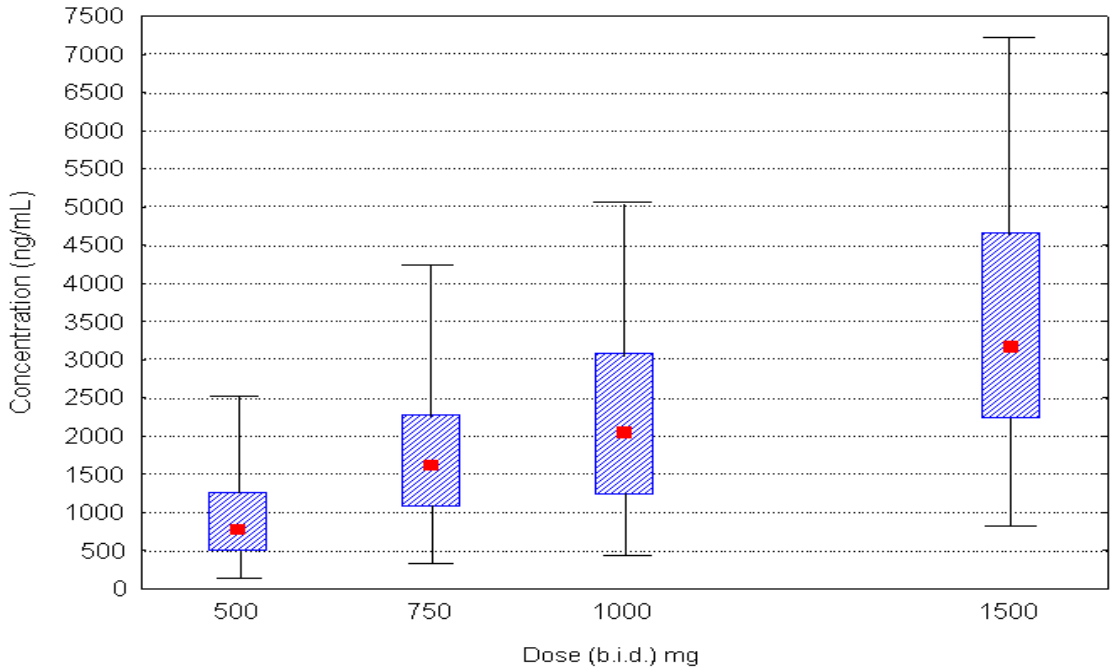
1. Significant increases in exercise performance are not invariably accompanied by significant decreases in end-exercise RPP. In MARISA, ranolazine 500 mg b.i.d. significantly increased all three treadmill efficacy variables at both peak and trough without statistically significant or clinically meaningful effects on end-exercise RPP. This was also true at peak for both doses in CARISA.
2. For all three key ETT efficacy parameters, for each dose in MARISA, the ranolazine effect at peak was greater than the effect at trough. With the single exception of exercise duration on 1000 mg b.i.d., the same relationship (i.e., peak effect > trough effect) was apparent for the three key ETT efficacy parameters on both doses in CARISA. In contrast, the pattern of ranolazine effects on end-exercise RPP was opposite to that observed for the ETT efficacy parameters; i.e., the decrease in end-exercise RPP at peak was substantially smaller than at trough in every case except 1500 mg b.i.d. in MARISA. Clearly then, decreases in MVO_2 due to decreases in RPP cannot fully explain increases in the ischemic threshold on ranolazine.

Finally, in comparable studies in chronic angina patients, the increases in exercise performance observed with calcium channel blockers, and especially with beta-blockers,[34-38] are generally associated with substantially larger decreases in end-exercise RPP than the small but significant decreases in end-exercise RPP observed with some doses of ranolazine at some time points in MARISA and CARISA.

4.4 Relationships among Dose, Plasma Concentration and Anti-Anginal Effects of Ranolazine

In general, plasma concentrations increase with ranolazine dose (see Figure 4-15) and the therapeutic response increases with plasma concentrations.

Figure 4-15 Dose-Concentration Response in MARISA and CARISA



The small rectangle is the median, the shaded box shows the 25th and 75th percentiles, and the bars represent the 5th and 95th percentiles.

MARISA (All/Near Completers Population); CARISA (ITT Population).

A population-based analysis was performed to explore the relationship between ETT duration and ranolazine plasma concentration. The influence of demographics and co-morbidities on this relationship was also examined. The analysis population included 1397 patients with angina (1073 males and 324 females) enrolled in MARISA, CARISA, Studies RAN080, or RAN1514. A brief description of each study is presented in Section 4.1, Table 4-1. The following variables were assessed as covariates for inclusion in the model building process: (1) Age, (2) Weight, (3) Gender, (4) Race, (5) CHF status, (6) Diabetes status, and (7) Concomitant medications. The model included a term for the learning effect such that the ranolazine net effect could be estimated.

The demographic factors of age, weight, race, and co-morbidities (CHF with NYHA Class I–II, diabetes) had no influence on the concentration-response for efficacy. The absence, presence, or class of anti-anginal background therapy

also did not influence the concentration-response for efficacy, indicating that the efficacy data from the monotherapy study, MARISA, are not inconsistent with those from the combination therapy study, CARISA.

In the population-based analysis, gender was a significant predictor of the response to ranolazine as assessed by treadmill exercise testing. The average increase in treadmill duration that can be attributed to ranolazine is 6.4 seconds/1000 ng/mL ranolazine concentration in females and 16.8 seconds/1000 ng/mL in males. This is not unexpected, as it is known that ETT and variables such as exercise capacity and ST-segment changes may be influenced by gender.[4] Many women are unable to exercise to maximal aerobic capacity,[4] which may limit the ability to detect their full response to an anti-anginal agent as measured by improvement in exercise testing.

Consistent with this hypothesis, gender effects have also been observed in the efficacy of other anti-anginal drugs as assessed by exercise testing. In Study RAN080, for example, in which the same patient received ranolazine, atenolol and placebo in three randomized periods, females in the study had less improvement in all exercise parameters than males not only on ranolazine, but also on atenolol, an anti-anginal that is widely used to treat women.

Improvements in ETT parameters were smaller in women than in men with both ranolazine and atenolol treatment, although the number of women was limited (see Table 4-12).

Table 4-12 Exercise Performance by Gender in Study RAN080 (All Patients Analysis)

	Placebo Subgroup		Atenolol 100 mg q.d. Subgroup		Ranolazine 400 mg t.i.d. Subgroup	
	Male N = 135	Female N = 17	Male N = 136	Female N = 17	Male N = 135	Female N = 18
Exercise Duration						
LSMEAN ± SE	424.0 ± 10.7	338.6 ± 30.3	440.2 ± 10.7	347.1 ± 30.3	461.2 ± 10.7	375.6 ± 29.8
Active vs Placebo Difference ± SE	–	–	16.2 ± 7.9	8.5 ± 22.7	37.2 ± 7.9	37.0 ± 22.6
p-value	–	–	0.041	0.71	< 0.001	0.10
Treatment by Subgroup Interaction p-value = 0.93						
Time to Onset of Angina						
LSMEAN ± SE	363.2 ± 10.9	315.0 ± 30.9	406.0 ± 10.9	313.6 ± 30.9	418.0 ± 10.9	328.4 ± 30.4
Active vs Placebo Difference ± SE	–	–	42.8 ± 8.8	-1.4 ± 25.4	54.8 ± 8.8	13.3 ± 25.2
p-value	–	–	< 0.001	0.96	< 0.001	0.60
Treatment by Subgroup Interaction p-value = 0.17						
Time to 1-mm ST-Segment Depression						
LSMEAN ± SE	335.1 ± 11.0	330.0 ± 31.2	392.8 ± 10.9	309.6 ± 31.2	391.7 ± 11.0	343.4 ± 30.6
Active vs Placebo Difference ± SE	–	–	57.7 ± 9.3	-20.4 ± 26.9	56.5 ± 9.3	13.3 ± 26.7
p-value	–	–	< 0.001	0.45	< 0.001	0.618
Treatment by Subgroup Interaction p-value = 0.02						

Note: LS means and p-values from ANOVA model with effects for site, patient within site, period, treatment, gender, and the gender by treatment interaction.

Gender effects have also been observed with calcium channel blockers. In a pooled analysis of mibefradil, at a dose level of 50 mg, male patients (N = 312) showed 15.5 seconds greater improvement in total ETT duration than female patients (N = 71). At the 100 mg dose level, both genders showed improvement over the 50 mg dose, but the gender difference widened to 19.2 seconds (males > females).[39] Furthermore, studies in the literature suggest that ETT may not be as precise in determining angina response in women compared to men as evidenced by a higher false-positive rate in predicting the presence of significant coronary artery disease in women (38–67%) than in men (7–44%).[40,41]

These data demonstrate that a smaller improvement in exercise test parameters in women compared to men is not unique to ranolazine, and may reflect a

relative insensitivity of exercise testing to represent a therapeutic response in women.

Further supporting the view that treadmill testing may underestimate anti-anginal efficacy of a therapy in women is the fact that in CARISA, males and females had similar reductions in frequency of angina and nitroglycerin consumption, parameters that may be better measurements than ETT of the anti-anginal effect in women (see Table 4-13).

Table 4-13 Angina Diary Data by Gender from CARISA (ITT Population)

	Placebo Subgroup		Ranolazine SR 750 mg b.i.d. Subgroup		Ranolazine SR 1000 mg b.i.d. Subgroup	
	Male (N = 193)	**Female (N = 65)**	**Male (N = 213)**	**Female (N = 59)**	**Male (N = 210)**	**Female (N = 51)**
Angina Frequency (attacks/week)						
Mean at Baseline ± SE	4.7 ± 0.4	4.4 ± 0.8	4.6 ± 0.4	3.6 ± 0.6	4.6 ± 0.4	3.6 ± 0.6
Mean on Treatment ± SE	3.4 ± 0.3	3.0 ± 0.6	2.6 ± 0.3	2.0 ± 0.5	2.3 ± 0.3	1.5 ± 0.3
Change from Baseline Mean ± SE	-1.3 ± 0.3	-1.4 ± 0.5	-2.0 ± 0.3	-1.6 ± 0.6	-2.3 ± 0.3	-2.1 ± 0.5
p-value vs placebo	–	–	0.029	0.071	< 0.001	0.017
Treatment by Subgroup Interaction p-value = 0.87						
	Male (N = 179)	**Female (N = 64)**	**Male (N = 195)**	**Female (N = 57)**	**Male (N = 190)**	**Female (N = 47)**
Nitroglycerin Use (number/week)						
Mean at Baseline ± SE	4.2 ± 0.5	3.8 ± 0.8	4.3 ± 0.6	2.9 ± 0.6	4.0 ± 0.5	2.4 ± 0.6
Mean on Treatment ± SE	3.1 ± 0.4	3.2 ± 0.9	2.2 ± 0.3	2.0 ± 0.5	2.0 ± 0.3	1.0 ± 0.2
Change from Baseline Mean ± SE	-1.0 ± 0.4	-0.6 ± 0.9	-2.2 ± 0.5	-0.9 ± 0.5	-2.1 ± 0.4	-1.4 ± 0.5
p-value vs placebo	–	–	0.030	0.33	0.004	0.063
Treatment by Subgroup Interaction p-value = 0.89						

Note: P-values are generated from ANCOVA model fitted to ranked data including effects for treatment, baseline covariate, pooled site, background therapy, gender category, and treatment by gender interaction.

4.5 Anti-Anginal and Anti-Ischemic Effects of Ranolazine in a Broad Population of Chronic Angina Patients: Subgroup Analyses

In order to assess whether the efficacy of ranolazine is consistent within the broad population of chronic angina patients studied, exploratory analyses were conducted in patient subgroups of particular interest. These subgroups included patients with low BP, slow HR, or prolonged AV conduction; CHF; diabetes; reactive airway disease; or any one of the former criteria. These patients are often intolerant of other anti-anginals.

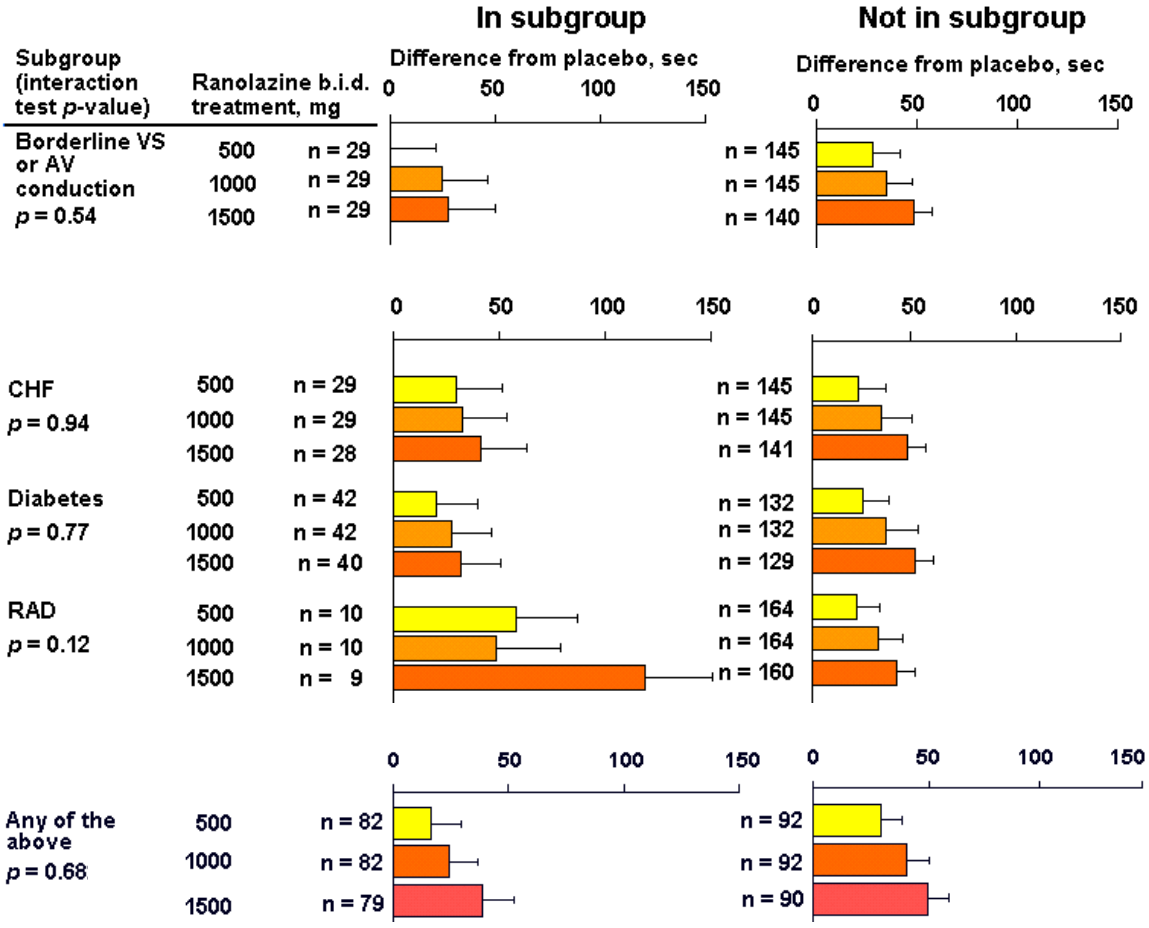
4.5.1 Efficacy of Ranolazine in Angina Patients With Low BP, Slow HR, or Prolonged AV Conduction or With Other Co-existing Medical Conditions

Data from MARISA and CARISA suggest that symptomatic angina patients with low BP, slow HR, or slow AV conduction (i.e., baseline standing SBP $\leq$ 100 mmHg, HR $\leq$ 60 bpm, or PR Interval $\geq$ 200 msec) or who have co-existing conditions (i.e., CHF, diabetes, and reactive airway disease) that make treatment with existing anti-anginal drugs potentially problematic or sub-optimal, may potentially benefit from ranolazine, as its anti-anginal and anti-ischemic effects do not depend on hemodynamics at therapeutic plasma concentrations and it has minimal effects on PR interval.

There was no statistical evidence for differences in the treatment effects of ranolazine as measured by trough exercise duration, the primary endpoint in the subgroups analyzed in MARISA and CARISA, respectively (see Figure 4-16 and Figure 4-17), although the power of the test (treatment-by-subgroup interaction) was limited in some subgroups by the small sample sizes.

Analyses of key secondary efficacy parameters (exercise duration at peak, time to angina and time to 1-mm ST-segment depression at trough and peak, angina frequency and nitroglycerin use) gave no indication that the effects of ranolazine were diminished within particular subgroups.

Figure 4-16 Exercise Duration at Trough, Treatment-by-Subgroup Interaction Test in MARISA ([Low BP, Slow HR, or Prolonged AV Conduction][a]; CHF; Diabetes; Reactive Airway Disease; or Any One of the Former Criteria)



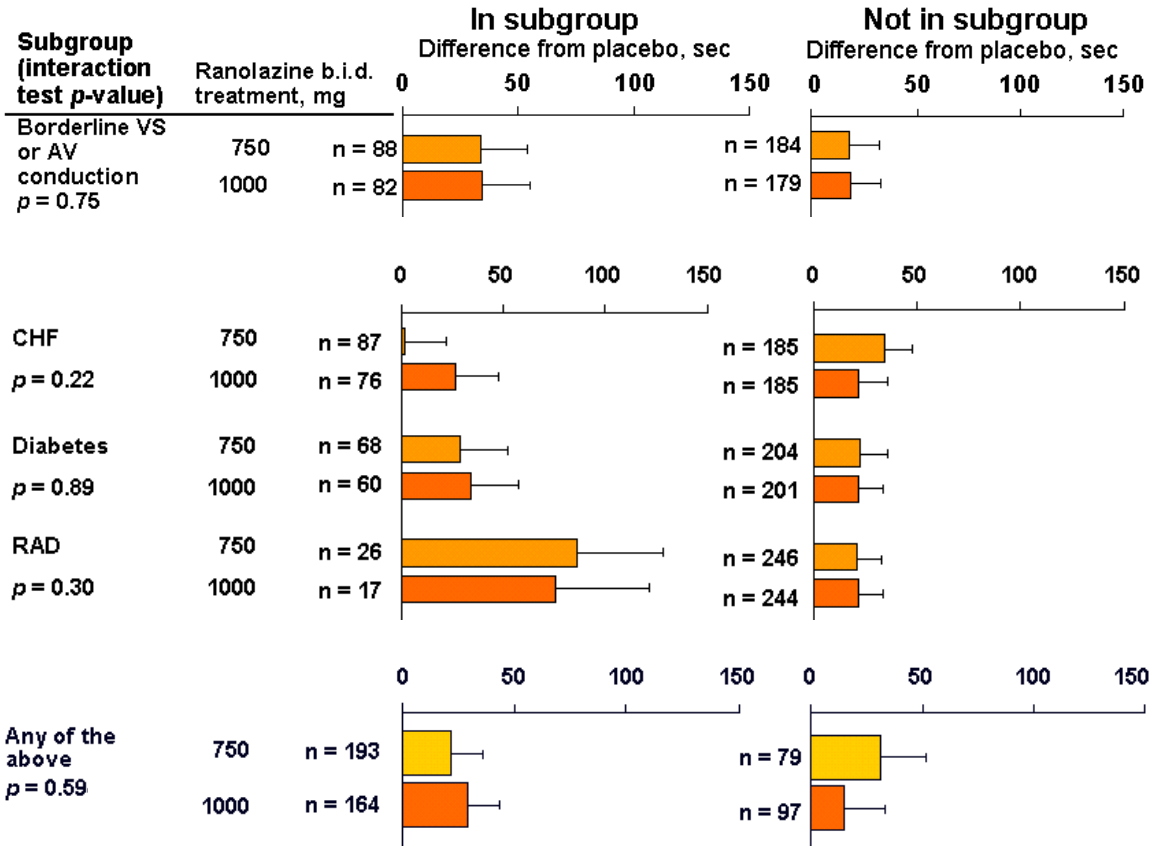
[a] Baseline Standing SBP ≤ 100 mmHg, HR ≤ 60 bpm, or PR Interval ≥ 200 msec.

Data presented as LS mean ± SE.

PR Interval = represents the time required for cellular depolarization to travel from the atrium to the ventricles; HR = heart rate; SBP = systolic blood pressure.

Note: A p-value ≤ 0.05 would indicate that the treatment effect differs in patients who belong to the subgroup compared to those who do not.

Figure 4-17 Exercise Duration at Trough, Treatment-by-Subgroup Interaction Test in CARISA ([Low BP, Slow HR, or Prolonged AV Conduction][a]; CHF; Diabetes; Reactive Airway Disease; or Any One of the Former Criteria)



[a] Baseline Standing SBP ≤ 100 mmHg, HR ≤ 60 bpm, or PR Interval ≥ 200 msec.

Data presented as LS mean ± SE.

PR Interval = represents the time required for cellular depolarization to travel from the atrium to the ventricles; HR = heart rate; SBP = systolic blood pressure.

Note: A p-value ≤ 0.05 would indicate that the treatment effect differs in patients who belong to the subgroup compared to those who do not.

Similar results in the analyses of the primary and secondary endpoints were obtained in integrated analyses of patients meeting the same criteria from Studies RAN080, RAN072, and RAN1514.

These results suggest that the effects of ranolazine are consistent across the broad population of chronic angina patients studied.

4.6 Efficacy Summary

Results of MARISA, CARISA, and a population-based analysis including 1397 chronic angina patients demonstrated that ranolazine SR at doses ≥ 500 mg b.i.d. resulted in statistically significant, clinically meaningful, concentration-related improvements in ETT parameters throughout the planned 12-hour dosing interval. Decreases in angina frequency and nitroglycerin consumption on ranolazine vs placebo in CARISA corroborated these observations. CARISA also showed that the efficacy of ranolazine SR doses of 750 mg b.i.d. and 1000 mg b.i.d. were effective and maintained over time for up to 12 weeks when administered with effective doses of other anti-anginal agents. Furthermore, CARISA demonstrated no rebound increase in angina threshold following abrupt discontinuation of ranolazine.

Improvements in exercise duration at trough in MARISA and CARISA (ranging from 24 to 46 seconds, collectively) compared favorably to those observed with the calcium channel blocker diltiazem (Tiazac®, Cardizem® CD), a commonly prescribed anti-anginal. In a double-blind, parallel group, placebo-controlled study of patients with chronic stable angina evaluated by ETT using a Bruce protocol, doses of diltiazem (Tiazac) between 120–540 mg/day were administered. At trough, 24 hours post-dosing, mean change from placebo in exercise duration increased by 12, 27, 19, and 18 seconds at 120 mg, 240 mg, 360 mg, and 540 mg/day treatment groups, respectively.[7,42] Efficacy appeared to plateau at 240 mg. Similarly, in a double-blind, parallel group, placebo-controlled, dose-response study of diltiazem (Cardizem CD), mean changes from placebo in exercise times (Bruce exercise protocol) at trough were 11, 27, 22, 40,

and 39 seconds at 60 mg, 120 mg, 240 mg, 360 mg, and 480 mg/day treatment groups, respectively. The anti-anginal efficacy did not increase at doses above 360 mg.[43,44]

In Study RAN080, ranolazine IR 400 mg t.i.d. was at least as effective as the active control atenolol 100 mg q.d., increasing all exercise parameters compared to placebo. In contrast to the significant decrease in end-exercise RPP observed with atenolol in Study RAN080, the significant increase in both ETT times and end-exercise RPP demonstrated on ranolazine vs placebo reflect a pharmacodynamically unique anti-anginal and anti-ischemic profile. The statistically significant and clinically meaningful increases in ETT parameters and small decreases in end-exercise RPP observed on some doses at some time points in MARISA and CARISA are not inconsistent with this hypothesis. Supporting the findings in MARISA, CARISA, and Study RAN080, Studies RAN072 and RAN1514 demonstrated statistically significant improvements in exercise treadmill parameters without statistically significant changes in HR or SBP in a broad population of chronic angina patients. In these studies, the therapeutic effects of ranolazine are dose and plasma concentration related.

Study RAN072 demonstrated the efficacy of ranolazine in combination with maximally effective or adequate doses of either beta-blockers or calcium channel blockers, respectively. These observations support the utility of ranolazine in patients who remain symptomatic while receiving doses of either atenolol or diltiazem under conditions of maximal or adequate effect.

Collective analyses of ETT variables (MARISA, CARISA, RAN080, RAN072, and RAN1514) and angina frequency and nitroglycerin consumption (CARISA) in subgroups analyzed did not reveal differences in the efficacy of ranolazine within the subgroups (low BP, slow HR, or prolonged AV conduction; CHF; diabetes; reactive airway disease; or any of the former criteria) that were examined.

4.7 Efficacy Conclusions

The anti-anginal and anti-ischemic efficacy of ranolazine is consistent throughout a broad population of chronic angina patients. The therapeutic effects of ranolazine are dose and plasma concentration related.

In contrast to other currently available anti-anginal agents, ranolazine's efficacy is achieved with a fundamentally different pharmacodynamic profile than that of a beta-blocker or calcium channel blocker. The anti-anginal and anti-ischemic efficacy of ranolazine, which does not depend on decreases in BP or HR, has been demonstrated as monotherapy, in addition to beta-blocker therapy or calcium channel blocker background therapy, under conditions approximating maximal or adequate anti-anginal effect of atenolol or diltiazem, respectively, and consistently throughout a broad population of chronic angina patients.

Based on its unique pharmacodynamic profile, ranolazine may be used as a monotherapy or in combination with existing anti-anginal therapies. Ranolazine can provide added benefit to a broad population of patients with angina. Ranolazine can particularly benefit those whose borderline hemodynamics or AV conduction and/or co-morbid diseases can limit the use of anti-anginal drugs which lower BP, slow HR, and/or slow AV nodal conduction.

5 CLINICAL SAFETY SUMMARY

5.1 Introduction

Ranolazine has been shown to be safe and well tolerated. Adverse Events (AEs) are well-described, generally mild to moderate, and related to dose.

The overall safety experience with ranolazine is substantial. The clinical development program included 3021 subject/patients, 2783 of whom received ranolazine, and 1460 of whom received ranolazine SR. This represents 1714 subject/patient years of exposure to any formulation of ranolazine, including 1282 subject/patient years exposure to ranolazine SR. The mean duration of exposure to ranolazine SR in Phase 3 angina trials was 495 days. Ranolazine has been studied in a broad range of chronic angina patients including patients with diabetes, CHF, or reactive airway disease, or with low blood pressure (BP), low heart rate (HR), or prolonged AV conduction. Safety was assessed in patients who were treated both with and without other concomitant cardiovascular drugs, including other anti-anginals (beta-blockers, calcium channel blockers, long-acting nitrates), diuretics, and ACE inhibitors.

The most common (≥ 2%) AEs in the Phase 3 controlled angina studies over the dose range 500 mg b.i.d. to 1000 mg b.i.d. that occurred more frequently on ranolazine treatment than on placebo were dizziness, constipation, nausea, asthenia, headache, dyspepsia, abdominal pain, and pain. The incidence of dizziness, constipation, nausea, and asthenia was dose-related. The most common AEs leading to discontinuations that occurred more frequently on ranolazine than on placebo were dizziness and nausea. SAEs were sporadic; most of the cases were single occurrences and there was no apparent pattern or dose relationship. In the long-term open-label studies, increased duration of exposure to ranolazine did not alter the AE profile.

AEs occurred in a dose-dependent pattern, usually soon after the initiation of treatment, and reversed promptly with a reduction of dose or upon discontinuation of treatment. AEs, therefore, should be manageable with appropriate dose titration. Patients or subjects who achieved ranolazine plasma concentrations above the therapeutic range were likely to experience AEs, including nausea or dizziness, and at very high levels, visual disturbances, that can be recognized by the patient and provide a signal to seek medical attention.

Ranolazine had no discernable effects on BP or HR at the recommended starting dose of 500 mg b.i.d. At the upper end of its dose range, ranolazine caused only minimal changes in BP and HR, in contrast with currently available anti-anginal therapies. Ranolazine produced a mean decrease in HR of less than 2 bpm and a mean decrease in SBP of less than 3 mmHg in Phase 3 trials with a dose of 1000 mg b.i.d. BP and HR changes were similar in angina patients with and without diabetes, CHF, reactive airway disease, patients with low BP, low HR, or prolonged AV conduction.

While mean changes in BP were small, postural hypotension has been observed in a very limited number of subjects/patients treated with ranolazine, particularly at higher doses, and especially at doses beyond the recommended range (i.e., $\geq$ 1500 mg b.i.d.). The infrequent episodes of syncope that occurred during ranolazine studies are likely attributable to postural hypotension and orthostasis. The phenomenon of orthostasis related to postural hypotension is more apparent in healthy volunteers than in patients. There is no evidence that any of the cases of syncope observed during these trials were associated with TdP. In addition, during clinical trials of excessive ranolazine concentrations, continuous ECG monitoring of volunteers who experienced syncope showed no evidence of arrhythmia.

Nonclinical evidence of α_1-adrenergic and β-adrenergic blockade offers a possible mechanism for orthostasis caused by ranolazine. The risk of orthostasis is clinically manageable by appropriate dosing and titration, and where appropriate, BP monitoring.

Ranolazine does not cause deleterious changes in laboratory parameters. In angina patients and volunteers there were small mean increases in creatinine (0.1 mg/dL), which appear to be due to a modest inhibition of tubular secretion with no decline in glomerular filtration. Small mean decreases in hematocrit (1%) were seen with no evidence of red cell destruction or gastrointestinal blood loss. Diabetic angina patients had a mean decrease (0.5–0.9% units from baseline) in HbA_{1c} after 12 weeks of treatment with ranolazine SR. Hypoglycemia attributed to ranolazine was not observed.

5.2 Safety Database

The ranolazine development program included a total of 81 studies, 65 of which included doses ≥ 120 mg ranolazine IR. While several different formulations of ranolazine were used in the clinical development program, including IR, SR, and IV, they all resulted in systemic exposure to the identical ranolazine moiety. No important differences were observed in safety between healthy volunteers and patients, nor among the multiple formulations included in the overall safety database.

In total, 3021 healthy volunteers or patients enrolled in clinical trials, 2783 of whom have been exposed to any formulation of ranolazine. Patient exposures to ranolazine are shown in Table 5-1. Ranolazine IR 400 mg t.i.d., the highest IR dose given to patients, was associated with anti-anginal efficacy, and resulted in average plasma concentrations comparable to ranolazine SR 500 mg b.i.d. and peak concentrations comparable to ranolazine SR 750 mg b.i.d and is summarized in addition to the total IR exposure. The number of subjects/patients exposed to ranolazine SR was 1460 and the total exposed to ranolazine SR or ranolazine IR 400 mg t.i.d. was 1978.

Table 5-1 Subjects/Patients Enrolled and Exposed to Ranolazine in Clinical Trials

	Number of Subjects/Patients
Total enrolled	3021
Total exposed to ranolazine	2783
Total exposed to ranolazine IR	1299
Total exposed to ranolazine IR 400 mg t.i.d.	518
Total exposed to ranolazine IR 400 mg t.i.d. or ranolazine SR	1978
Total exposed to ranolazine SR	1460

The total exposure to all formulations of ranolazine is 1714 subject/patient years. The mean duration of exposure to any ranolazine formulation is 225 days. Among all subjects and patients:

- 914 subjects/patients have been exposed to ranolazine for > 6 months;
- 695 subjects/patients have been exposed to ranolazine > 12 months;
- 293 subjects/patients have been exposed to ranolazine for > 24 months.

The overall mean duration of exposure to ranolazine SR, the formulation for commercial use, is 321 days, providing a total of 1282 subject/patient years of exposure (healthy volunteers and patients).

Among patients with angina in Phase 3 controlled angina studies and their long-term, open-label follow-on studies, the mean duration of exposure to ranolazine SR is 495 days:

- 867 patients have been exposed to ranolazine SR for ≥ 28 days;
- 681 patients have been exposed to ranolazine SR for > 6 months;
- 502 patients have been exposed to ranolazine SR for > 12 months;
- 259 patients have been exposed to ranolazine SR for > 24 months.

Of the 867 patients exposed to ranolazine SR for ≥ 28 days, 526 patients were exposed during the controlled angina studies (MARISA and CARISA) and an additional 327 patients who had less than 28 days of exposure in MARISA or had

received placebo during CARISA subsequently received ranolazine SR in the open label follow-on studies. Doses in the follow-on studies ranged from 500 mg b.i.d. to 1000 mg b.i.d.

5.3 Adverse Events, Serious Adverse Events, and Discontinuations

The AE profile of ranolazine is well described and AEs are generally mild to moderate. Discontinuations due to AEs were infrequent and SAEs were uncommon. The frequency of AEs is dose-dependent. Common AEs generally occur early after initiation of treatment and reverse promptly with reduction of dose or discontinuation of therapy. The AE profile does not change with increasing duration of exposure.

Adverse Events

Table 5-2 summarizes the incidence of AEs in the Phase 3 controlled angina studies MARISA and CARISA. The most frequently reported AEs over the dose range 500 mg b.i.d. to 1000 mg b.i.d. were dizziness, constipation, nausea, angina pectoris, asthenia, headache, dyspepsia, abdominal pain, and pain, although angina was reported at a slightly higher frequency in patients treated with placebo (Table 5-2). The events that were most clearly dose-dependent were dizziness, constipation, nausea, and asthenia. The increase in the incidence of AEs with the 1500 mg dose is disproportionately larger than the increase in anti-anginal efficacy. Consequently, doses of ranolazine greater than 1000 mg b.i.d. are not proposed.

Table 5-2 Treatment-Emergent Adverse Events ≥ 2%: MARISA and CARISA

Number (%) of Angina Patients							
	MARISA b.i.d. dosing for 1 week each treatment				CARISA b.i.d. dosing for 12 weeks		
	Placebo N = 179	500 mg N = 181	1000 mg N = 180	1500 mg† N = 187	Placebo N = 269	750 mg N = 279	1000 mg N = 275
Any AE	26 (14.5)	28 (15.5)	37 (20.6)	62 (33.2)	71 (26.4)	87 (31.2)	90 (32.7)
Body as a Whole	10 (5.6)	6 (3.3)	9 (5.0)	25 (13.4)	28 (10.4)	22 (7.9)	29 (10.5)
Abdominal pain	1 (0.6)	1 (0.6)	2 (1.1)	1 (0.5)	2 (0.7)	2 (0.7)	7 (2.5)
Asthenia	3 (1.7)	0	3 (1.7)	11 (5.9)	6 (2.2)	5 (1.8)	13 (4.7)
Headache	4 (2.2)	1 (0.6)	2 (1.1)	5 (2.7)	4 (1.5)	7 (2.5)	6 (2.2)
Pain	0	2 (1.1)	4 (2.2)	1 (0.5)	3 (1.1)	2 (0.7)	1 (0.4)
Cardiovascular	16 (8.9)	9 (5.0)	11 (6.1)	20 (10.7)	29 (10.8)	35 (12.5)	28 (10.2)
Angina pectoris	8 (4.5)	8 (4.4)	2 (1.1)	6 (3.2)	12 (4.5)	11 (3.9)	8 (2.9)
Palpitation	3 (1.8)	0	1 (0.6)	4 (2.1)	2 (0.7)	2 (0.7)	1 (0.4)
Digestive System	3 (1.7)	2 (1.1)	8 (4.4)	25 (13.4)	18 (6.7)	36 (12.9)	41 (14.9)
Constipation	0	0	3 (1.7)	8 (4.3)	2 (0.7)	18 (6.5)	20 (7.3)
Dyspepsia	0	1 (0.6)	1 (0.6)	2 (1.1)	4 (1.5)	7 (2.5)	5 (1.8)
Nausea	0	1 (0.6)	2 (1.1)	16 (8.6)	2 (0.7)	9 (3.2)	14 (5.1)
Vomiting	0	0	1 (0.6)	4 (2.1)	1 (0.4)	2 (0.7)	4 (1.5)
Nervous System	4 (2.2)	3 (1.7)	15 (8.3)	29 (15.5)	9 (3.3)	17 (6.1)	28 (10.2)
Dizziness	1 (0.6)	2 (1.1)	9 (5.0)	22 (11.8)	5 (1.9)	10 (3.6)	19 (6.9)
Urogenital System	0	1 (0.6)	2 (1.1)	8 (4.3)	1 (0.4)	2 (0.7)	11 (4.0)
Urine abnormality	0	0	1 (0.6)	4 (2.1)	0	0	3 (1.1)

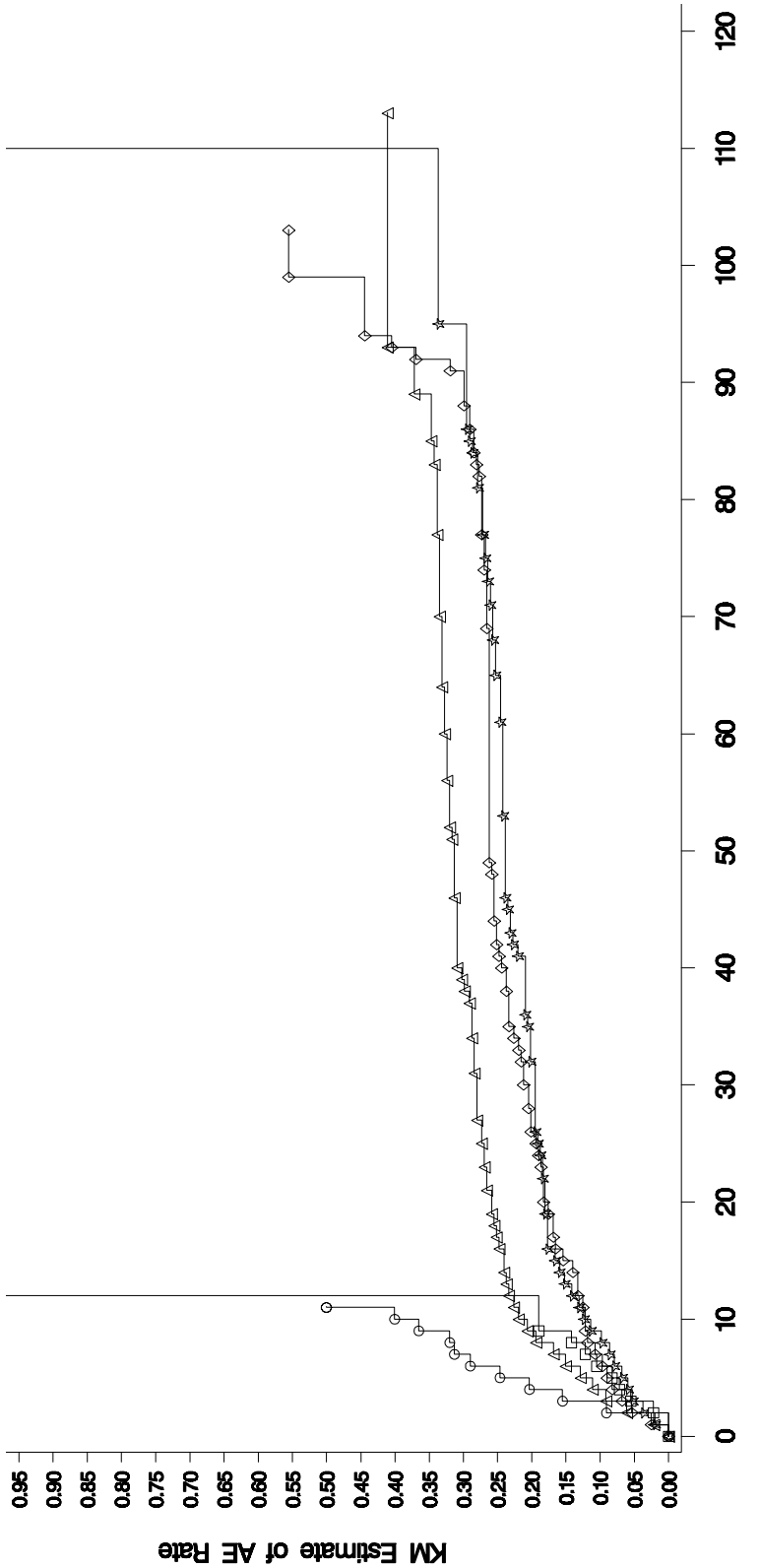
† 1500 mg b.i.d. is not proposed for clinical use.

Few AEs were considered to be severe during either ranolazine or placebo treatment. Severe AEs were somewhat more frequent in patients treated with ranolazine (6.1%, 46/749) than placebo (3.1%, 14/455).

AEs tended to occur early in treatment, particularly at the highest dose (Figure 5-1).

The nature and frequency of the most common AEs did not change with increasing duration of exposure. There was no clinically meaningful difference in the overall AE profile among patients exposed to ranolazine in the long-term open-label studies compared to patients in the controlled angina studies.

Figure 5-1 Kaplan-Meier Estimate of Adverse Event Rate Over Time by Treatment Category



Rates of 1.0 at the ends of the placebo and 500 mg b.i.d. curves are the result of an event occurring with only one patient still at risk.

Myocardial Infarction

The overall frequency of MI is not inconsistent with that anticipated in this population of patients with severe CAD. During the Phase 2/3 controlled angina trials, MIs occurred in 10 patients on ranolazine (0.6%, 10/1737) and two on placebo (0.2%, 2/1266). However, only 7 patients (0.4%, 7/1737) assigned to active treatment were actually taking ranolazine at the time the MI occurred. The Kaplan-Meier estimate of the annual rate of MI at 12 months among patients treated with ranolazine in MARISA, CARISA, and their long-term follow-on studies (CVT 3032 and CVT 3034) is 2.8%, a rate that is consistent with reports in the literature.[5.] Among patients in the Phase 2/3 controlled angina trials and their long-term follow-on studies, the incidence of MI per patient year of treatment was 2.4% ranolazine and 1.7% on placebo (based on total follow-up time of 1193 patient years on ranolazine treatment and 114 patient years on placebo). The incidence per patient year of the combined endpoint of MI or death was 4.1% on ranolazine and 4.3% on placebo.

In general, the frequency of independent cardiovascular risk factors (including history of previous MI, hypertension, prior revascularization procedures, and diabetes) and concomitant medication use was higher among the patients with MI reported from the Phase 2/3 controlled angina studies, compared with the overall Phase 2/3 population.

Serious Adverse Events

Table 5-3 summarizes all treatment-emergent SAEs. Angina was the most commonly reported SAE and occurred with similar frequency on ranolazine (1.7%) and placebo (1.8%). No other SAE was reported at a frequency greater than 1%. Although SAEs occurred more frequently in the Phase 2/3 SR controlled angina studies among ranolazine patients compared with placebo, most of the cases were single incidences and there was no apparent pattern or dose relationship.

Dizziness was the most frequent SAE considered by the investigators to be possibly/probably related to study drug.

Table 5-3 Summary of Serious Adverse Events in Phase 2/3 Ranolazine SR Controlled Angina Studies

	Number (%) of Subjects/Patients				
	Placebo (N = 455)	**500 mg (N = 181)**	**750 mg (N = 279)**	**1000 mg (N = 459)**	**1500 mg† (N = 187)**
Any SAE	16 (3.5)	3 (1.7)	20 (7.2)	21 (4.6)	7 (3.7)
Body as a Whole	2 (0.4)	0	2 (0.7)	3 (0.7)	3 (1.6)
Accidental injury	0	0	0	0	1 (0.5)
Allergic reaction	0	0	0	0	1 (0.5)
Asthenia	0	0	0	1 (0.2)	0
Carcinoma	0	0	1 (0.4)	0	0
Death	1 (0.2)	0	0	0	0
Headache	0	0	0	2 (0.4)	1 (0.5)
Sudden death	1 (0.2)	0	1 (0.4)	1 (0.2)	0
Cardiovascular System	11 (2.4)	3 (1.7)	15 (5.4)	15 (3.3)	4 (2.1)
Angina pectoris	8 (1.8)	1 (0.6)	7 (2.5)	3 (0.7)	2 (1.1)
Atrial fibrillation	1 (0.2)	0	0	0	0
Bradycardia	0	0	0	1 (0.2)	0
Cerebral ischemia	0	0	0	1 (0.2)	0
Cerebrovascular accident	0	0	0	1 (0.2)	0
Coronary artery disorder	2 (0.4)	1 (0.6)	2 (0.7)	1 (0.2)	0
Heart arrest	0	0	0	1 (0.2)	0
Hypotension	0	0	0	1 (0.2)	0
Myocardial infarct	0	0	4 (1.4)	2 (0.4)	0
Myocardial ischemia	0	0	2 (0.7)	0	0
Postural hypotension	0	0	0	0	1 (0.5)
Shock	0	0	0	1 (0.2)	0
Sinus bradycardia	0	0	0	1 (0.2)	0
Syncope	0	0	0	3 (0.7)	1 (0.5)
Ventricular fibrillation	0	1 (0.6)	0	0	0

Table 5-3 Summary of Serious Adverse Events in Phase 2/3 Ranolazine SR Controlled Angina Studies (Cont'd)

	Number (%) of Subjects/Patients				
	Placebo (N = 455)	500 mg (N = 181)	750 mg (N = 279)	1000 mg (N = 459)	1500 mg† (N = 187)
Digestive System	0	0	1 (0.4)	2 (0.4)	0
Cholecystitis	0	0	0	1 (0.2)	0
Colitis	0	0	1 (0.4)	0	0
Nausea	0	0	0	1 (0.2)	0
Metabolic and Nutritional Disorders	0	0	1 (0.4)	0	0
Dehydration	0	0	1 (0.4)	0	0
Musculoskeletal System	1 (0.2)	0	0	0	0
Arthritis	1 (0.2)	0	0	0	0
Nervous System	0	0	1 (0.4)	4 (0.9)	1 (0.5)
Dizziness	0	0	0	3 (0.7)	1 (0.5)
Meningitis	0	0	1 (0.4)	0	0
Vertigo	0	0	0	1 (0.2)	1 (0.5)
Respiratory System	2 (0.4)	0	0	1 (0.2)	0
Bronchitis	1 (0.2)	0	0	0	0
Pneumonia	1 (0.2)	0	0	1 (0.2)	0
Skin and Appendages	0	0	0	1 (0.2)	0
Sweating	0	0	0	1 (0.2)	0
Special Senses	0	0	0	1 (0.2)	0
Tinnitus	0	0	0	1 (0.2)	0

† 1500 mg b.i.d. is not proposed for clinical use.

Discontinuations

Of the 1025 patients treated in Phase 2/3 SR controlled angina studies, 8.3% (62/749) of patients treated with ranolazine and 4.0% (18/455) of patients treated with placebo discontinued from the studies because of AEs. The most common AEs leading to discontinuation that occurred more frequently on ranolazine than on placebo were dizziness and nausea (Table 5-4). The majority of these events

were not considered to be treatment-related. The frequency of discontinuation due to angina was the same for both ranolazine and placebo.

Table 5-4 Incidence of Most Common Treatment-Emergent Adverse Events Resulting in Discontinuation Reported for ≥ 1% of Subjects/Patients in Phase 2/3 Ranolazine SR Controlled Angina Studies Population

Category	Number (%) of Subjects/Patients	
	Total Ranolazine (N = 749)	Placebo (N = 455)
Mean Duration of Exposure (Days)	66	53
Total Subjects/Patients Who Discontinued Due to AEs	62 (8.3)	18 (4.0)
Cardiovascular System		
Angina Pectoris	10 (1.3)	6 (1.3)
Digestive System		
Nausea	10 (1.3)	0
Nervous System		
Dizziness	13 (1.7)	1 (0.2)

5.4 Intolerability at High Doses

Patients/subjects who achieved ranolazine plasma concentrations above the therapeutic range were likely to experience AEs that can be recognized by the patient and provide a signal to seek medical attention.

There is clinical evidence that ranolazine, particularly at higher doses and plasma concentrations, caused symptoms including nausea, vomiting, dizziness, vertigo, abnormal vision, confusion, and in some cases postural hypotension and syncope without evidence of arrhythmia.

Data from subjects/patients who achieved ranolazine plasma concentrations > 8000 ng/mL were examined for two reasons. First, in subjects treated with the highest proposed dose of ranolazine (1000 mg b.i.d.) along with ketoconazole 200 mg b.i.d., the mean ranolazine level achieved was 8000 ng/mL and the

average increase in QTc with ranolazine was 20 msec during this condition of maximum inhibition of CYP3A4. Second, a population QTc model (see Section 6.3.3) also predicts that a ranolazine plasma concentration of 8300 ng/mL would result in an average QTc increase of 20 msec. This has been suggested as a value above which QTc increases may cause greater concern.[45]

Study CVT 3111 provided valuable information on AEs at high concentrations. This study was conducted to assess the effects of ranolazine on the QTc interval at target plasma ranolazine concentrations of 4000, 10,000, and 15,000 ng/mL, respectively, using an iv infusion of ranolazine administered over 72 hours to healthy volunteers. These target concentrations represent, respectively, plasma concentrations at the upper end of the therapeutic range, higher than therapeutic concentrations, and much higher than therapeutic concentrations. Table 5-5 shows the increasing incidence of AEs including nausea, dizziness, vertigo, postural hypotension, syncope, paresthesia, diplopia, and somnolence with increasing dose. Because of these AEs, it was not possible to achieve the highest targeted dose of 15,000 ng/mL. During iv infusion targeting this dose, all subjects reached concentrations of approximately 8000 ng/mL or higher but 6 of 7 discontinued from the study because of intolerable AEs (Table 5-6). The one subject who completed the infusion had symptoms of amblyopia and paresthesia but elected to continue in the study.

Table 5-5 Incidence of Selected Adverse Events in Study CVT 3111

	Target Ranolazine Concentration (ng/mL)			
Adverse Event	2000 (N = 31)	4000 (N = 22)	10,000 (N = 22)	15,000 (N = 7)
Nausea	2 (6.5%)	6 (27.3%)	10 (45.5%)	2 (28.6%)
Dizziness	2 (6.5%)	9 (41%)	14 (63.6%)	5 (71.4%)
Postural Hypotension	3 (9.7%)	3 (13.6%)	5 (22.7%)	2 (28.6%)
Syncope	1 (3.2%)	0	2 (9%)	1 (14.3%)
Paresthesia	1 (3.2%)	1 (4.5%)	1 (4.5%)	1 (14.3%)
Diplopia	0	0	2 (9%)	2 (28.6%)
Somnolence	0	0	2 (9%)	2 (28.6%)

Table 5-6 Adverse Events in Study CVT 3111 (Target Dose 15,000 ng/mL)

Subject Number	Time of Concentration > 8000 ng/mL (h)	Stop Time of Infusion (h)	Concentration at End of Infusion (mg/mL)	AEs at Concentrations > 8000 ng/mL
3403	24	24	8220	Syncope
3410	36–72	72	8740	Amblyopia, paresthesia
3411	24–28	26	10,700	Nausea, tinnitus, headache, incoordination, hypersthesia
3412	24–32	32	7950	Amblyopia, dizziness, somnolence, diplopia
3415	20–26	25	9810	Postural hypotension, diplopia
3418	20–26	25	8880	Dizziness, nausea, vomiting
3424	24–28	28	8370	Dizziness, vomiting

A similar pattern was seen in healthy subjects enrolled in Study CVT 301-10, a study to examine the pharmacokinetics of ranolazine during essentially complete inhibition of cytochrome CYP3A4 via concomitant administration of ketoconazole. When ranolazine 1000 mg b.i.d. was co-administered with ketoconazole 200 mg b.i.d., a total of 4 of 12 subjects developed ranolazine concentration exceeding 8000 ng/mL. All 4 subjects reported AEs as presented in Table 5-7.

Table 5-7 Adverse Events at Ranolazine Concentrations Exceeding 8000 ng/mL in Study CVT 301-10

Subject	Concentration (ng/mL)	Adverse Events and Severity
2503	10,700	Moderate postural hypotension, mild nausea, and abnormal vision
2519	9530	Mild postural hypotension, nausea, and dizziness
2609	9600	Mild dizziness and somnolence (groggy)
2620	8510	Moderate dizziness

Among the 933 patients who received ranolazine 500 mg b.i.d., 750 mg b.i.d., or 1000 mg b.i.d. in the Phase 3 trials MARISA, CARISA, and their respective long-term follow-on Studies CVT 3032 and CVT3034, 10 (1.1%) had plasma concentrations exceeding 8000 ng/mL. Nine of ten were receiving doses of 1000 mg b.i.d; one was receiving 750 mg b.i.d. AE data from the same studies

indicate that more than half of these patients developed adverse effects typical of high concentrations of ranolazine including nausea, vomiting, and dizziness. Therefore, < 1% of patients would be expected to develop ranolazine concentrations > 8000 ng/mL and be unaware of symptoms. Furthermore, with appropriate initial dosing and titration, many patients will be treated with doses less than 1000 mg b.i.d. Data from the subjects in Study CVT 301-10 indicate that with maximal CYP3A4 inhibition, the mean ranolazine plasma concentration on 1000 mg b.i.d. was approximately 8000 ng/mL. In CVT 301-10 as well as in Study CVT 3111, higher concentrations were not well tolerated because of symptoms similar to those seen in patients with high concentrations.

5.5 Vital Signs

Ranolazine had no discernable effects on BP or HR at the recommended starting dose of 500 mg b.i.d. Minimal changes in mean HR (< 2 bpm) and systolic BP (< 3 mmHg) were observed in patients with chronic angina treated with ranolazine 1000 mg b.i.d. in controlled studies. At the higher dose of 1500 mg b.i.d., these effects were more prominent (see Table 4-11 in Section 4.3).

5.5.1 Postural Hypotension and Syncope

While mean changes in BP were small, postural hypotension has been observed in a very limited number of subjects/patients treated with ranolazine, particularly at higher doses, and especially at doses beyond the recommended range (i.e., ≥ 1500 mg b.i.d.).

As discussed in Section 5.4, postural hypotension and syncope may be preceded or accompanied by other symptoms such as nausea and dizziness. Nonclinical data showing weak α_1-adrenergic blockade and β-adrenergic blockade provide a possible mechanism for orthostatic changes in BP or HR that could have caused these events. The incidence of postural hypotension and/or syncope associated with ranolazine is similar to that reported for drugs with known α_1- and β-adrenergic blocking activities in their respective US package inserts (atenolol: postural hypotension 2%; carvedilol: postural hypotension 2%, syncope 8%;

prazosin: syncope 1%; doxazosin: postural hypotension 0.3%; terazosin: postural hypotension 0.5–0.6%).

5.5.1.1 Postural Hypotension and Syncope in Healthy Subjects

The phenomenon of postural hypotension on ranolazine treatment is more apparent in healthy volunteers than in patients. The two studies that best characterize this phenomenon are Studies RAN0201 and CVT 3111. RAN0201 was a placebo-controlled, crossover design study in which subjects received ranolazine 1500 mg b.i.d. and 2000 mg b.i.d., the highest dose of oral ranolazine ever administered. These doses resulted in significant orthostatic changes in BP compared to placebo 4–6 hours post-dosing. The mean plasma ranolazine concentrations at the same time points ranged from 4925 to 4633 ng/mL on 1500 mg b.i.d. and from 7223 to 6328 ng/mL on 2000 mg b.i.d. Some subjects became too symptomatic on standing to complete BP measurements [1500 mg (N = 3) and 2000 mg (N = 2)], usually at 2–6 hours post-dose.

CVT 3111 was a study of high doses of intravenous ranolazine in healthy subjects described in Section 5.4. Subjects in this study developed postural hypotension at a frequency that increased with increasing concentrations and there were four episodes of syncope (Table 5-8); two of the syncopal events occurred when the subjects stood for erect vital signs. None of the ECGs for these subjects showed signs of cardiac arrhythmia with continuous monitoring. The syncopal events were preceded by other AEs including dizziness and nausea. These findings are consistent with those in Study RAN0201; i.e., that ranolazine, particularly in high concentrations, can result in orthostasis and syncope. This may be accompanied by other symptoms that may provide a clinical signal of potential risk for orthostatic or postural hypotension and may warrant downward titration of the ranolazine dose. Table 5-8 gives details of the eleven cases of syncope in healthy subjects.

Table 5-8 Listing of Healthy Subjects With Syncope

Study / Pt. No.	Age / Sex	Dose / Formulation	Event Date	Days on Ranolazine	QTc[a] (change from baseline) msec / Date	Medications	Narrative
CVT 301-13 / 2612353	33 / M	RAN 1000 mg b.i.d. / SR	16SEP01	12	413 (6) / 16SEP01	None	While standing to urinate, felt lightheaded, and fainted while being assisted.
CVT 3015 / 2223043	74 / M	RAN 1500 mg b.i.d. / SR	16MAY00	12	428 (25) / 16MAY00	None	Syncope lasting for 2 minutes, dizziness persisted for the next 25 minutes.
CVT 3111 / 6053403	37 / M	15,000 ug/mL[b] / iv	16JUN01	11	408 (-9) / 16JUN01	None	Syncope while returning from the toilet in a wheelchair.
CVT 3111 / 6053424	28 / M	10,000 ug/mL[b] / iv	23JAN01	5	406 (23) / 23JAN01	None	Syncope upon standing.
CVT 3111 / 6053426	42 / F	2000 ug/mL[b] / iv	14DEC00	1	449 (30) / 14DEC00	None	Syncope upon standing for the measurement of her erect vital signs.
CVT 3111 / 6053432	34 / F	10,000 ug/mL[b] / iv	30MAR01	7	483 (69) / 30MAR01	None	In the lavatory, fell and hit her head, was not responsive but was moving all four limbs (not in a manner suggesting seizure). Regained consciousness. No significant head injury.
RAN0102 / 607DS004	23 / M	RAN 342 mg single dose / IR	26AUG93	1	414 (0) / 26AUG93	None	Syncope during the measurement of his erect vital signs.
RAN0112 / 607SA023	29 / M	RAN 2000 mg q.d. / SR	03DEC93	2	391 (5) / 03DEC93	None	Reported to have fainted.

[a] Bazett correction; Fridericia not available.

[b] Target concentration.

Table 5-8 Listing of Healthy Subjects With Syncope (Cont'd)

Study / Pt. No.	Age / Sex	Dose / Formulation	Event Date	Days on Ranolazine	QTc[a] (change from baseline) msec / Date	Medications	Narrative
RAN063 / 607RM020	20 / M	RAN 320 mg single dose / IR	27MAY91	1	399 (-7) / 27MAY91	None	Syncope during the measurement of his erect vital signs.
RAN068 / 607RK005	22 / M	RAN 240 mg t.i.d. / IR	11NOV92	7	393 (12) / 11NOV92	Diltiazem	Syncope during the measurement of his erect BP.
RAN090 / 607LD010	19 / M	RAN 200 mg single dose / IR	02NOV92	1	N/A / 02NOV92	None	Syncope during performance of a venipuncture.

[a] Bazett correction; Fridericia not available.

[b] Target concentration.

5.5.1.2 Postural Hypotension and Syncope in Patients

In Phase 2/3 controlled and uncontrolled trials in patients, 38 patients had reports of syncope while on ranolazine (either the IR or SR formulation). More than half of the patients with syncope were over the age of 65 years (22/38) and 82% (31/38) were taking one or more vasoactive medication, factors which increase the risk of syncope.

In the pivotal trials MARISA and CARISA, eight cases of syncope were reported. All were on the highest dose of ranolazine used in each respective study. In MARISA, 3 patients were taking 1500 mg b.i.d.; and in CARISA, 5 patients were taking 1000 mg b.i.d., 4 of whom were on concomitant diltiazem, a drug known to increase the plasma concentration of ranolazine. In the 4 patients in whom plasma concentrations were available, the mean plasma concentration in the patients with syncope was 5913 ng/mL. The syncope cases occurred relatively early in treatment (see Figure 5-2). There was no syncope on 500 mg or 750 mg b.i.d. in these trials suggesting that some cases of syncope may be avoided by proper dose initiation and titration, as is standard practice with anti-anginal medications.

In the long-term open-label trials, the relationship to dose and plasma concentration was less clear, in part because syncope is not uncommon in this population. Its occurrence is influenced by a variety of other factors including sympathetic tone, activity, heat, diet, and the use of concomitant vasoactive medications. The incidence per patient year of syncope in controlled and uncontrolled trials in angina patients on ranolazine was 2.1% and 1.0% on placebo. The syncope rate on ranolazine is consistent with the orthostatic responses seen in the healthy volunteers and the rates are consistent with those of other α_1- and β-blocking agents (see Section 5.5.1). Table 5-9 gives details of the cases of syncope in patients.

Figure 5-2 Kaplan-Meier Estimate of Syncope Rate by Treatment Category, Phase 2/3 Controlled Studies

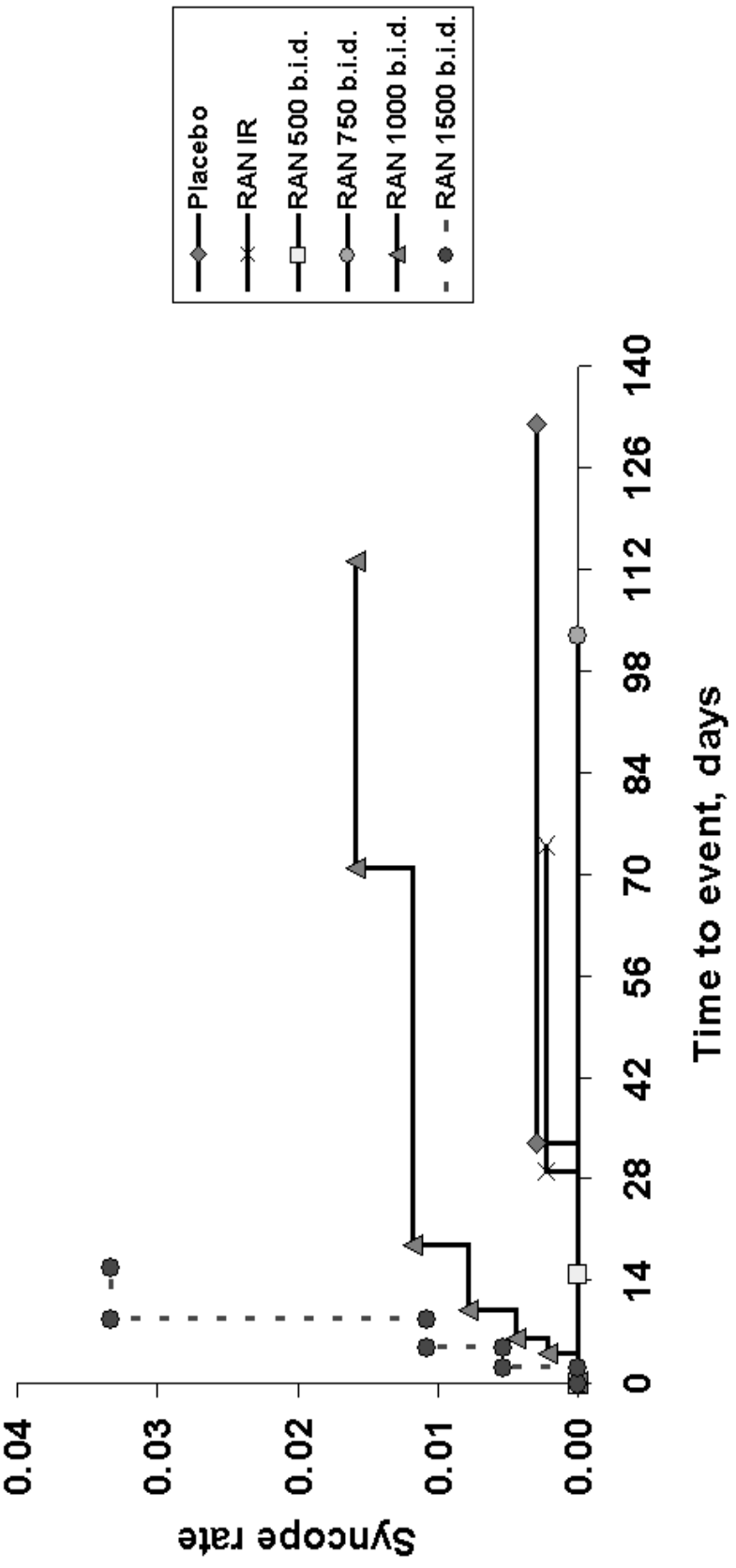


Table 5-9 Listing of Patients With Syncope

Study / Pt. No.	Age / Sex	Dose / Formulation	Event Date	Days on Ranolazine	QTc[a] (change from baseline) msec / Date	Relevant Medications	Narrative
Controlled Trials							
CVT 3031 / 1331024	80 / F	RAN 1500 mg b.i.d. / SR	24JUL98	2	N/A	None	Syncopal episode; on same day had hematuria and nausea.
CVT 3031 / 1771465	76 / F	RAN 1500 mg b.i.d. / SR	29MAR99	20	N/A	None	History of syncope associated with the use of nitrates or diltiazem; experienced syncope. Admitted 6 days later with CHF, fever, urinary tract infection, bronchitis; admission QTc 397 msec.
CVT 3031 / 1771466	61 / M	RAN 1500 mg b.i.d. / SR	20APR99	24	396 (-14) / 22APR99	Quinapril GTN	Syncopal episode. Spontaneous recovery.
CVT 3033 / 1747012	65 / M	RAN 1000 mg b.i.d. / SR	26FEB00	4	N/A	Enalapril GTN Diltiazem	Lowered his head down to take a nap; later found with head back, unresponsive. Awoke spontaneously. In emergency ward normal ECG including QT.
CVT 3033 / 1777406	77 / M	RAN 1000 mg b.i.d. / SR	19MAR01	19	427 (16) / 14MAR01	Indapamide Prazosin Diltiazem	Patient reported loss of consciousness twice for approximately 30 sec each while standing to void.
CVT 3033 / 5307169	74 / M	RAN 1000 mg b.i.d. / SR	30JUN00	10	N/A	GTN Enalapril Diltiazem	Shortly after defecation, fainted and fell. Regained consciousness spontaneously. Two ECGs post-event were normal.

[a] Fridericia unless noted.

[b] Bazett correction; Fridericia not available.

Table 5-9 Listing of Patients With Syncope (Cont'd)

Study / Pt. No.	Age / Sex	Dose / Formulation	Event Date	Days on Ranolazine	QTc[a] (change from baseline) msec / Date	Relevant Medications	Narrative
Controlled Trials							
CVT 3033 / 5497219	65 / M	RAN 1000 mg b.i.d. / SR	19APR00	6	479 (10) / 28APR00	GTN Quinapril Diltiazem	Following 2 puffs of GTN lost consciousness for 5–10 min.
CVT 3033 / 5628071	86 / F	RAN 1000 mg b.i.d. / SR	27APR00	71	390 (-25) / 01MAY00	Enalapril Atenolol Hydro-chlorothiazide Cordil	Hospitalized for syncope with mild dehydration and vomiting. Reported two episodes of vomiting prior to the syncope.
RAN054 / 6854106	62 / M	RAN 120 mg t.i.d. / SR	01SEP89	57	367[b] (-55) / 01SEP89	None	Reported to experience a vasovagal attack.

[a] Fridericia unless noted.

[b] Bazett correction; Fridericia not available.

Table 5-9 Listing of Patients With Syncope (Cont'd)

Study / Pt. No.	Age / Sex	Dose / Formulation	Event Date	Days on Ranolazine	QTc[a] (change from baseline) msec / Date	Relevant Medications	Narrative
Uncontrolled Trials							
CVT 3032 / 1491193	63 / M	RAN 750 mg b.i.d. / SR	28OCT98	107	428 (22) / 02NOV98	Furosemide Metoprolol	Several episodes of reported syncope upon standing, bending; two associated with documented atrial fibrillation and flutter. Seven months after the last reported episode died suddenly while walking on the beach. Last QTcF prior to death (1 month prior) was 374 msec.
		RAN 1000 mg b.i.d. / SR	08NOV98	118	500 (94) / 09NOV98		
		RAN 1000 mg b.i.d. / SR	10NOV98	120	500 (94) / 09NOV98		
CVT 3032 / 1531287	68 / M	RAN 1000 mg b.i.d. / SR	22FEB02	1040	451 (1) / 12NOV01	Doxazosin Amlodipine Hydro-chlorothiazide GTN Metoprolol	Reported a single episode of increased angina accompanied by blurred vision and vagal response.
CVT 3032 / 1552002	66 / M	RAN 750 mg b.i.d. / SR	10MAY99	188	425 (-19) / 29MAY99	Lisinopril Furosemide	Experienced a near-syncopal episode during removal of a toenail.

[a] Fridericia unless noted.

[b] Bazett correction; Fridericia not available.

Table 5-9 Listing of Patients With Syncope (Cont'd)

Study / Pt. No.	Age / Sex	Dose / Formulation	Event Date	Days on Ranolazine	QTc[a] (change from baseline) msec / Date	Relevant Medications	Narrative
Uncontrolled Trials							
CVT 3032 / 1671273	48 / M	RAN 1000 mg b.i.d. / SR	16APR02	1162	417 (-32) / 11MAR02	Doxazosin Metoprolol	Experienced three syncopal episodes 8 days after falling out of a boat. Reported difficulty visually focusing after the fall.
CVT 3032 / 5121368	53 / M	RAN 1000 mg b.i.d. / SR	06JUN00	421	395 (-7) / 06JUN00	GTN	Experienced syncope following an injection.
CVT 3034 / 1257207	60 / F	RAN 1000 mg b.i.d. / SR	18MAR01	130	413 (-12) / 22MAR01	GTN Hydro-chlorothiazide Diltiazem Losartan	Experienced intermittent severe dizziness and a single episode of blacking out for 1 minute. Upon hospitalization, Holter monitoring revealed A-V block (Mobitz II) leading to a dose reduction in diltiazem.
CVT 3034 / 1418124	67 / M	RAN 1000 mg b.i.d. / SR	22JAN02	442	437 (4) / 09JAN02	Lisinopril Atenolol	A patient with cholestasis probably due to cholangio carcinoma experienced a syncopal episode and was admitted for antibiotics and biliary drainage. One week after discharge, died from biliary sepsis.

[a] Fridericia unless noted.

[b] Bazett correction; Fridericia not available.

Table 5-9 Listing of Patients With Syncope (Cont'd)

Study / Pt. No.	Age / Sex	Dose / Formulation	Event Date	Days on Ranolazine	QTc[a] (change from baseline) msec / Date	Relevant Medications	Narrative
Uncontrolled Trials							
CVT 3034 / 1457037	75 / F	RAN 1000 mg b.i.d. / SR	17APR02	337	455 (15) / 16APR02	Atenolol Diltiazem GTN Furosemide	Hospitalized after taking 3 GTN tablets for chest pain. On admission, had a cardiopulmonary arrest. Successfully resuscitated; 7 days later, a pacemaker was implanted.
CVT 3034 / 1777326	50 / F	RAN 1000 mg b.i.d. / SR	14FEB02	352	409 (7) / 25FEB02	Diltiazem GTN Ramipril	Experienced mild vasovagal response to laser eye surgery without loss of consciousness.
CVT 3034 / 1818445	66 / M	RAN 1000 mg b.i.d. / SR	20APR01	178	480 (-22) / 24APR01	Amiloride/ Hydro-chlorothiazide Furosemide GTN Atenolol	Experienced two syncopal episodes while hospitalized for unstable angina. Two weeks later, patient died while hospitalized again for acute MI complicated by pulmonary edema, pericarditis, and finally wide complex tachycardia.
CVT 3034 / 1887011	78 / M	RAN 750 mg b.i.d. / SR	19MAY01	285	411 (14) / 23APR01	GTN Diltiazem	Experienced syncope. Holter and echcardiogram were non-diagnostic.

[a] Fridericia unless noted.

[b] Bazett correction; Fridericia not available.

Table 5-9 Listing of Patients With Syncope (Cont'd)

Study / Pt. No.	Age / Sex	Dose / Formulation	Event Date	Days on Ranolazine	QTc[a] (change from baseline) msec / Date	Relevant Medications	Narrative
Uncontrolled Trials							
CVT 3034 / 4939516	69 / M	RAN 1000 mg b.i.d. / SR	17AUG02	61	402 (-19) / 08AUG02	GTN	Experienced vertigo and fell while walking without loss of consciousness. Amiloride and enalapril were discontinued. Was being treated for prostate cancer. Sixty-six days later and 44 days after discontinuation of study drug, patient died of prostate cancer.
CVT 3034 / 4939680	63 / M	RAN 1000 mg b.i.d. / SR	05AUG02	166	418 (11) / 11JUL02	Enalapril GTN	Attempted to stand after taking 3 GTN tablets for chest pain, fell with complete loss of consciousness for 1 to 2 seconds, and fractured L1.
CVT 3034 / 5028347	77 / M	RAN 750 mg b.i.d. / SR	04JUL01	369	398 (21) / 04JUL01	Trandolapril Atenolol GTN Furosemide	Became hot and diaphoretic, collapsed on his right leg and broke his right ankle. Echocardiogram and ECG were non-diagnostic.
CVT 3034 / 5127162	54 / F	RAN 500 mg b.i.d. / SR	03MAY02	661	393 (-53) / 29APR02	Captopril Diltiazem GTN	Experienced single episode of syncope (without loss of consciousness) while standing on a hot day. Did not eat breakfast that day (history of diabetes on tolbutamide).
CVT 3034 / 5458049	75 / M	RAN 750 mg b.i.d. / SR	29NOV01	373	455 (-41) / 14NOV01	Atenolol GTN Isosorbide	Collapsed while climbing stairs. Collapse was preceded by lightheadedness, weakness, paleness, and diaphoresis. Hospitalized 1 day and released.

[a] Fridericia unless noted.

[b] Bazett correction; Fridericia not available.

Table 5-9 Listing of Patients With Syncope (Cont'd)

Study / Pt. No.	Age / Sex	Dose / Formulation	Event Date	Days on Ranolazine	QTc[a] (change from baseline) msec / Date	Relevant Medications	Narrative
Uncontrolled Trials							
CVT 3034 / 5499273	70 / F	RAN 750 mg b.i.d. / SR	APR01 (day N/A)	Approx. 150	410 (-3) / 09APR01	GTN Amlodipine Quinapril Cilazapril Losartan	Felt unwell while shopping and collapsed back into a chair. Holter was non-diagnostic.
CVT 3034 / 5628188	66 / M	RAN 750 mg b.i.d. / SR	22APR02	609	427 (10) / 04MAR02	Atenolol Nifedipine Disothiazide Cordil Doxazosin Nifedipine Deralin Isosorbide Dinitrate	Experienced loss of consciousness during a period of ventricular fibrillation while hospitalized for acute coronary syndrome. Successfully defibrillated.
CVT 3034 / 5697065	64 / M	RAN 1000 mg b.i.d. / SR	08APR01	119	376 (3) / 25APR01	Isosorbide Diltiazem	Hospitalized for syncope associated with dizziness and vertigo. CT scan, Holter, EEG were non-diagnostic.
CVT 3034 / 6498721	78 / M	RAN 750 mg b.i.d. / SR	14MAY02	21	415 (-7) / 07MAY02	Furosemide Atenolol	Experienced a single episode of loss of consciousness for a few seconds upon getting a standing position, that was preceded by dizziness and sweating.

[a] Fridericia unless noted.

[b] Bazett correction; Fridericia not available.

Table 5-9 Listing of Patients With Syncope (Cont'd)

Study / Pt. No.	Age / Sex	Dose / Formulation	Event Date	Days on Ranolazine	QTc[a] (change from baseline) msec / Date	Relevant Medications	Narrative
Uncontrolled Trials							
CVT 3034 / 7219636	60 / M	RAN 750 mg b.i.d. / SR	10JUL02	179	400 (7) / 20AUG02	GTN Atenolol Isosorbide Enalapril	After taking 4 tablets of GTN and 4 tablets of isosorbide dinitrate for angina attack at rest, the patient collapsed. Three months later he died suddenly from hemotamponade due to rupture of the ascending aorta.
RAN081 / 6476186	50 / M	RAN IR 400 mg t.i.d. / IR	20NOV92	191	444 (-11)[b] / 07MAY93	None	Experienced intermittent dizziness and syncope. Holter monitoring showed episodes of atrial tachycardia and intermittent A-V block, and suggested mild sick sinus syndrome.
RAN1515 / 25732506	71 / M	RAN 60 mg t.i.d. / IR RAN 60 mg t.i.d. / IR RAN 60 mg t.i.d. / IR	07NOV91 13NOV91 17NOV91	525 531 535	423 (4)[b] / 30DEC91 423 (4)[b] / 30DEC91 423 (4)[b] / 30DEC91	Captopril Furosemide Doxazosin GTN	Experienced three "black-out" spells.
RAN1515 / 43784204	80 / F	RAN 30 mg t.i.d. / IR	01MAY91	290	N/A	Furosemide	Experienced mild intermittent syncopal episodes temporally associated with frequent falls, generalized weakness, and bronchodialator treatment for asthma.

[a] Fridericia unless noted.

[b] Bazett correction; Fridericia not available.

Table 5-9 Listing of Patients With Syncope (Cont'd)

Study / Pt. No.	Age / Sex	Dose / Formulation	Event Date	Days on Ranolazine	QTc[a] (change from baseline) msec / Date	Relevant Medications	Narrative
Uncontrolled Trials							
RAN2074 / 186210005	65 / M	400 mg t.i.d. / IR	18FEB94	325	400 (-20)[b] / 05APR94	Metoprolol	Fainted, was hospitalized and his metoprolol was discontinued when he was found to be hypotensive.
RAN2074 / 394324001	54 / M	400 mg t.i.d. / IR	21APR94	461	339 (-70)[b] / 21APR94	Metoprolol Diltiazem Furosemide GTN	Experienced a vaso-vagal episode during an iv injection of cosyntropin.
RAN2074 / 394518002	82 / F	267 mg t.i.d. / IR	13JAN94	428	439 (-5)[b] / 27JAN94	Atenolol Nifedipine GTN	Experienced two episodes of pre-syncopes concurrent with episodes of unstable angina and an additional episode of "blacking out".
RAN2074 / 405122001	74 / F	267 mg t.i.d. / IR	03JAN94	151	394 (28)[b] / 17MAR94	Amlodipine GTN	Experienced an isolated episode of syncope concurrent with gastritis.
CVT 3021 / 1493248	58 / F	750 mg b.i.d. / IR	01MAY01	5	470 (-11) / 01MAY01	Coreg Spirono-lactone Lasix Lotensin	Experienced syncope during iv injection of pyrophosphate for MUGA scan.

[a] Fridericia unless noted.

[b] Bazett correction; Fridericia not available.

5.5.2 Summary of Postural Hypotension and Syncope

In some patients and subjects, treatment with ranolazine resulted in postural hypotension or disturbance of the orthostatic response consistent with weak α_1-adrenergic and β-adrenergic blockade. There was no evidence that syncope was associated with TdP. In addition, during clinical trials of excessive ranolazine concentrations, continuous ECG monitoring of volunteers who experienced syncope showed no evidence of arrhythmia.

Particularly among the individuals who reported syncope, symptoms of nausea and dizziness were not uncommon. The emergence of these symptoms may provide a clinical signal of high ranolazine concentration and potential risk for orthostatic or postural hypotension. Consequently, the presence of these symptoms along with clinical evidence of orthostatic changes in BP may warrant downward titration of the ranolazine dose.

5.6 Clinical Laboratory Data

Ranolazine has not been associated with any deleterious changes in laboratory parameters. No clinically meaningful changes were observed for electrolytes, liver function, or urinalysis in ranolazine-treated patients. Small changes in renal parameters, hematology indices, and lipids were observed; decreases in glycosylated hemoglobin (HbA_{1c}) were seen in diabetic patients with angina. Changes in laboratory parameters associated with ranolazine treatment appeared benign and were not associated with clinical sequelae.

Renal Function

Small mean increases from baseline were observed in BUN (1.2 mg/dL) and creatinine (0.1 mg/dL) in ranolazine-treated patients. The onset and magnitude of changes for both parameters were similar in healthy volunteers and patients. The changes occurred soon after onset of ranolazine treatment, did not progress over time, and were rapidly reversible after discontinuation of treatment. Furthermore, these small increases in BUN and creatinine occurred in the

absence of changes in electrolytes, phosphate, uric acid, CPK levels, proteinuria, or urinary casts.

In a study conducted to explore the mechanism of these changes (CVT 301-16), there was a reduction in creatinine clearance with no concomitant change in inulin clearance as a measure of GFR, suggesting that ranolazine inhibits renal tubular secretion of creatinine. This is a well known effect of other drugs, for example, cimetidine and trimethoprim.

Hematology

Transient eosinophilia was observed infrequently in angina patients treated with ranolazine. With long-term exposure to ranolazine, the eosinophil count decreased; therefore, this finding is of doubtful clinical significance.

Similarly, small mean decreases in hematocrit (1%) were observed in patients treated with ranolazine in the controlled angina studies with no further decrease in the long-term open-label follow-on studies. Occult blood tests did not reveal evidence of gastrointestinal blood loss and RBC indices as well as LDH and bilirubin levels failed to provide evidence for increased red cell destruction. The mechanism of these findings is not known and they are unlikely to be clinically important.

Lipids and Hemoglobin A_{1c}

Short-term exposure (3 months or less) to ranolazine tended to result in small mean increases (within the normal range) in all plasma lipid levels among patients in the Phase 2/3 SR controlled angina studies. In contrast, with longer-term exposure to ranolazine statistically significant decreases in total cholesterol and LDL were seen (cholesterol: -14 mg/dL per year, $p < 0.0001$; LDL: -12 mg/dL per year, $p = 0.0001$). Mean values for HDL and HDL/LDL ratio were unchanged.

In general, plasma glucose levels were unaltered with short-term exposure to ranolazine in healthy volunteers and angina patients. In contrast, in CARISA, diabetic patients on ranolazine treatment had decreases in HbA_{1c} levels from baseline to the end of study. The effect was more pronounced on the 1000 mg b.i.d. dose than on the 750 mg b.i.d. dose and more pronounced in the patients taking insulin (Table 5-10). The decreases in HbA_{1c} developed gradually over approximately 100 days and was maintained in the open-label phase of treatment. Hypoglycemia attributed to ranolazine was not observed.

Table 5-10 HbA_{1c} for Diabetic Patients in CARISA at Baseline and Change to End of Study

	Insulin Treated			Non-Insulin Treated		
	Placebo	750 mg b.i.d.	1000 mg b.i.d.	Placebo	750 mg b.i.d.	1000 mg b.i.d.
Baseline	8.13[a]	8.32	7.81	7.28	7.55	7.74
Change	0.32	-0.63	-0.83	-0.11	-0.54	-0.86
Difference from placebo (95% CI)[b]	--	-0.836 (-1.514, -0.158)	-1.053 (-1.83, -0.276)	--	-0.351 (-0.753, 0.052)	-0.546 (-0.943, -0.149)
p-value[b]	--	0.0161	0.0083	--	0.0869	0.0074

[a] Units of %.

[b] Based on ANCOVA model including effects for baseline, treatment, pooled site, background therapy, insulin dependence, and treatment and insulin dependence interaction.

5.7 ECG Results

The effects of ranolazine on ECG parameters were measured in healthy volunteers and chronic angina patients, including those with congestive heart failure, diabetes, and reactive airway disease.

Among patients treated with ranolazine in the Phase 2/3 SR controlled angina studies, the mean increase in QTc was 2–5 msec over the dose range 500 mg to 1000 mg b.i.d. The clinical significance of this finding is unknown. Clinical effects on repolarization are discussed in detail in Section 6.

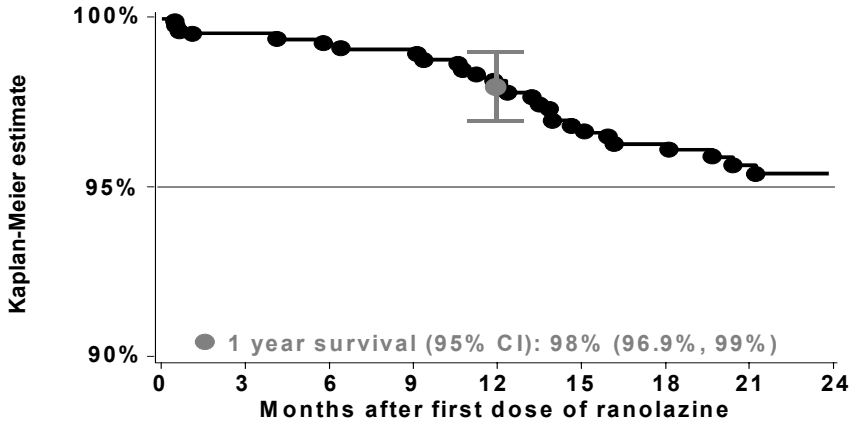
5.8 Mortality

Overall, there is no evidence that survival in patients with chronic angina is adversely affected by treatment with ranolazine. Eleven of the 57 reported deaths occurred during the controlled observation period of the Phase 2/3 controlled angina studies (both IR and SR studies combined). Of the eleven patients, seven (0.4%, 7/1737) were taking ranolazine and four (0.3%, 4/1266) were taking placebo at the time of death. In the Phase 2/3 SR controlled studies, the proportion of patients on ranolazine at the time of death (0.5%, 4/749) was less than that of patients on placebo at the time of death (0.7%, 3/455).

Of the 57 deaths, 45 (79%) were due to cardiovascular events, an outcome not unexpected in a population with severe coronary disease. Twenty-three (40%) were reported as sudden or caused by ventricular tachycardia, ventricular fibrillation, or cardiac arrest. This is consistent with recent data showing that approximately 60% of cardiac deaths are sudden.[46]

Figure 5-3 shows that the 1-year estimate of mortality associated with ranolazine treatment in the pivotal trials MARISA and CARISA and their respective long-term follow-on Studies CVT 3032 and CVT 3034 was 2% (95% CI 96.9–99%; on-treatment analysis includes all patients who took at least one dose of study drug. Data were censored 1 day after the last recorded day of treatment.) The 2-year estimate of mortality is below 5%.

Figure 5-3 Survival of Chronic Angina Patients on Ranolazine SR: MARISA and CARISA and their Respective Long-Term Follow-On Studies (CVT 3032 and CVT 3034)



At risk, n	941	741	696	642	594	573	533	387	272
With event, n	0	4	6	7	14	21	24	27	28

This mortality estimate can be put in perspective by comparing this mortality estimate to values derived from the literature for patients of similar risk. The Duke treadmill score (DTS) has been used to assess risk in cardiovascular patients.[16] The DTS calculates a risk score using Bruce protocol exercise duration, the occurrence and nature of exercise-induced angina, and the magnitude of exercise-induced ST-segment depression, as follows:

Duke Treadmill Exercise Score =

(Bruce exercise time [minutes]) – (5 x max ST deviation [mm]) – (4 x angina score)

where: no angina = 0; non-limiting angina = 1; exercise limiting angina = 2.

A DTS of ≥ 5 represents low risk; a DTS of ≥ -10 but < 5 represents intermediate risk; and a DTS of < -10 is associated with a high risk of subsequent cardiovascular events.

The exercise treadmill criteria used to select patients for MARISA and CARISA included the requirement to stop exercising primarily because of angina (thus giving an angina score of 2 at baseline), to stop exercise in 3–9 minutes on a

modified Bruce protocol, and to have ST-segment depression of at least 1 mm in at least 1 ECG lead. In MARISA and CARISA, the mean qualifying DTS (at trough) was -14. First-year mortality rates associated with high-risk DTS of < -10 have been published ranging from 3% to as high as 13%.[4,16,47–50]

Acknowledging the limitations of comparisons of data from MARISA and CARISA with published results, the mortality rates on ranolazine are not higher than those previously reported.

5.9 Safety in Subgroups

Safety data for angina patients with congestive heart failure, diabetes, and reactive airway disease, as well as those with low BP, low HR, and/or prolonged AV nodal conduction were examined. Data in males vs females and young vs older patients were also examined. In general, the safety profile of ranolazine was similar among the subgroups. The patients ≥ 75 years of age had a higher rate of AEs on both ranolazine and placebo, with higher event rates on ranolazine (placebo: 28.8%, 23.2%, and 32.3%; ranolazine: 54.2%, 52.9%, and 66.3%, respectively, for those < 65 years, 65 to < 75 years, and ≥ 75 years). The higher event rate in an elderly population is not unexpected. Otherwise, the effects of ranolazine on AEs, vital signs, laboratory values, and electrocardiographic findings were similar in each of the subgroups.

In CVT 3016, a study of patients with mild, moderate, and severe renal impairment, those patients with severe renal impairment exposed to ranolazine 500 mg b.i.d. had mean increases in diastolic BP of 10–15 mmHg. These hemodynamic effects, not observed in any other population or subgroup of subjects/patients, are not explained by the known pharmacodynamic properties of the drug.

5.10 Summary of Clinical Safety

The safety profile for ranolazine is well described and shows this drug to be safe and well tolerated in a broad range of populations and disease states, and with

and without other concomitant cardiovascular drugs. No major organ toxicities were identified.

The most common (≥ 2%) AEs in the Phase 3 controlled angina studies over the dose range 500 mg b.i.d. to 1000 mg b.i.d. that occurred more frequently on ranolazine treatment than on placebo were dizziness, constipation, nausea, asthenia, headache, dyspepsia, abdominal pain, and pain. Because most AEs were dose-related and occurred soon after the initiation of treatment, the most common treatment-related AEs could be avoided by dose-titration, as is the typical practice with currently available anti-anginal drugs.

Patients or subjects who achieved ranolazine plasma concentrations above the therapeutic range were likely to experience AEs, including nausea or dizziness, and at very high levels, visual disturbances. This concentration-dependent emergence of signs and symptoms offers the potential for early recognition of possible ranolazine toxicity and subsequent review of the patient's treatment regimen.

A small number of cases of syncope, often preceded by these symptoms, also occurred without evidence of an arrhythmia. In some cases, syncope appeared to be related to higher ranolazine doses and elevated plasma concentrations and often, change to an upright posture was a precipitant. Nonclinical data showing weak α_1-adrenergic and β-adrenergic blockade, provide a possible mechanism for the orthostatic changes and syncope.

Small changes in laboratory parameters appeared benign and were not associated with clinical sequelae. In patients with both insulin-dependent and non-insulin-dependent diabetes, long-term exposure to ranolazine resulted in a decrease in mean HbA_{1c}, but did not result in hypoglycemia attributed to ranolazine.

6 CLINICAL EFFECTS ON CARDIAC REPOLARIZATION

6.1 Introduction

The QTc effect of ranolazine has been well characterized in clinical studies across a broad population and across a broad range of plasma concentrations, including concentrations 4 to 5 times higher than those observed at the highest recommended dose (1000 mg b.i.d.) at peak. Over 25,000 ECGs have been examined; two studies obtained sufficient off-drug ECGs to calculate individualized correction factors (CVT 3111 and CVT 301-10). Over the dose range 500 mg b.i.d. to 1000 mg b.i.d., the QTc effect of ranolazine is small, with a mean increase from baseline of 2 to 5 msec. The difference from placebo is slightly greater due to an approximately 2 msec decrease from baseline on placebo. No cases of TdP occurred during the clinical program in over 2783 subjects/patients encompassing 1714 subject/patient years and no arrhythmias have been observed during continuous ECG monitoring in high dose studies of ranolazine in healthy volunteers.

A population analysis shows that the extent of QTc prolongation is related linearly to ranolazine plasma concentration, with an increase of 2.4 msec in QTc per 1000 ng/mL applicable over the entire tolerable concentration range. The QTc effect is independent of gender, CHF, diabetes, age, background anti-anginal therapy, baseline QTc, and baseline HR.

The effect of ranolazine on QTc is not more pronounced at slower HRs which is a potentially important clinical finding. Drugs that inhibit I_{Kr}, (rapid component of the delayed rectifier potassium current of the action potential) and cause TdP generally exhibit more pronounced QTc prolongation at lower HRs.[51–53]

QTc outliers (> 500 msec or increase ≥ 60 msec from baseline) were uncommon and sporadic. In those patients for whom an outlier value was reported, most had only one occurrence and no patients had persistent QTc outlier values. While there was a higher frequency of outliers on ranolazine than on placebo, the frequency of these observations was influenced by the ECG lead used for

measurement, the correction factor used, the baseline QTc value, and the number of ECGs per patient.

In subjects treated with the maximum proposed dose of ranolazine (1000 mg b.i.d.) along with ketoconazole 200 mg b.i.d., the average increase in QTc with ranolazine was approximately 20 msec and the mean ranolazine concentration was approximately 8000 ng/mL under this condition of maximum CYP3A4 metabolic inhibition. The population QTc model also predicts that a ranolazine plasma concentration of 8300 ng/mL would result in an average QTc increase of 20 msec. However, few patients will achieve high plasma concentrations and remain asymptomatic.

The small mean dose and concentration-related QTc prolongation on ranolazine is of unknown clinical significance. TdP has not been observed during 1714 subject/patient years of ranolazine treatment and there is no evidence that survival in patients with chronic angina is adversely affected by treatment with ranolazine. The 1-year estimate of mortality of angina patients enrolled in the Phase 3 trials is 2%.

6.2 Methodology of QT Measurement

The inherent correlation between the RR and QT intervals requires the use of a correction formula in order to accurately evaluate drug effects on the QT interval. While ranolazine had no clinically meaningful effect on HR over a dose range of 500–1500 mg b.i.d., subjects and patients have normally occurring variability in HR that requires correction.

The importance of correction of QT for HR, even for a drug that does not affect HR, is illustrated by the following data from CARISA (CVT 3033). In the placebo group, there were no increases in QTcF (Fridericia) of ≥ 60 msec from baseline. For uncorrected QT, there were a total of nine increases of ≥ 60 msec and 10 decreases of ≥ 60 msec. The increases in QT were all associated with a

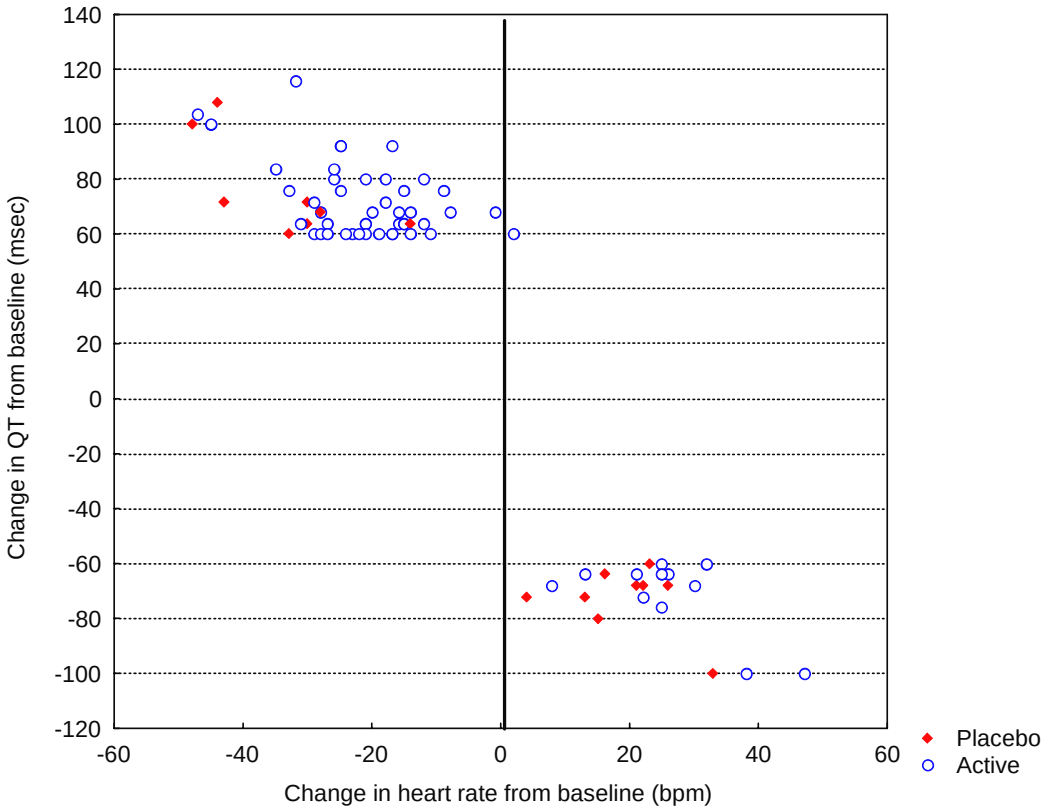
decrease in HR at the time of the measurement, and the decreases in QT were all associated with an increase in HR.

In the active treatment groups, there were a total of three increases in QTcF of ≥ 60 msec from baseline. For uncorrected QT, there were 46 increases of ≥ 60 msec and 12 decreases of ≥ 60 msec. With the exception of one observation in a patient who had an increase in QT of 60 msec associated with an increase in HR of 2 bpm, the increases in QT were all associated with a decrease in HR. All decreases in QT of ≥ 60 msec were associated with an increase in HR.

Figure 6-1 shows the relationship between change in HR and change in QT by treatment for all changes of ≥ 60 msec.

Thus, the increased incidence of changes in uncorrected QT of ≥ 60 msec from baseline, as compared with the corresponding changes in QTcF, were primarily caused by spontaneous variability in HR. This finding underlies the importance of correcting QT measurements for HR even for a drug that has no meaningful effect on HR.

Figure 6-1 Relationship Between Change in Heart Rate and Change in QT Interval Where QT Change ≥ 60 msec



The Bazett formula ($QTc = QT/RR^{0.5}$) and the Fridericia formula ($QTc = QT/RR^{1/3}$) are the most widely used HR correction factors. Bazett's correction was the protocol-specified default procedure in the majority of ranolazine clinical studies. Many studies also used the Fridericia correction. In a population QTc analysis, the optimal value of the exponent α in the formula $QTc = QT/RR^{\alpha}$ was assessed for each study included in the analysis. The average value across studies was 0.329, i.e., close to identical to the Fridericia correction formula. Gender and presence of CHF did not significantly affect the α value. Therefore, the Fridericia correction formula was selected as the most appropriate correction factor for the population QTc analyses.

In CVT 301-10, a study to evaluate the pharmacokinetics of concomitant administration of ranolazine and ketoconazole, and in CVT 3111, a study to assess the QTc effects of ranolazine at high plasma concentrations, individually optimized correction formulae were developed. These studies included more off-drug ECG recordings per subject than most other studies, enabling a more accurate determination of the correction formulae. Both studies provided specific information on the effects on QTc at high ranolazine concentrations.

In all ranolazine studies conducted by CV Therapeutics, the QT was measured as the longest QT among the 12 leads on the electrocardiogram (QT_{max}). Lead II data were also evaluated as has been suggested by a recent preliminary concept paper.[45] Lead II data are presented for mean changes in QTc from baseline for the Phase 3 trials MARISA (CVT 3031) and CARISA (CVT 3033). Lead II data are also presented for evaluation of QTc outlier values.

6.3 Effect of Ranolazine on the QTc Interval

Table 6-1 summarizes mean change from baseline QTc during the Phase 3 studies MARISA and CARISA. Small mean increases from baseline of 2–5 msec with either Bazett or Fridericia correction formulae were seen across the dose range of 500 mg b.i.d. to 1000 mg b.i.d. The difference from placebo is slightly greater due to an approximately 2 msec decrease from baseline on placebo. Lead II QT data were similar, with small decreases in QTc at 500 mg b.i.d. and slightly larger increases on 1000 mg b.i.d. compared to values obtained using QT_{max}.

Table 6-1 Changes from Baseline (mean ± SD) in QTc Intervals: MARISA and CARISA

	Ranolazine Dose				
	Placebo	**500 mg b.i.d.**	**750 mg b.i.d.**	**1000 mg b.i.d.**	**1500 mg b.i.d.†**
QT_{max}					
N	436	177	269	434	173
Bazett	-2.0 ± 19.1	2.1 ± 24.7	3.7 ± 13.6	4.6 ± 17.2	8.7 ± 25.9
Fridericia	-2.3 ± 15.6	1.9 ± 20.6	4.9 ± 12.6	5.4 ± 14.7	9.5 ± 22.3
Lead II QT					
N	390	148	240	383	146
Bazett	-1.2 ± 21.0	-0.8 ± 25.5	3.6 ± 16.8	5.7 ± 20.4	5.6 ± 26.8
Fridericia	-1.7 ± 17.6	-0.6 ± 23.1	4.7 ± 15.8	6.5 ± 17.5	6.9 ± 23.6

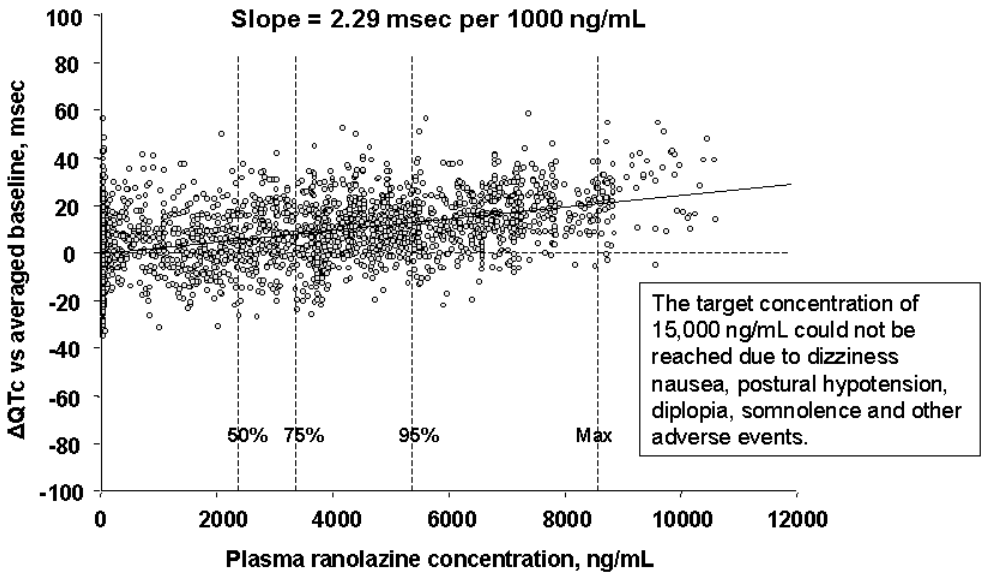
† 1500 mg b.i.d. is not proposed for clinical use.

Note: Baseline is the last observation prior to start of first dosing; data represent the mean of all available timepoints combined.

6.3.1 Effects at High Concentrations

Study CVT 3111 was conducted to assess the effects of ranolazine on the QTc interval at target plasma ranolazine concentrations of 4000, 10,000, and 15,000 ng/mL. These target concentrations represent plasma concentrations at the upper end of the therapeutic range, higher than therapeutic concentrations, and much higher than therapeutic concentrations, respectively. An iv infusion of ranolazine was administered over 72 hours to healthy volunteers on three separate occasions in a forced titration design to achieve both PK and PD steady-state for ranolazine and its metabolites. Multiple ECGs were recorded over the treatment interval. The average slope of plasma ranolazine concentration vs the change in QTc from baseline was 2.29 msec per 1000 ng/mL, using individually optimized correction formulae (Figure 6-2). There was no effect of gender on the slope.

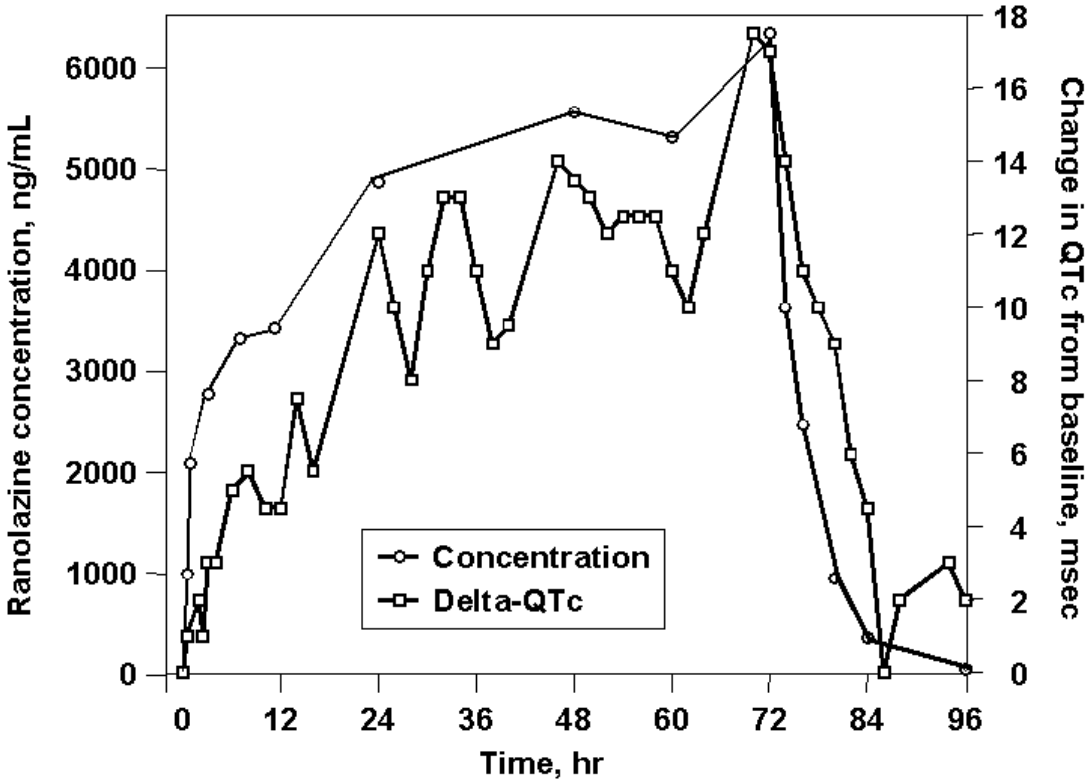
Figure 6-2 Ranolazine Effect on ΔQTc Remains Linear Even During Controlled Overdosing: Infusion to Intolerability in Study CVT 3111



Individually optimized regressions of mean RR intervals and median QT intervals.
Percentiles are peak concentrations on 1000 mg bid in CVT 3031 and CVT 3033 shown for comparison.

There was no delay in the effect on QTc interval in relation to the concentration-time profile of ranolazine, indicating that QT changes are likely related to ranolazine and not its metabolites (Figure 6-3).

Figure 6-3 Plasma Ranolazine Concentration and QTc Change in Parallel in Study CVT 3111



No subject in this study had an increase in QTc from baseline of more than 60 msec, based on the median QT interval for each ECG. When the maximum QT interval for each ECG was used, 2 of the 31 subjects had increases from baseline of between 60 and 80 msec on a total of 3 ECGs. The more pronounced increases in QTc were not related to ranolazine plasma concentrations in these 2 subjects. No ventricular arrhythmias were noted in any subject with continuous ECG monitoring.

As described in Section 5.4, due to the development of adverse effects in the concentration range 8000–10,000 ng/mL, including dizziness, nausea/vomiting, paresthesia, diplopia, confusion, and occasionally syncope, the highest target concentration of 15,000 ng/mL could not be achieved. This suggests that it is likely that patients who experience excessive ranolazine concentrations for

whatever reason will seek medical attention for adverse events before potential QTc effects may manifest.

6.3.2 Effects Under Maximal CYP3A4 Inhibition

Study CVT 301-10 was conducted to compare the pharmacokinetics of multiple oral doses of ranolazine SR when administered alone and following the co-administration of ketoconazole under steady-state conditions of both drugs. Ranolazine is primarily metabolized by CYP3A4 and plasma levels of ranolazine are increased in the presence of the potent CYP3A4 inhibitor ketoconazole. Because of the pharmacokinetic interaction between ketoconazole and ranolazine, ranolazine concentrations up to approximately 10,000 ng/mL were achieved during co-administration. The average slope of ranolazine concentration vs change in QTc from baseline was 2.86 msec per 1000 ng/mL when using a study specific correction formula. This was similar to the slope determined in Study CVT 3111. No ventricular arrhythmias were noted in any subject with continuous ECG monitoring. Gender and co-administration of ketoconazole had no effect on the slope. An additional analysis of the effects on QTc has been conducted using individually optimized HR correction formulae. At a ranolazine dose of 1000 mg b.i.d. co-administered with ketoconazole 200 mg b.i.d., QTc was prolonged by, on average, 19.77 msec (95% CI 11.08–28.45 msec) when corrected for the ketoconazole effect. The mean increase from baseline was 23.09 msec (95% CI 16.25–29.94 msec). Thus, under conditions of maximal CYP3A4 inhibition at the highest proposed clinical ranolazine dose, the QTc interval is prolonged by approximately 20 msec.

6.3.3 Population Analysis

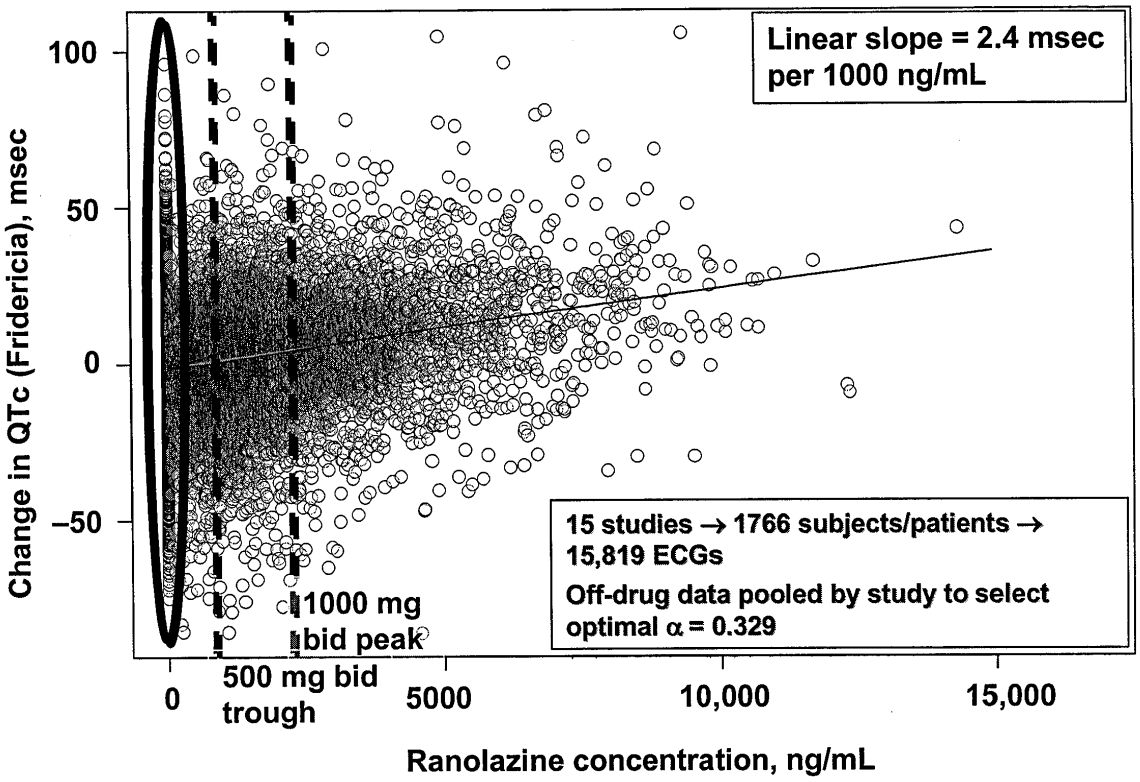
A population-based analysis was undertaken using data from 15 clinical studies in which plasma ranolazine concentrations and ECGs were obtained at corresponding time points. This analysis included data from 1766 subjects/patients and 15,819 ECGs.

The aim of the population analysis was to identify and quantify factors that were present among angina patients in the efficacy trials. Therefore, specific drug-drug interaction studies and pharmacokinetic studies in patients with renal or hepatic impairment were not included but have been analyzed separately. The effect of ranolazine on the QTc interval in patients with hepatic impairment is discussed in Section 6.3.6, and the effect during conditions of maximal CYP3A4 inhibition by ketoconazole is discussed in Section 6.3.2.

Figure 6-4 shows the relationship between concentration and change from baseline QTc interval for the population analysis. Mean plasma concentrations expected for the therapeutic dose range are shown between the dotted lines.

The range of changes from baseline in QTcF on placebo nearly encompassed the variability in the overall population (oval, Figure 6-4). The slope of the population concentration-QTc relationship was estimated to be 2.4 msec per 1000 ng/mL plasma ranolazine concentration, similar to results obtained in Studies CVT 3111 and CVT 301-10. Age, weight, gender, race, diabetes, CHF (including NYHA class), potassium-depleting diuretic use, baseline HR, baseline QTc, dose (single and total daily dose), patient status (healthy volunteer/patient), formulation, and study did not affect the slope of the relationship, indicating that the estimated increase in QTc with ranolazine concentration is appropriate for all populations included in the analysis.

Figure 6-4 QTc† vs Plasma Ranolazine Concentration, Population Analysis



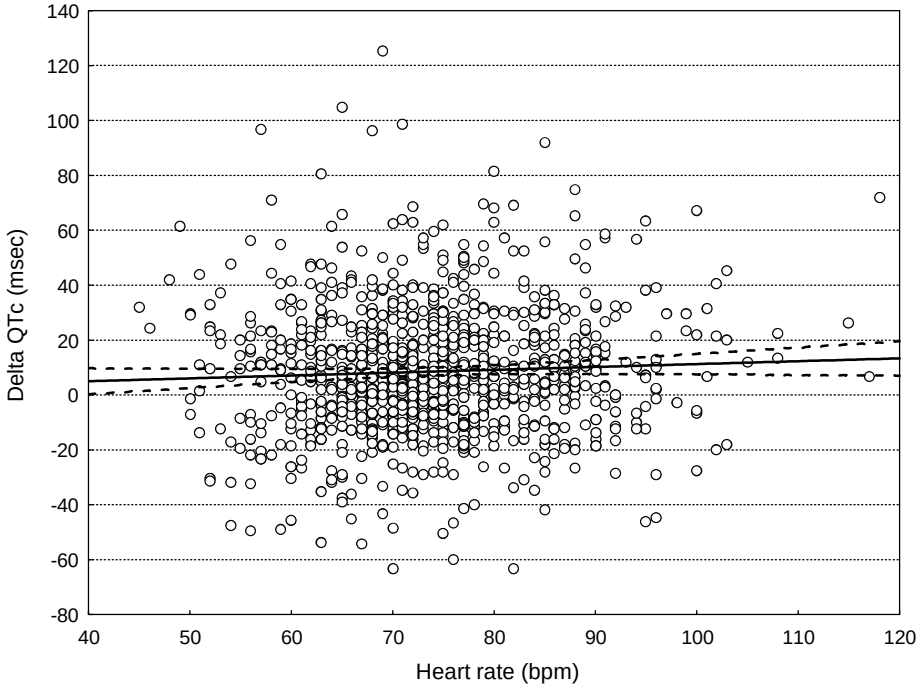
† Fridericia's Correction.

6.3.4 Relationship With Heart Rate

An analysis of the relationship between plasma ranolazine concentration, HR, and change in QTc from baseline was performed on data from MARISA. The data demonstrate that the increase in QTc was slightly less pronounced at lower HRs than at higher HRs at comparable plasma ranolazine concentrations (see Figure 6-5). This is a potentially significant clinical finding which is supported by similar results from nonclinical studies (Section 7.3). Drugs that inhibit I_{Kr}, (rapid components of the delayed rectifier potassium current of the action potential) generally exhibit an inverse relationship to HR with more pronounced QTc prolongation at lower HRs.[51–53] This phenomenon may be responsible, in part, for bradycardia as a risk factor for the induction of TdP in Long QT II syndrome by drugs that are known to inhibit I_{Kr}.[54] The absence of an

inverse relationship between change in QTc and HR observed with ranolazine (possibly as a net result of opposing effects on I_{Kr} and late I_{Na}) may contribute to the observed lack of arrhythmogenic activity. No documented episodes of TdP have been observed in subjects/patients even at very high levels of exposure to ranolazine.

Figure 6-5 Change in QTc from Baseline as a Function of Heart Rate in MARISA†



† Linear Regression with 95% CI.

6.3.5 QTc Outliers

Two criteria have been used to define "outliers" for the QTc values (Bazett and Fridericia correction) obtained from all patients randomized into MARISA and CARISA and their respective long-term, open-label, follow-on Studies CVT 3032 and CVT 3034:

- Increases from baseline ≥ 60 msec, regardless of value.
- Values > 500 msec, regardless of baseline.

In addition, gender specific criteria were used to define QTc outliers (> 450 msec for males and > 470 msec for females).

A total of 980 patients were randomized into MARISA or CARISA and had both baseline and at least one post-randomization QT measurement. Of these patients, 744 also elected to continue ranolazine treatment in the respective open-label studies, CVT 3032 and CVT 3034. Both Bazett and Fridericia HR corrections were applied to each QT measurement.

In general, outlier values were more frequent among patients treated with ranolazine than with placebo. The highest incidence of outliers was associated with 1500 mg b.i.d., a dose that will not be recommended for clinical use (see Table 6-2).

QTc outliers were uncommon and sporadic. In those patients for whom an outlier value was reported, most had only one instance and no patients had persistent QTc outlier values. In addition to the ranolazine effect, the frequency of these outlier observations was influenced by the correction factor, ECG lead, baseline value, and number of ECGs per patient.

Correction Factor

Using the Fridericia correction factor there are fewer outliers than with the Bazett correction. Using QT_{max}, a total of 86 outliers were reported using the Bazett correction, whereas 47 outliers were reported for the same population using the Fridericia correction factor. The difference between the two correction factors was similar using Lead II data. Table 6-2 summarizes the incidence of QTc outliers by treatment, by correction factor, and by lead.

ECG Lead

There were fewer outliers when Lead II data was used compared to QT_{max} data, using either the Bazett or Fridericia correction factor (Table 6-2). The lowest

frequency of outlier values was seen using Lead II data and the Fridericia correction.

Table 6-2 QTc Outliers*: MARISA, CARISA, and Long-Term Follow-On Studies (CVT 3032 and CVT 3034)

	Ranolazine Dose				
	Placebo	**500 mg b.i.d.**	**750 mg b.i.d.**	**1000 mg b.i.d.**	**1500 mg b.i.d.†**
QT_{max}					
N	436	694	720	620	173
Bazett	11 (2.5%)	16 (2.3%)	13 (1.8%)	25 (4.0%)	21 (12.1%)
Fridericia	3 (0.7%)	9 (1.3%)	9 (1.3%)	15 (2.4%)	11 (6.4%)
Lead II QT					
N	422	647	694	609	162
Bazett	8 (1.9%)	8 (1.2%)	11 (1.6%)	24 (3.9%)	14 (8.6%)
Fridericia	3 (0.7%)	8 (1.2%)	7 (1.0%)	17 (2.8%)	7 (4.3%)

*Defined as QTc > 500 msec or QTc change ≥ 60 msec.

† 1500 mg b.i.d. is not proposed for clinical use.

Note: Baseline is the last observation prior to start of first dosing.

Additional analyses were performed using the gender specific cut-offs of > 450 msec for males and > 470 msec for females.

Again, there were fewer outliers using the Fridericia correction factor and Lead II data. Among males, the frequency of values > 450 msec was less on ranolazine 500 mg b.i.d. than on placebo using either correction factor or either lead (Table 6-3). Among females, the frequency of values > 470 msec was less on ranolazine 500 mg b.i.d. and 750 mg b.i.d. than on placebo using either correction factor or either lead (Table 6-4).

Table 6-3 QTc Outliers*: Males in MARISA, CARISA, and Long-Term Follow-On Studies (CVT 3032 and CVT 3034)

	Ranolazine Dose				
	Placebo	**500 mg b.i.d.**	**750 mg b.i.d.**	**1000 mg b.i.d.**	**1500 mg b.i.d.†**
QT_{max}					
N	325	533	557	477	128
Bazett	97 (29.8)	121 (22.7)	139 (25.0)	192 (40.3)	83 (64.8)
Fridericia	54 (16.6)	71 (13.3)	97 (17.4)	134 (28.1)	55 (43.0)
Lead II QT					
N	313	495	535	468	119
Bazett	40 (12.8)	49 (9.9)	74 (13.8)	113 (24.1)	47 (39.5)
Fridericia	14 (4.5)	22 (4.4)	50 (9.3)	80 (17.1)	25 (21.0)

*Defined as QTc > 450 msec.

† 1500 mg b.i.d. is not proposed for clinical use.

Table 6-4 QTc Outliers*: Females in MARISA, CARISA, and Long-Term Follow-On Studies (CVT 3032 and CVT 3034)

	Ranolazine Dose				
	Placebo	**500 mg b.i.d.**	**750 mg b.i.d.**	**1000 mg b.i.d.**	**1500 mg b.i.d.†**
QT_{max}					
N	111	161	163	143	45
Bazett	16 (14.4)	16 (9.9)	16 (9.8)	22 (15.4)	18 (40.0)
Fridericia	5 (4.5)	6 (3.7)	5 (3.1)	12 (8.4)	9 (20.0)
Lead II QT					
N	109	152	159	141	43
Bazett	8 (7.3)	8 (5.3)	8 (5.0)	12 (8.5)	10 (23.3)
Fridericia	2 (1.8)	2 (1.3)	1 (0.6)	3 (2.1)	3 (7.0)

*Defined as QTc > 470 msec.

† 1500 mg b.i.d. is not proposed for clinical use.

Baseline QTc Values

For both ranolazine and placebo, the frequency of increases ≥ 60 msec was generally greater in those patients with lower baseline values, while the frequency of values > 500 msec was greater in those with higher baseline values irrespective of the correction factor used. In these studies, patients were allowed to enroll with baseline values up to 500 msec which would influence the frequency of outlier values above 500 msec. Table 6-5 summarizes the incidence of QTc outliers by baseline QTc and correction factor using the longest QTc from any ECG lead (QT_{max}).

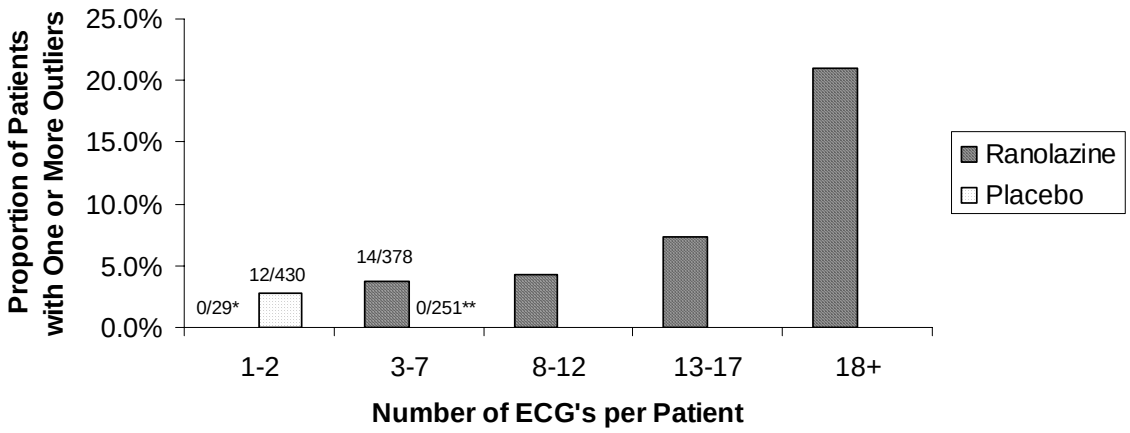
Table 6-5 QTc Outliers by Baseline QTc and Correction Factor: MARISA, CARISA, and Long-Term Follow-On Studies (CVT 3032 and CVT 3034)

Baseline QTc	Treatment	Number of Patients		Number (%) of Patients with a QTc Increase ≥ 60 msec from Baseline		Number (%) of Patients with a QTc > 500 msec	
		Bazett	Fridericia	Bazett	Fridericia	Bazett	Fridericia
≤ 410 msec	Ranolazine	222	316	16 (7.2)	16 (5.1)	1 (0.5)	0
	Placebo	157	231	3 (1.9)	1 (0.4)	0	0
≤ 420 msec	Ranolazine	362	496	22 (6.1)	21 (4.2)	3 (0.8)	1 (0.2)
	Placebo	264	356	4 (1.5)	1 (0.3)	1 (0.4)	0
≤ Median (427 msec)	Ranolazine	446	447	24 (5.4)	19 (4.3)	4 (0.9)	1 (0.2)
	Placebo	319	319	5 (1.6)	1 (0.3)	1 (0.3)	0
> Median (427 msec)	Ranolazine	454	453	12 (2.6)	9 (2.0)	27 (5.9)	13 (2.9)
	Placebo	362	362	2 (0.6)	0	7 (1.9)	2 (0.6)
≥ 480 msec	Ranolazine	35	10	2 (5.7)	1 (10)	11 (31)	4 (40.0)
	Placebo	33	9	0	0	4 (12)	0
≥ 490 msec	Ranolazine	18	7	2 (11)	0	7 (39)	2 (29)
	Placebo	18	6	0	0	3 (17)	0

Number of ECGs

As expected, the number of outliers observed using QT_{max} data was also affected by sampling frequency. Patients who had a higher number of ECGs performed also had a higher numbers of outlier values (Figure 6-6). The maximum number of ECGs per patients is 7 in the placebo group and 30 in the ranolazine group since ECGs on placebo were obtained only during the controlled trials. This may also partially explain the higher percentages of outliers observed in the ranolazine group.

Figure 6-6 Proportion of QTcB Outliers* vs Number of ECGs Performed



* 0/29 on ranolazine with 1–2 ECGs.

** 0/251 on placebo with 3–7 ECGs.

6.3.6 Effects in Patients With Hepatic Impairment

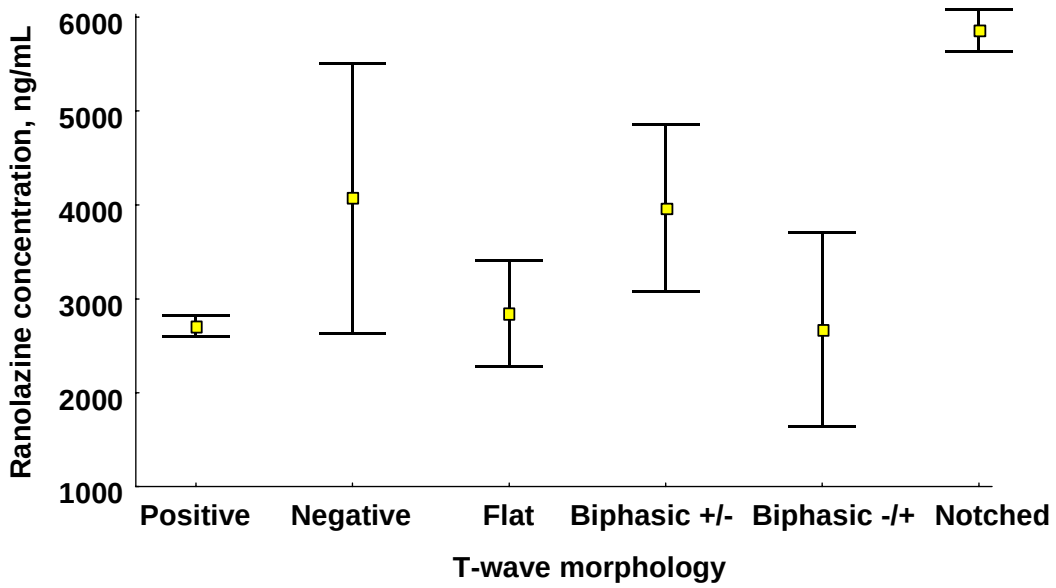
Study CVT 3018 was conducted to evaluate the pharmacokinetics of ranolazine in subjects with mild and moderate hepatic impairment. Mild hepatic impairment had no significant effect on ranolazine pharmacokinetics, whereas moderate impairment was associated with a 1.8-fold increase in ranolazine exposure, on average. The slopes of change in QTc from baseline vs the ranolazine plasma concentration are of a similar magnitude for patients with mild and moderate hepatic impairment when applying a linear regression function (6.62 and

7.42 msec per 1000 ng/mL, respectively). There were no ventricular arrhythmias observed with continuous monitoring and there were no associated clinical events. The mechanism for the greater increase in these patients compared to other populations studied is not understood. It has been demonstrated that patients who develop liver cirrhosis develop, in parallel, QTc prolongation.[56,57] This prolongation is reversible after liver transplantation.

6.4 Effect of Ranolazine on T-wave Morphology

Non-specific repolarization abnormalities were seen in association with ranolazine administration in some subjects. Notched T-wave morphology was observed in association with a reduction of T-wave amplitude. As plasma ranolazine concentration increased, T-wave amplitude gradually decreased, reaching a plateau at a concentration of approximately 3000 ng/mL. On the other hand, the notched T-wave phenomenon was more specific to high exposure and occurred at average plasma ranolazine concentrations of 5860 ng/mL. This is approximately twice the average peak concentration of 2476 ng/mL that was achieved in patients treated with ranolazine 1000 mg b.i.d. Figure 6-7 shows the occurrence of T-wave abnormalities by plasma ranolazine concentration achieved.

Figure 6-7 T-wave Morphology (Study CVT 3111)



Mean ranolazine concentration with 95% CI associated with ECGs with T-waves of different shape.

The clinical observation that ranolazine can cause notching and flattening of T-waves was reproduced in isolated guinea pig hearts, as described in Section 7.4.3. The concentration-dependence of this phenomenon was similar to that observed in patients. The notched T-waves seen with ranolazine were morphologically distinct from these provided by E-4031, a drug known to cause arrhythmias and TdP. Because ranolazine concentrations associated with T-wave notching had antiarrhythmic effects in isolated guinea pig and rabbit hearts, preclinical data do not suggest that T-wave notching with ranolazine is a signal of proarrhythmia.

Similarly, in a clinical setting, notching was not associated with proarrhythmia (see Table 6-6). ECGs from MARISA, CARISA, and their long-term follow-on Studies CVT 3032 and CVT 3034 were prospectively examined for T-wave notching and ventricular arrhythmias.

T-wave notching was more common on ECGs from patients on ranolazine. However, no ECG with T-wave notching had evidence of ventricular arrhythmia

(Table 6-6), while approximately 3% of ECGs without T-wave notching showed ventricular arrhythmia. This apparent reduction in the likelihood of ventricular arrhythmia in the presence of T-wave notching reached statistical significance among ranolazine-treated patients. A similar trend among placebo-treated patients was not significant due to the small sample size.

These data provide no evidence that the likelihood of ventricular arrhythmia increases in the presence of T-wave notching.

Table 6-6 Number and Percentage of ECGs Showing Ventricular Arrhythmia† Classified by the Presence of T-wave Notching: MARISA, CARISA, and Long-Term Follow-On Studies (CVT 3032 and CVT 3034)

	Patients, n/N (%)	
	Placebo	**Ranolazine**
ECGs with T-wave notching	0/15 (0.0%)	0/160 (0.0%)
ECGs without T-wave notching	76/2074 (3.7%)	326/10,446 (3.1%)
	p = 1.0‡	p = 0.01‡

† Includes premature ventricular contractions (PVCs); premature atrial contractions (PACs) plus PVCs.

‡ Fisher's exact test (2-sided).

Study CVT 301-16 was conducted with the primary objective of investigating the effects of ranolazine on different measures of renal function. Healthy male volunteers received a ranolazine loading dose of 1500 mg followed by 1000 mg b.i.d. for up to 5 days or placebo in a cross-over design. Frequent digital ECG recordings were collected during the trial and were utilized to evaluate changes to the morphology of repolarization patterns. The T-wave morphological analysis was based on previously published work[58,59] and included several factors describing different facets of the 12-lead morphology of the T/U wave. The variable T-wave residua represents the extent of repolarization signals that cannot be attributed to the single dipole movement of a 3-dimensional loop, and has been attributed to the heterogeneity of the repolarization sequence.[59] It was found that ranolazine reduced the value of this variable both compared to

baseline and compared to placebo. Since it has been demonstrated that increased values of T-wave residua are associated with an increased risk of death in cardiac patients and in the general population,[60,61] the conclusion was that ranolazine is more likely to be anti-arrhythmic than pro-arrhythmic.

6.5 Summary

The QTc effect of ranolazine is small, with a mean increase from baseline of 2 to 5 msec over the dose range 500 mg b.i.d. to 1000 mg b.i.d. The difference from placebo is slightly greater due to an approximately 2 msec decrease from baseline on placebo. No cases of TdP occurred during 1714 patient/subject years of exposure and no arrhythmias have been observed during continuous ECG monitoring in high dose studies of ranolazine in healthy volunteers, even during witnessed syncope during ranolazine infusions to supra-therapeutic plasma concentrations.

The relationship between ranolazine concentrations and change in QTc based on Fridericia's correction factor can be described by a linear model. The slope of this relationship is small and indicates that a large change in ranolazine concentration results in only a small change in QTc (approximately 2.4 msec per 1000 ng/mL of ranolazine). Of note, there was no effect of gender or of CHF status on the slope.

QTc outliers (> 500 msec or increase ≥ 60 msec) were uncommon and sporadic. The number of outliers in a clinical development program is influenced by the correction factor used, the lead used to measure the QTc, and the number of ECGs per patient. The Fridericia correction was determined to be optimal for this population and there are fewer outlier values observed when this correction was used compared to Bazett. The QT data from Lead II were also evaluated, in accordance with a recent preliminary concept paper[45] and fewer outliers were seen with the Lead II data than using the QT_{max}. Finally, the number of outlier values increases with the number of ECGs recorded. The patients in the clinical trials MARISA, CARISA, and their long term follow-on Studies CVT 3032 and

CVT 3034 have been treated for an average of 495 days and have had ECGs at every study visit (mean of 12 ECGs/patient). It is not surprising that there are occasional outlier values given this degree of sampling and baseline values permitted to 500 msec.

Flattened and notched T-waves have been observed in ECGs for patients with high plasma concentrations of ranolazine. The significance of this finding is unknown. Clinical data including an analysis of T-wave residua show a reduction in this value. Again, the significance of this is unknown; however, higher T-wave residua have been associated with an increased incidence of sudden death. Nonclinical data show that ranolazine concentrations associated with T-wave notching had antiarrhythmic effects.

Ranolazine is predominantly metabolized by CYP3A4. Under conditions of maximum CYP3A4 metabolic inhibition with ketoconazole, subjects treated with ranolazine 1000 mg b.i.d. (the maximum proposed dose) had mean ranolazine concentrations of approximately 8000 ng/mL and a mean increase in QTc of 20 msec due to ranolazine. This is consistent with the population QTc model that predicts a ranolazine plasma concentration of 8300 ng/mL would result in an average QTc increase of 20 msec. However, it is estimated that few patients will attain ranolazine concentrations of > 8000 ng/mL without adverse symptoms that would bring them to medical attention.

The absence of any apparent deleterious effect on survival underscores the uncertainty around the clinical significance of the small ranolazine-related increase in QTc.

7 NONCLINICAL EFFECTS ON CARDIAC ELECTROPHYSIOLOGY

7.1 Introduction

Ranolazine is associated with a small increase in the mean duration of the QTc interval over the clinical dose range 500 mg b.i.d. to 1000 mg b.i.d. (Section 6). To understand the relevance of the QTc prolongation caused by ranolazine to the potential risk of inducing torsade de pointes (TdP), extensive nonclinical pharmacologic characterization of the cardiac electrophysiologic properties of ranolazine has been performed.

All drugs that prolong the QTc interval are not associated with an increased risk for TdP.[54,62–64] Further, the magnitude of QTc interval prolongation caused by drugs does not predict the incidence of TdP. Review of the literature indicates that drugs known to prolong the QTc interval and cause TdP in humans also induce early afterdepolarizations (EADs) and/or increase dispersion of ventricular repolarization in nonclinical models, whereas drugs that do not induce EADs or increase dispersion of ventricular repolarization in nonclinical models are less likely to cause or do not cause TdP in humans (see Table 7-1). Hence, EADs and/or increased dispersion of ventricular repolarization appear to be better predictors of TdP than QTc prolongation alone.

Table 7-1 Cardiac and Non-cardiac Drugs Reported to Block I_{Kr} and Also Reported to Cause TdP, Induce EADs, and/or Increase Dispersion of Ventricular Repolarization[a,b]

Drug[c]	Blocks I_{Kr}	Prolongs QTc Interval	TdP Reported	Induces EADs	Increases Dispersion of Repolarization[d]	References
Anti-arrhythmics						
Almokalant	+	+	+	+	+	65–70
Amiodarone	+	+	+	–	±	71–78
Azimilide	+	+	+	+	+	79–83
Dofetilide	+	+	+	+	+	71,82,84–88
Ibutilide	+	+	+	+	+	71,87,89–92
Quinidine	+	+	+	+	+	71,85,86, 93–99
D-Sotalol	+	+	+	+	+	81,87,100–107

Table 7-1 Cardiac and Non-cardiac Drugs Reported to Block I_{Kr} and Also Reported to Cause TdP, Induce EADs, and/or Increase Dispersion of Ventricular Repolarization[a,b] (Cont'd)

Drug[c]	Blocks I_{Kr}	Prolongs QTc Interval	TdP Reported	Induces EADs	Increases Dispersion of Repolarization[d]	References
Antihistamines						
Astemizole	+	+	+[e]	+	+	108–113
Terfenadine	+	+	+[e]	+	+	86,108–110, 114–117
Antibiotics						
Erythromycin	+	+	+[e]	+	+	118–126
Clarithromycin	+	+	+[e]	+	+	127–131
Ca^{2+} Channel Blockers						
Diltiazem	+	±	–	–	–	52,132–135
Verapamil	+	±	–	–	–	71,132,133, 135–140
Mibefradil	+	+	+	+	–	137,141,142
Bepridil	+	+	+	+	+	135,143–147
Psychotherapeutics						
Sertindole[f]	+	+	+	+	+	102,148–152
Droperidol	+	+	+	+	?	153–157
Miscellaneous						
Cisapride	+	+	+[e]	+	+	158–163
Sodium pentobarbital	+	+	–	–	–	164,165
Ketanserin	+	+	+	+	+	166–168

[a] Many drugs known to cause TdP, prolong the QT interval and inhibit the rapid component of the delayed rectifier K^+ current (I_{Kr}), were not included because information regarding whether or not they cause EADs or increase dispersion of ventricular repolarization was not found.

[b] Symbols: +, response to drug noted; –, lack of response to drug noted; ±, response noted in some studies but not observed in other studies; ?, data not found.

[c] Results shown are based on the literature on QT-prolonging drugs that are reported to inhibit I_{Kr}. Some of the drugs have also been shown to inhibit other ion currents. Data are derived from humans, nonclinical models, or both. Nonclinical models include anesthetized animals, isolated hearts, and multicellular and single cardiac-cell preparations.

[d] Dispersion of repolarization includes both QT dispersion (i.e., interlead variability of QT interval in humans) and/or transmural and interventricular dispersion of repolarization (i.e., differences in action potential duration) in nonclinical models.

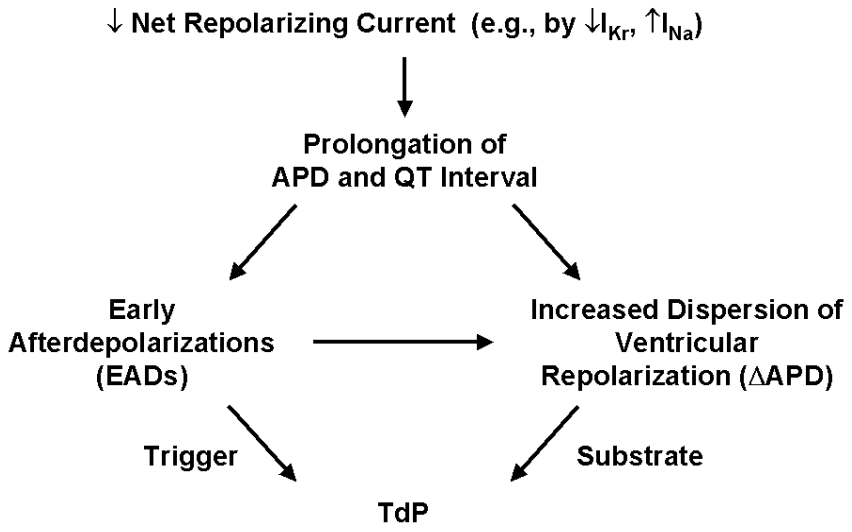
[e] Drugs that are associated with a very low incidence of TdP (e.g., < 0.1%), and that induce TdP mostly when administered in combination with inhibitors of their metabolism or in the presence of other predisposing factors for TdP.

[f] The electrophysiological effects of sertindole (e.g., triggered activity) appear to occur only at supratherapeutic concentrations.

EADs are transient depolarizations that arise during the repolarization phase of the action potential (AP), and are most often observed in the setting of prolonged

AP duration (APD), i.e., prolonged QT interval. EADs can contribute to spatial dispersion of ventricular repolarization, including transmural dispersion of repolarization (TDR) which refers to differences in APD across the left ventricular (LV) wall.[169] EADs can also lead to single or multiple extrasystoles that initiate re-entrant ventricular tachycardia (VT) and/or cause triggered activity directly eliciting VT, including polymorphic VTs such as TdP (see Figure 7-1).[63, 69, 74,169–173]

Figure 7-1 Role of EADs and Dispersion in Drug-Induced TdP



The major electrophysiological events known to play a role in the genesis of TdP. The drug causes a reduction in the net repolarizing current, which results in prolongation of the ventricular APD. Resulting EADs can generate ectopic beats that might serve as a trigger to initiate re-entry to perpetuate TdP. Dispersion of ventricular repolarization refers to the differences in APD (ΔAPD) across the left ventricular wall (transmural dispersion of repolarization; TDR), between the left and right ventricles, or between the base and apex of the heart. The increase in dispersion of ventricular repolarization leads to heterogeneity of refractoriness, which serves as a substrate for re-entry.

In order to identify the underlying basis for the observed electrophysiological effects of ranolazine, the effects of ranolazine on the ion channel currents that contribute to the AP (e.g., I_{Na}, $I_{Ca,L}$, I_{Kr}, I_{Ks}) were determined. Because EADs and increased TDR are known to contribute to the genesis of TdP, the potential risk for ranolazine to cause TdP in humans was assessed by determining, in numerous nonclinical model systems, whether ranolazine (1) induces EADs,

triggered activity, or VT; (2) affects delayed afterdepolarizations (DADs); or (3) increases dispersion of ventricular repolarization. The effect of ranolazine to induce arrhythmogenic activity in nonclinical models, under conditions known to predispose to TdP in humans, such as low potassium concentrations, slow pacing rates (including 3- to 5-second pacing pauses), site of pacing (endocardial versus epicardial) and the pharmacological equivalents of ion channel genetic polymorphisms that affect ventricular repolarization (i.e., long QT syndromes 1, 2, and 3), was also evaluated. The ion current and other electrophysiologic effects of ranolazine were often determined in the same preparation, conditions, and laboratory as those of QTc prolonging drugs known to cause EADs, to increase dispersion of ventricular repolarization (e.g., TDR), and to induce TdP (quinidine, sotalol, E-4031, chromanol 293B, sea anemone toxin ATX-II, terfenadine, cisapride, and erythromycin). However, it should be pointed out that not all comparisons between ranolazine and other drugs were carried out in old models used to determine the electrophysiological effects of ranolazine. Regardless, the studies were designed to discern the relevant similarities and differences between ranolazine and these drugs.

The concentrations of ranolazine used in these studies (up to 300 μM) were chosen to cover and exceed the therapeutic plasma concentration range. As a point of reference, the mean peak steady-state plasma concentration associated with the ranolazine dose of 1000 mg b.i.d. is approximately 2500 ng/mL (5.8 μM). Plasma concentrations of ranolazine associated with administration of this dose (1000 mg b.i.d.) are unlikely to exceed 20 μM in any patient.

7.2 Transmembrane Ion Currents

The QT interval of the surface electrocardiogram (ECG) reflects the duration of the ventricular AP.[174] Repolarization of the AP is determined by a delicate balance between inward (depolarizing) and outward (repolarizing) currents.[175,176] A reduction in net outward current leads to prolongation of the AP and hence to prolongation of the QT interval. In addition, as previously described, EADs may provide the trigger for initiation of TdP via induction of extra beats. Most drugs

that induce EADs, increase TDR, and cause TdP in laboratory animals do so by inhibiting outward (repolarizing) potassium currents such as I_{Kr} (the rapid component of the delayed rectifier potassium current), and/or increasing depolarizing inward currents such as late $I_{Ca,L}$ (L-type calcium current) or late I_{Na} (sodium current). All drugs reported to cause TdP in humans have been observed to inhibit I_{Kr} or increase late I_{Na}. Regardless, the effects of ranolazine on transmembrane ion currents were therefore studied to determine whether or not the effects fit the profile typical of a TdP-inducing drug.

In canine LV myocytes (midmyocardial and epicardial cells), ranolazine concentration dependently inhibited I_{Kr}, late I_{Na}, and late $I_{Ca,L}$ (Table 7-2). The potency (IC_{50}) of ranolazine to inhibit late I_{Na} was dependent on the voltage-clamp test potential and frequency (basic cycle length or BCL) of depolarization, and ranged from 5 to 21 μM. Although ranolazine only weakly inhibited late $I_{Ca,L}$ (IC_{50} = 50 μM), a ranolazine concentration of 5 μM inhibited this current by 25–30%. The inhibition of late I_{Na} and late $I_{Ca,L}$ (depolarizing currents) are expected to oppose the electrophysiologic effects of ranolazine's inhibition of the repolarizing outward current (i.e., I_{Kr}). The drug weakly inhibited I_{Na-Ca} (inward sodium-calcium exchanger current) and peak $I_{Ca,L}$, and had no appreciable effect on the slow component of the delayed rectifier potassium current (I_{Ks}), the outward rectifier potassium current (I_{K1}), or the transient outward potassium current (I_{to}).

Table 7-2 Effects of Ranolazine on Cardiac Transmembrane Ion Currents in Canine LV Myocardial Cells

Abbreviation	Name	Type of Current	Inhibitory Potency (IC_{50})
I_{Kr}	rapid component of the delayed rectifier potassium current	outward repolarizing	12 μM
late I_{Na}	late sodium current	inward depolarizing	5 to 21 μM (depending on the voltage-clamp test potential and frequency of depolarization)
late $I_{Ca,L}$	late L-type calcium current	inward depolarizing	50 μM (25% inhibition at 5 μM)
I_{Na-Ca}	inward sodium-calcium exchanger current	inward depolarizing	91 μM
peak $I_{Ca,L}$	peak L-type calcium current	inward depolarizing	296 μM
I_{Ks}	slow component of the delayed rectifier potassium current	outward repolarizing	no effect (≤ 20% inhibition at ≥ 30 μM)
I_{K1}	outward rectifier potassium current	outward repolarizing	no effect
I_{to}	transient outward potassium current	outward repolarizing	no effect

In summary, the ion current effects of ranolazine in the therapeutic concentration range include inhibition of I_{Kr}, and the late I_{Na} and late $I_{Ca,L}$ currents. The net effect of ranolazine on the surface ECG is believed to result from inhibition of I_{Kr}, to prolong the AP of cardiac tissues and cells, and late I_{Na} and possibly late $I_{Ca,L}$, to shorten the AP. The clinical consequence of inhibition of these ion currents is a small increase in the QTc interval over the ranolazine therapeutic range.

7.3 Action Potential

The effects of ranolazine on the action potential (AP) were determined in a number of experiments, at lower and at normal extracellular potassium concentrations ($[K^+]_o$). Ranolazine had no effect on resting membrane potential in a variety of ventricular preparations and in canine Purkinje fibers, except at high ranolazine concentrations (100 μM) but only when $[K^+]_o$ was normal (4 mM), and not when $[K^+]_o$ was reduced (3 mM).

In canine midmyocardial tissue slices, epicardial cell preparations from the LV wall, and Purkinje fibers, ranolazine at concentrations < 50 μM had no effect on

AP amplitude or overshoot, even under conditions of low $[K^+]_o$. The effects of ranolazine on AP amplitude and overshoot were small and became statistically significant only at concentrations ≥ 50 μM (well above the expected plasma levels in clinical use). Ranolazine was shown to reduce the maximal upstroke velocity (V_{max}) of the AP in guinea pig right ventricular papillary muscle (> 10 μM) and in free running Purkinje fibers isolated from canine right and left ventricle (≥ 50 μM). The minimal effects of ranolazine on the amplitude, overshoot, and V_{max} of the AP likely reflect the drug's weak inhibition of peak I_{Na}.

Experiments were also conducted to explore the effect of ranolazine on APD, with various pacing rates, because reverse rate-dependent prolongation of APD (i.e., greater prolongation of APD at slower pacing rates relative to faster pacing rates) is characteristic of I_{Kr} blockers known to cause EADs, increase TDR, and induce TdP. Ranolazine at concentrations < 10 μM (10 μM is approximately twice the mean peak steady-state plasma level associated with the ranolazine dose of 1000 mg b.i.d.) caused a small or no prolongation of APD in single LV myocytes (guinea pig or human myocytes, and canine midmyocardial cells), or in canine Purkinje fibers measured at 90% of repolarization (APD_{90}). In epicardial cells from canine LV, ranolazine prolonged APD_{90} at all concentrations tested (1–100 μM). Ranolazine did not prolong the APD to a greater extent at slow pacing rates than at fast pacing rates (i.e., did not cause reverse rate-dependent prolongation of the APD). These results are consistent with the clinical finding from the MARISA study that the effect of ranolazine on the QTc interval was not more pronounced at slower heart rates (Section 6.3.4). Thus, although ranolazine has been shown to modestly prolong the APD, these findings indicate that it differs from other I_{Kr} blockers that are associated with proarrhythmic effects in that prolongation of the APD is not greater at slow pacing rates, that is, the prolongation of the APD by ranolazine is not reverse rate-dependent.

7.4 Arrhythmogenic Potential

Numerous experiments in a variety of animal models were conducted to test the effects of ranolazine on cardiac rhythm. Ranolazine did not induce EADs,

triggered activity, or polymorphic VTs, and did not increase TDR in any model tested. In fact, ranolazine suppressed the arrhythmogenic activities induced by other QT-prolonging drugs, including I_{Kr} blockers known to be proarrhythmic.

7.4.1 Early Afterdepolarizations

Ranolazine at concentrations up to 300 μM, more than 50-fold the peak steady-state therapeutic plasma concentration (~ 5.8 μM), did not induce ectopic beats or EADs, which can lead to triggered activity or re-entrant VT, in any of seven preparations, from single cells to isolated whole hearts, including conditions of slow heart rates and low $[K^+]_o$. In guinea pig isolated perfused hearts, ranolazine prolonged LV monophasic action potential duration at 90% repolarization ($MAPD_{90}$) by up to 22% but did not cause EADs or VT despite lengthening the AP. The prolongation of $MAPD_{90}$ by ranolazine in this system, like the prolongation of APD_{90} in canine isolated LV epicardial cells, was not dependent on the pacing rate.

Ranolazine (1 μM and 10 μM) decreased the amplitude of delayed afterdepolarizations (DADs) induced by isoproterenol in guinea pig isolated ventricular myocytes, but did not affect the amplitude of forskolin or ouabain-induced DADs. In this model, ranolazine (10 μM) abolished isoproterenol-induced triggered activity. These findings suggest that an anti-β_1-adrenergic receptor mediated mechanism may underlie this action of ranolazine.

Several drugs that affect specific cardiac ion channels have been used in various nonclinical models to mimic the electrophysiological phenotype of the long QT syndromes. For example, sotalol (I_{Kr} blocker) is used to simulate long QT syndrome 2, and it has been shown to induce EADs, increase TDR, and cause TdP. Likewise, the effects of chromanol 293B (I_{Ks} blocker), E-4031 (a dofetilide derivative and pure I_{Kr} blocker), and the sea anemone toxin ATX-II (enhancer of late I_{Na}), similarly mimic the long QT syndromes 1, 2, and 3, respectively. Ranolazine has been shown to affect the activity of other drugs on cardiac rhythm, as follows:

- At relatively low concentrations (5 μM and 10 μM), ranolazine suppressed EADs induced by the proarrhythmic agents quinidine (multi-channel blocker) and sotalol in guinea pig and canine ventricular myocytes and Purkinje fibers, and terminated triggered activity induced by quinidine in guinea pig isolated ventricular myocytes.
- Ranolazine (≥ 5 μM) abolished spontaneous and pause-triggered premature ventricular beats (singles or multiples) and VTs induced by E-4031 or ATX-II in the female rabbit isolated perfused heart. The female rabbit heart model is considered to be the most sensitive one currently used to investigate drugs with Class III anti-arrhythmic effects because the I_{Kr} current is down-regulated in female rabbit ventricular myocytes.
- In guinea pig isolated heart, ranolazine (5–30 μM) prevented or antagonized the proarrhythmic effects (prolongation of $MAPD_{90}$, EADs, and monomorphic and polymorphic VTs) of ATX-II administered alone or in combination with either E-4031 or chromanol 293B.

In summary, ranolazine has unique electrophysiologic properties suggestive of some anti-arrhythmic activity that not only prevent it from generating EADs and arrhythmias on its own, but also enabling it to suppress proarrhythmic effects of other drugs. Thus, ranolazine was found to effectively suppress the arrhythmogenic activities of drugs known to mimic long QT syndromes and to cause TdP in humans.

7.4.2 Transmural Dispersion of Repolarization

The effect of ranolazine on TDR, a substrate for re-entry and polymorphic VTs, was investigated in numerous model systems:

- In canine LV tissue slices of epicardial and midmyocardial cells, at normal $[K^+]_o$ (4 mM) or low $[K^+]_o$ (2 mM), and during slow pacing (BCL of 2000 msec), ranolazine (1–100 μM) did not significantly increase ventricular TDR, but at fast pacing (BCL of 500 msec), it actually decreased ventricular TDR. Ranolazine (1–100 μM) caused neither EADs nor TdP in this preparation.
- In canine arterially-perfused LV wedge preparations, ranolazine (1–100 μM) at normal or low $[K^+]_o$ and at all pacing rates tested had no significant effect on ventricular TDR. During epicardial stimulation (rather than endocardial stimulation) in this preparation, a condition known to sensitize the myocardium to the arrhythmogenic effects of QT-prolonging drugs due to an increase in TDR, cisapride (multi-channel blocker) increased TDR and caused TdP. Under these same conditions, ranolazine (1–100 μM) did not

increase (but did decrease under certain conditions) TDR, and did not induce TdP.

- In female rabbit isolated hearts, ranolazine (0.1–100 μM) prolonged the LV MAPD without increasing LV spatial dispersion of repolarization (apex versus base). In this preparation, ranolazine (5 μM and 10 μM) blocked the increase in spatial dispersion caused by E-4031.

In all nonclinical studies conducted, ranolazine did not increase dispersion of ventricular repolarization, and was shown in one study to reverse the increase in spatial dispersion of repolarization caused by E-4031. The lack of effect of ranolazine on dispersion of ventricular repolarization (in particular, apex versus base) is consistent with the clinical findings from the MARISA study showing that ranolazine (500, 1000, or 1500 mg b.i.d.) did not increase circumferential dispersion of repolarization (i.e., QT/QTc dispersion) relative to placebo.

7.4.3 T-wave Morphology

In congenital and acquired long QT syndromes, which can be associated with potentially fatal arrhythmias such as TdP, T-wave morphologic abnormalities are often observed.[177,178] Further, drugs that block I_{Kr} activity and cause QT prolongation often alter T-wave morphology.[172] No systematic study has shown an association between quantitative measures of T-wave morphology and the risk of arrhythmias.[179] Because of the clinical observation that ranolazine can cause notching and flattening of T-waves (Section 6.4), a preclinical study was undertaken to evaluate the effects of ranolazine on T-wave morphology and duration.

In guinea pig isolated perfused hearts, ranolazine concentration dependently increased the QT, QRS, and JT intervals, increased T-wave duration, and decreased T-wave amplitude (changes significantly different from control only at 10 μM and 30 μM, 2- and 6-fold the mean peak steady-state therapeutic concentrations associated with a ranolazine dose of 1000 mg b.i.d., respectively). At high concentrations (≥ 10 μM), ranolazine increased the incidence of overt T-wave notching. The notched T-waves caused by ranolazine had low, smooth peaks, whereas E-4031, a drug known to cause arrhythmias associated with

TdP, at concentrations ≥ 60 nM produced morphologically different notched T-waves with sharply higher second peaks. Because the ranolazine concentrations associated with T-wave notching in the guinea pig isolated heart (≥ 5 μM) had anti-arrhythmic effects in rabbit and guinea pig isolated hearts, it is unlikely that T-wave notching in the presence of ranolazine signals an increased risk of proarrhythmia.

7.4.4 Models of Arrhythmogenesis

The effects of ranolazine on cardiac rhythm were further explored in several animal models:

- In an anesthetized dog model with acute complete atrioventricular block, a model susceptible to drug-induced polymorphic VT, ranolazine at doses that prolonged the QT interval by approximately 5% to 11% above control, did not cause spontaneous TdP or TdP facilitated by iv bolus phenylephrine (which increases susceptibility to TdP) in five dogs, whereas sotalol induced TdP in all five dogs under these conditions.
- In canine LV wedge preparations, ranolazine (1–100 μM) did not cause TdP or any other arrhythmia, tested in normal or low $[K^+]_o$, and during slow or fast pacing, whereas, sotalol (100 μM) induced spontaneous TdP in 25% of the preparations, and in 50% of the preparations with programmed electrical stimulation.
- In several *in vivo* and *in vitro* models, including anesthetized rats, rat isolated perfused working hearts, and rabbit isolated Langendorff-perfused hearts, ranolazine reduced the occurrence of ventricular fibrillation (VF) upon reperfusion/re-oxygenation after ischemia or hypoxia.

7.4.5 Summary

Ranolazine did not induce EADs in any experiment, and it suppressed EADs, triggered activity, and VTs induced by the proarrhythmic drugs quinidine, sotalol, E-4031, or ATX-II alone or in combination with E-4031 or chromanol 293B. Ranolazine also decreased the amplitude of DADs and abolished triggered activity induced by isoproterenol. Ranolazine did not cause statistically significant increases in TDR in any model system evaluated; reduced the incidence of VF that occurs upon reperfusion/reoxygenation after ischemia or hypoxia; and did not induce TdP in a model susceptible to drug-induced

polymorphic VT at doses that prolonged the QT interval by up to 11%. Although ranolazine caused T-wave notching, the notching was morphologically distinct from that produced by E-4031, and ranolazine concentrations associated with T-wave notching were shown to have anti-arrhythmic effects. Most drugs that induce EADs, increase TDR, or induce TdP in laboratory animals do so by inhibiting I_{Kr} or increasing depolarizing inward currents such as late I_{Na} or late $I_{Ca,L}$. Although ranolazine inhibits I_{Kr}, its inhibitory effects on late I_{Na} and late $I_{Ca,L}$ may serve to counteract the potential for ranolazine to induce EADs and increase TDR.

7.5 Electrophysiologic Effects of Ranolazine Enantiomers and Metabolites

Ranolazine is a racemic mixture of its two enantiomers, S-ranolazine and R-ranolazine. To determine the source of the specific ion channel current effects of racemic ranolazine, the effects of the individual enantiomers of ranolazine on I_{Kr}, I_{Ks}, and late I_{Na} were evaluated in canine LV myocardial cells. In all cases, the S-enantiomer had slightly greater potency relative to the R-enantiomer (Table 7-3).

Table 7-3 Potency (IC_{50}) of Ranolazine and S- and R-Enantiomers on Cardiac Ion Channels in Canine LV Myocardial Cells

Ion Current	Ranolazine	S-Enantiomer	R-Enantiomer
I_{Kr}	12 μM	10 μM	28 μM
I_{Ks}	≤ 20% inhibition at ≥ 30 μM	27% inhibition at 30 μM	5% inhibition at 30 μM
late I_{Na}	5 μM	5 μM	8 μM

In rabbit isolated hearts, both S- and R-ranolazine prolonged LV $MAPD_{90}$ with EC_{50} values of 5.9 and 6.4 μM, with maximal prolongation of 28% and 21%, respectively. These findings suggest that the net effect of the slightly greater potency of the S-enantiomer on these cardiac ion currents, particularly I_{Kr}, is a small increase in the potency and maximal effect of the S-enantiomer to prolong the QT interval.

Ranolazine is metabolized by a least four different biochemical routes: CYP3A4, CYP2D6, glucuronidation, and excretion of unchanged ranolazine. Phase I metabolism by CYP3A4 and CYP2D6 yields eleven metabolites with a plasma disposition in humans above 1% relative to ranolazine. Because the most abundant ranolazine metabolite is present at approximately 30–40% relative to ranolazine in human plasma, the effects of these eleven metabolites on the ion channels, I_{Kr}, I_{Ks} and late I_{Na}, were determined at a minimal concentration of 10 μM in order to exceed by at least 5-fold the plasma concentration achieved by the most abundant metabolite at peak therapeutic plasma levels of ranolazine. Only four of the metabolites weakly inhibited I_{Kr} (40–50% at a concentration of 50 μM) and only one weakly inhibited I_{Ks} (40% at a concentration of 50 μM) in canine cardiomyocytes. Thus, the IC_{50} values for the eleven metabolites tested at I_{Kr} and I_{Ks} were > 50 μM. All eleven metabolites inhibited late I_{Na} by 12% to 57% at a concentration of 10 μM. Because the metabolites do not or only weakly inhibit I_{Kr} but reduce late I_{Na}, they are likely to produce less of a reduction in the net outward current (e.g., I_{Kr}) than the parent ranolazine, and are unlikely to contribute to QT prolongation following ranolazine administration.

7.6 Conclusions

The effects of ranolazine on cardiac ion currents at concentrations within the therapeutic range include inhibition of I_{Kr}, and late I_{Na} and late $I_{Ca,L}$. The net effect of ranolazine on the surface ECG is believed to result from inhibition of I_{Kr}, to prolong the AP of cardiac tissues and cells, and late I_{Na} and possibly late $I_{Ca,L}$, to shorten the AP. The clinical consequence of inhibition of these ion currents is a small increase in the mean QTc interval over the ranolazine therapeutic range. Ranolazine modestly prolonged the ventricular APD in the nonclinical models evaluated. However, the effect on prolongation differed from that of other drugs that block I_{Kr} and have proarrhythmic effects, in that prolongation of the APD was independent of pacing rate (i.e., was not greater at slow pacing rates), was not associated with EADs, triggered activity, or polymorphic VTs, and did not increase TDR in any model tested. In fact, ranolazine reversed or suppressed the arrhythmogenic activities induced by other QT-prolonging drugs, including

selective I_{Kr} blockers known to be proarrhythmic. The net effect of ranolazine on ion currents suggests that the decrease in repolarizing outward current (I_{Kr}) may be counterbalanced by inhibition of inward currents (primarily late I_{Na}, and possibly late $I_{Ca,L}$), such that EADs are not induced, TDR is not increased, and the potential for TdP is not created, but rather is suppressed.

Because the effect of ranolazine to prolong the APD and lengthen the QT interval was not reverse rate-dependent or associated with any type of arrhythmogenic activity (e.g., EADs or triggered activity) or increases in dispersion of ventricular repolarization in any experiment, and because ranolazine was shown to suppress the arrhythmogenic activities caused by interventions known to mimic or cause TdP, it can be concluded that ranolazine is fundamentally different from drugs that cause TdP. These crucial differences between ranolazine and QT-prolonging drugs that have been associated with TdP strongly support the hypothesis that ranolazine lacks the proarrhythmic action typically associated with drugs that cause TdP in humans.

8 CONCLUSIONS

As patients with chronic angina live longer, a substantial and increasing percentage suffer from a variety of common co-morbidities,[6,180] which can limit their therapeutic alternatives among the currently existing anti-anginal drug classes (i.e., beta-blockers, calcium channel blockers, and nitrates). Many angina patients suffer from activity-limiting angina because they cannot tolerate (or have indications against) medical therapy sufficient to control their symptoms. These include patients who remain symptomatic with angina but who cannot tolerate reductions in BP, HR or contractile performance, or prolonged AV nodal conduction.

The pharmacodynamic profile of ranolazine addresses an unmet need for a non-hemodynamic anti-anginal agent. In patients whose angina cannot be controlled by combinations of beta-blockers, calcium channel blockers and nitrates, it is often these drugs' depressive effects on BP, HR, contractile function and/or AV nodal conduction, as well as other dose-related side effects, which limit further dose escalation and preclude relief from angina. Myocardial revascularization cannot be accomplished in many of these patients, leaving them with no therapeutic alternative. Ranolazine is an anti-anginal drug that offers benefits in addition to existing drugs; because it lacks hemodynamic, AV nodal, and bronchospastic effects, ranolazine could provide a substantial clinical benefit to these patients.

The anti-anginal and anti-ischemic benefits of ranolazine have been demonstrated across a broadly representative population of chronic angina patients in two pivotal and three supportive trials. The efficacy of ranolazine has been demonstrated both as anti-anginal monotherapy and when given over a background of beta-blockers or calcium channel blockers, including atenolol or diltiazem, under conditions of maximal or adequate effect, respectively.

The novel pharmacologic mechanism underlying the therapeutic effect of ranolazine has not been fully elucidated, but unlike beta-blockers, calcium

channel blockers and long acting nitrates, the anti-anginal and anti-ischemic effects of ranolazine do not depend upon reductions in HR or BP. They have been proposed to be related to an improvement in the efficiency of myocardial oxygen use when myocardial metabolism is shifted away from fatty acid oxidation and toward glucose oxidation. It is unknown whether α_1- and β_1-adrenergic antagonism or blocking of the late I_{Na} current contributes to these effects.

Ranolazine is generally well tolerated. In clinical studies, AEs were primarily mild to moderate in severity, there were no serious organ toxicities, discontinuations were infrequent and drug-drug interactions have been well characterized. Adverse events generally occur early in treatment and respond promptly to dose reduction or discontinuation of treatment; consequently, appropriate initiation and titration of dosing can minimize or avoid their occurrence.

Accompanying the anti-anginal and anti-ischemic benefits of ranolazine is a well characterized effect to prolong the QTc interval by 2–5 msec, on average, over the dose range 500–1000 mg b.i.d. This effect is linearly correlated with plasma ranolazine concentrations. Even under conditions of maximal inhibition of its major elimination pathway via CYP3A4 using ketoconazole, the mean QTc increase in healthy subjects on ranolazine 1000 mg b.i.d. was 20 msec. A secondary elimination pathway (via CYP2D6) and intolerable side effects at supra-therapeutic plasma concentrations further limit the risk of exposure to plasma ranolazine concentrations which might be associated with QTc increases > 20 msec. The observed increase in QTc is not affected by bradycardia, potassium-depleting diuretics, heart failure or female gender, a profile that is different from drugs which increase QTc and which are known to cause torsade de pointes.

Extensive nonclinical data demonstrate that the cellular electrophysiological profile underlying the QTc effect of ranolazine is fundamentally different from that of drugs known to cause torsade de pointes, and similar to that of drugs known to increase the QTc interval without causing torsade de pointes. In numerous

nonclinical models, ranolazine does not provoke early afterdepolarizations or increase the dispersion of ventricular repolarization, phenomena which appear to be better markers of proarrhythmia than clinical QTc measurements. These nonclinical models confirm the arrhythmogenic potential of drugs such as terfenadine, mibefradil, and cisapride. An evaluation of the effect of ranolazine on cardiac ion currents that contribute to the action potential suggests that the inhibition of I_{Kr} may be counterbalanced by inhibition of late I_{Na}, such that early afterdepolarizations are not induced, and dispersion of repolarization is not increased. In fact, ranolazine prevents the development of, and even actively reverses, these proarrhythmic signals when they have been induced by drugs known to cause torsade de pointes.

Consistent with these observations, during 1714 subject/patient years of exposure in 2783 individuals, including 1460 subjects/patients who received ranolazine SR, there has never been a reported case of torsade de pointes. Among 941 chronic angina patients treated with ranolazine SR in Phase 3 studies, the mean treatment duration was 495 days. First-year mortality in chronic angina patients with severe coronary artery disease treated with ranolazine with a mean Duke Treadmill Exercise Score of −14 remains at 2%. The 2002 ACC/AHA Practice Guidelines for chronic angina management cite a 5% annual mortality in such patients.

Physicians can determine which of their patients benefit from ranolazine by observing directly a reduction in their patients' angina symptoms. Those patients who do not respond to ranolazine with a decrease in angina symptoms need not continue on the drug. For those patients in whom benefit is observed, ranolazine treatment may be chronic. Accordingly, as an important element of the introduction of a new chronic medication, CV Therapeutics proposes a comprehensive postmarketing risk management program to be discussed with FDA which could encompass initiatives such as: large randomized Phase 4 clinical trial(s), a registry investigating the frequency, severity and determinants

of post-infarction angina, and a comprehensive program of physician, pharmacist, and patient education.

Limitation of the upper end of the dose range to 750 mg b.i.d. could also serve to reduce any potential for risk due to ranolazine. The current proposed labeling gives a dose range of 500 mg b.i.d. to 1000 mg b.i.d. for most patients. A dose range of 375 to 750 mg b.i.d. is given for patients with severe renal impairment (CLcr < 30 mL/min), and for patients treated with diltiazem ≥ 240 mg/day or verapamil ≥ 360 mg/day. As described in this document, QTc increases by about 2–5 msec, on average, over the dose range 500 mg b.i.d. to 1000 mg b.i.d. When ketoconazole is co-administered, the QTc increase on ranolazine 1000 mg b.i.d. averages 20 msec. Because the QTc increases are linear with dose and plasma concentration, reduction of the maximum dose to 750 mg would proportionally limit the QTc increase with ketoconazole to about 15 msec. Furthermore, in the pivotal studies, syncope did not occur on 500 mg and 750 mg b.i.d., and adverse events in general were less frequent on these lower doses than on 1000 mg b.i.d. Accordingly, CV Therapeutics is willing to consider the exclusion of the 1000 mg dose from the label at the time of the initial launch.

In summary, ranolazine represents the first new class of drugs for the treatment of chronic angina in over 20 years, addressing the need for a new anti-anginal agent with a different pharmacodynamic profile from those that are currently marketed. The choice of drug therapy for individuals suffering from chronic angina must reflect an informed judgment of the balance of benefits and risks attributable to the drug. CV Therapeutics believes that the safety and efficacy of ranolazine have been established by data acquired during the clinical development program, making ranolazine tablets a safe and efficacious treatment option for these patients.

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