

MEMORANDUM
DIVISION OF CARDIO-RENAL DRUG PRODUCTS INTERNAL CONSULTATION

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NDA: 21526

Sponsor: CV Therapeutics, Inc.

Drug: RANEXA, Ranolazine

Proposed Clinical Indication: Angina

Date Completed: 09/03/03

Re: Nonclinical Electrophysiological and Proarrhythmic Effects of Ranolazine

Executive Summary

Ranolazine's nonclinical electrophysiological effects are generally consistent with QT interval prolongation observed in clinical trials. However, the sponsor provided information arguing against proarrhythmic properties of ranolazine.

According to theory, torsade de pointes with QT prolonging drugs arises from increased transmural dispersion of repolarization and triggered activity (early afterdepolarizations) rather than from QT interval prolongation, per se. The elegant models of Antzelevitch argue that findings in isolated canine ventricular strips and wedge preparations, in particular action potential lengthening and early afterdepolarizations in M-cells, transmural dispersion of repolarization, and induction of torsade-like arrhythmias in vitro can predict proarrhythmic potential of a drug. Theory is supported in part utilizing data from positive control drugs such as amiodarone, cisapride, d-sotalol, erythromycin, quinidine and terfenadine.

While findings with ranolazine are primarily negative in the isolated canine ventricular wedge preparation, ranolazine increases M-cell action potential duration and transmural dispersion of repolarization under conditions of hypokalemia, consistent with its ability to inhibit repolarizing currents, I_{Kr} and I_{Ks} , at concentrations similar to those required for its proposed mechanism of action. Moreover, proarrhythmic potential was not adequately evaluated since ranolazine was not tested under conditions necessary to capture cisapride-induced arrhythmias in this model. Additionally, in vivo evaluation for proarrhythmia was not comprehensive.

Additional regulatory concerns reflect the complex nature of any proarrhythmia model, lack of evaluation of metabolites in this in vitro model, and adequacy of testing for proarrhythmia, utilizing known risk factors for clinical arrhythmias, e.g. female gender, different pacing modalities (pause, acceleration), adrenergic influences, and heart failure.

For these reasons, study results provided by the sponsor cannot preclude the risk of proarrhythmia with ranolazine.

Review and Evaluation

Ionic Currents

Ranolazine inhibited both repolarizing currents (I_{Kr} and I_{Ks}), depolarizing currents ($I_{Na-Late}$ and I_{Ca-L}), and I_{NaCa} in isolated canine ventricular myocytes.

Rank order for potency on native currents was $I_{Kr} = I_{Ks} > I_{Na-Late} > I_{NaCa} > I_{Ca-L}$.

Ionic Current (Canine Ventricular Myocytes)	IC50 (μ M)
I_{Kr}	11.4
I_{Ks}	13.4
I_{K1}	> 100
I_{Ca-L}	296
$I_{Na-Late}$	21
I_{NaCa}	91

Ranolazine was also shown to weakly inhibit cloned human potassium channels (hERG and KvLQT1), with IC50s of 86 μ M and 1.46 mM, respectively. While this data demonstrates the ability of ranolazine to block human repolarizing currents, it is not useful for potency estimation since studies were performed using a *Xenopus* oocyte expression system, which greatly underestimates potency. For example, IC50s for concurrent positive controls dofetilide and verapamil were approximately 20-30 fold greater in oocytes than in mammalian expression systems (1,2). Additionally, KvLQT1 channels were not coexpressed with minK, which likely further underestimates ranolazine potency on this repolarizing channel (3,4).

Ionic Current (cloned human channel expressed in <i>Xenopus</i> oocytes)	IC50 (μ M)	
	hERG	KvLQT1
Ranolazine	83	1460
Dofetilide*	0.3	-
Verapamil*	5.27	-

* IC50s for inhibition of hERG expressed in mammalian expression system: dofetilide, 0.015 μ M; verapamil 0.143 μ M (literature reference values (1,2).

The sponsor evaluated effects of several metabolites at a single concentration of 50 μ M on I_{Kr} in canine ventricular myocytes. Several metabolites inhibited I_{Kr} by about 50% at this concentration. The sponsor did not evaluate effects of metabolites on other ionic currents, including I_{Ks} .

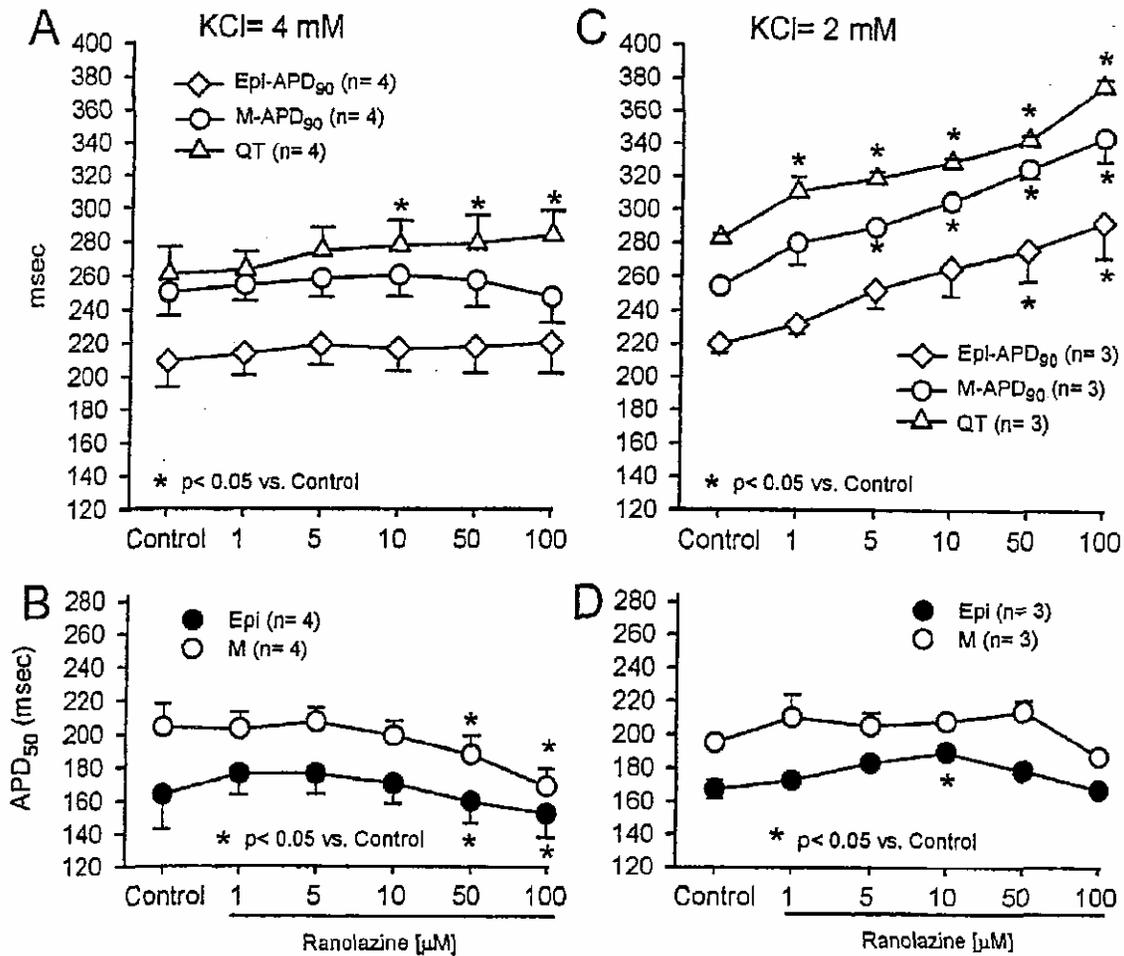
Action Potential Duration

Ranolazine was evaluated for effects on action potential duration in several systems, including epicardium and M-cells from canine left ventricular strips. Concentrations evaluated ranged from 1 to 100 μM . In canine epicardial strips, ranolazine ($\geq 5 \mu\text{M}$) lengthened APD90 in a concentration dependent way. Effects were potassium and rate dependent, with lengthening slightly more pronounced with hypokalemia (2 vs 4 mM potassium) and a more rapid stimulation rate (500 ms vs 2000 ms basic cycle lengths; i.e., 120 vs 30 beats per minute). Ranolazine did not lengthen APD90 in M-cell strips.

Ranolazine was also evaluated for effects on action potential duration in isolated, buffer perfused canine ventricular wedge preparations. Ranolazine was evaluated in epicardium and M-cells at concentrations of 1- 100 μM , under conditions of normokalemia and hypokalemia (4 and 2 mM potassium) using basic cycle lengths of 500 and 2000 ms (stimulation frequencies of 120 and 30 beats per min, respectively).

In the presence of normokalemia, ranolazine did not lengthen APD90 in epicardium and M-cells. However, in the presence of hypokalemia, ranolazine lengthened APD90 in a concentration dependent way in both of these tissues.

LV Wedge (anterior wall) BCL=2000 msec



Ranolazine also prolonged transmural QT interval, T_{peak} to T_{end}, and transmural dispersion of repolarization, and altered T-wave morphology (wide, low, notched; see below). Ranolazine (10 and 100 μM) also lowered maximum upstroke velocity, indicating sodium channel blockade at concentrations evaluated. Maximum upstroke velocity was lowered by approximately 50% at 100 μM. Exposure duration and time course of effects were not provided.

Canine Left Ventricular Wedge: 4 mM [KCl]_o, BCL=2000

Concentration	Epicardium		M region		QT _{end}	T _{peak} - T _{end}	TDR
	APD50 ± SE	APD90 ± SE	APD50 ± SE	APD90 ± SE			
control	164 ± 21	209.3 ± 15.76	204.5 ± 13.9	250 ± 13.93	261.1 ± 15.76	34.25 ± 2.56	43 ± 6
1 μM	176.3 ± 12.25	213.8 ± 13.28	203.3 ± 9.621	254.3 ± 9.15	263.5 ± 10.56	34.5 ± 3.202	26.75 ± 8.045
5 μM	176.5 ± 11.85	219 ± 12.12	207.5 ± 8.627	258.3 ± 11.08	274.5 ± 13.73	37.75 ± 4.09	36 ± 2.449
10 μM	170.5 ± 12.03	216.5 ± 13.41	199 ± 9.083	260.3 ± 12.66	277.8 ± 14.99*	39.25 ± 5.54	30.75 ± 10.46
50 μM	159.5 ± 12.82*	218 ± 15.91	187.8 ± 11.21*	257.5 ± 15.47	279.3 ± 17.21*	41.25 ± 8.37	32.5 ± 6.278
100 μM	152.5 ± 14.44*	220.5 ± 18.26	169 ± 10.5*	247.8 ± 15.32	284.5 ± 14.39*	40.5 ± 4.94	23.75 ± 2.689

* p<0.05 vs. control

n≤4

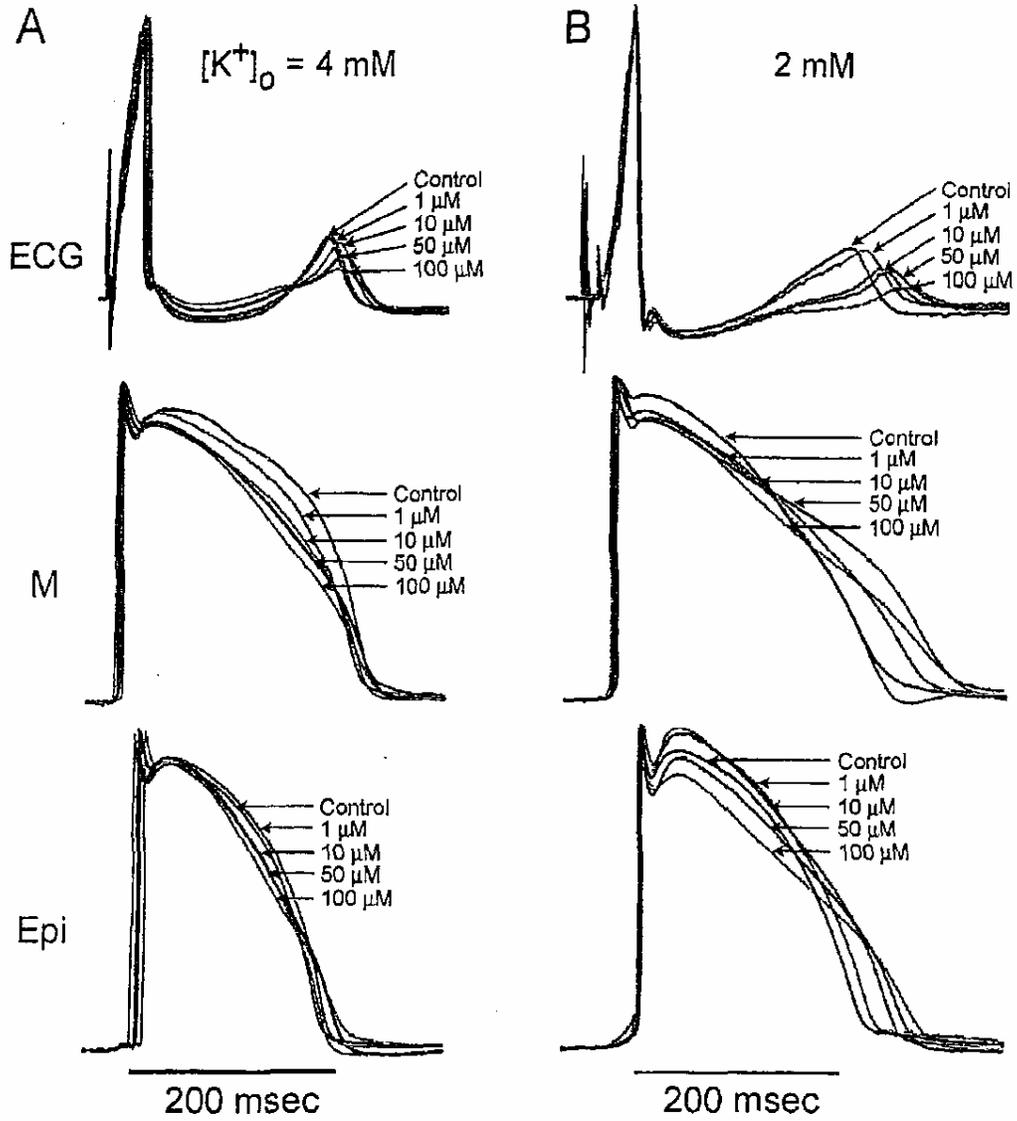
Canine Left Ventricular Wedge: 2 mM [KCl]_o, BCL=2000

Concentration	Epicardium		M region		QT _{end}	T _{peak} - T _{end}	TDR
	APD50 ± SE	APD90 ± SE	APD50 ± SE	APD90 ± SE			
control	167.3 ± 5.548	220 ± 5.568	195.3 ± 3.283	254.3 ± 0.882	283 ± 2.08	24 ± 12.57	16 ± 9.238
1 μM	173 ± 2	232 ± 5.508	210.7 ± 13.53	280.3 ± 12.72	311 ± 9.5	35 ± 4.70	28.33 ± 11.46
5 μM	183.5 ± 1.5	252.5 ± 10.5	205.7 ± 7.881	289.7 ± 2.848*	319 ± 4.58	33 ± 1.33	15 ± 7
10 μM	190 ± 2*	265.5 ± 16.5	208.3 ± 3.48	305.3 ± 4.978*	329 ± 2.33	36 ± 4.09	23.5 ± 1.5
50 μM	179 ± 1	276.5 ± 18.5*	214.3 ± 6.333	325.5 ± 5.5*	343 ± 2.84	41 ± 6.35	35.5 ± 3.5
100 μM	167.5 ± 0.5	293.5 ± 21.5*	187.7 ± 4.978	345 ± 14.36*	376 ± 4.48	55 ± 1.00	35 ± 11

*p<0.05 vs. control

n≤4

LV Wedge (anterior wall) BCL=2000 msec



In comparison, most but not all positive control drugs showed pronounced M-cell APD90 lengthening and increased transmural dispersion of repolarization in canine ventricular strips or wedges (5-12).

Drug	Pronounced Effects	
	M-cell	Transmural Dispersion of Repolarization
Amiodarone (chronic)	no	no
Azimilide*	yes	yes
Cisapride*	yes	yes
Erythromycin	yes	yes
Quinidine	yes	yes
d-Sotalol	yes	yes
Terfenadine^	yes	yes

* Biphasic concentration – response relationship, with prolongation at low concentrations, and shortening or attenuation of effect at high concentrations.

^ Requires extended perfusion period (120 min) and hypokalemia (2 mM potassium) for effects.

In canine Purkinje fibers, ranolazine (1 to 100 μ M) shortened APD90 and depressed maximal upstroke velocity. APD90 effects appeared independent of extracellular potassium (2 vs 4 mM) and basic cycle length (500 vs 2000 ms). Similar to findings in M-cells, ranolazine (10 and 100 μ M) decreased maximum upstroke velocity, with approximately 50% inhibition at 100 μ M. Ranolazine (5 and 10 μ M) shortened d-sotalol induced APD lengthening and suppressed EADs in a concentration related way. Lack of action potential duration lengthening in canine Purkinje fibers with ranolazine is not impressive considering the poor sensitivity of this model to torsadogenic drugs such as terfenadine and terodiline (13, 14).

Proarrhythmia

Ranolazine (1- 100 μ M) did not induce early afterdepolarizations (EADs) in canine ventricular M-cell strips and Purkinje fibers. Ranolazine (5 and 10 μ M) reversed d,l-sotalol induced APD90 lengthening and prevented EADs in both canine M-cell strips and Purkinje fibers. Lower ranolazine concentrations were not evaluated for this property.

In comparison, the historical positive control erythromycin induced EADs in 2 of 10 M-cell strips at the highest concentration evaluated (8). Quinidine (3.3 μ M) induced EADs in 3 of 5 M-cell strips and EAD-induced triggered activity in 2 of 5 M-cell strips with hypokalemia (2 mM potassium) but not with normokalemia (4 mM potassium) (9). M-cell strips from chronically amiodarone treated dogs did not show EADs or triggered activity (5). Additionally, chronic amiodarone attenuated d-sotalol induced APD90 lengthening and EADs.

The sponsor evaluated ranolazine for torsade-like polymorphic arrhythmias (TdP, spontaneous and programmed electrical stimulation (PES) inducible) in isolated canine ventricular wedge preparations. Ranolazine was evaluated in the presence and absence of hypokalemia (2 mM potassium). PES consisted of a single extrastimulus (S2) applied to the epicardial surface of the wedge preparation with the basic stimuli (S1) applied to the endocardium at basic cycle lengths of 500 and 2000 ms.

Ranolazine did not induce torsade like arrhythmias in these studies. However, the sample size was quite small (n = 4 for normokalemia, and n = 3 for hypokalemia), and positive historical control data from the Antzelevitch laboratory shows TdP incidences for d-sotalol, erythromycin and cisapride to be fairly low in this in vitro model (7, 8, 10, 11). Additionally, cisapride's proarrhythmic effects were limited to a single concentration, with negative proarrhythmia findings at both lower and higher concentrations, consistent with cisapride's biphasic effect on APD90 and transmural dispersion of repolarization. Most importantly, induction of TdP with cisapride required epicardial pacing (S1), which doubled baseline transmural dispersion of repolarization. As only endocardial pacing (S1) was utilized in the ranolazine experiments, cisapride's positive torsadogenic effect in this model is not applicable to the ranolazine experiments.

Indeed, the inability of cisapride to induce TdP in this model using endocardial pacing (S1), argues against the model's sensitivity to torsadogenic drugs when evaluated in this manner.

Drug	TdP Incidence	
	Spontaneous	PES-Inducible
Ranolazine (1-100 μ M)	0 of 4	0 of 3
d-Sotalol (100 μ M)	2 of 6 2 of 8	3 of 6 4 of 6
Erythromycin (100 μ M)	no data	3 of 4
Cisapride (0.1 -5 μ M)	none	2 of 6*

* TdP inducible at 0.2 μ M cisapride (only); required epicardial pacing (S1)

In Vivo Effects: QT Interval Prolongation and Proarrhythmia

Acute intravenous infusion of ranolazine was evaluated for effects on QT interval and proarrhythmia in anesthetized dogs with acute AV block. Ranolazine was administered at a dose of 0.5 mg/kg plus 1, 3 and 15 mg/kg/hr iv for 30 minutes/dose level (n=6). In one additional dog, ranolazine was administered at a dose of 1.5 mg/kg plus 15 and 30 mg/kg/min iv for 30 minutes per dose level. Sotalol (8 mg/kg followed by 4 mg/kg/hr iv for 20 minutes served as a positive control (n=5). Left ventricular effective refractory periods, QT interval, and QRS duration were determined at basic cycle lengths of 300, 400, 600 and 1000 ms following each dose of ranolazine or sotalol. All dogs then received bolus intravenous doses of phenylephrine (10, 20, 30, 40 and 50 μ g/kg iv) in order to elicit arrhythmias.

In this study, ranolazine increased QT interval by approximately 10% (not statistically significant). The QT effect was biphasic, with the maximum increase observed at 3 mg/kg/hr. Ranolazine increased left ventricular refractoriness but only at the fastest stimulation rate (300 ms basic cycle length). Ranolazine increased QRS interval by 10% (statistically significant) at the next higher dose of 15 mg/kg/hr. Proarrhythmia was not observed with ranolazine in the presence of phenylephrine. The highest ranolazine dose of 30 mg/kg/hr induced acute heart failure and death.

In contrast to findings with ranolazine, sotalol induced a large increase in QT interval (33% increase at 1000 ms basic cycle length), and increased left ventricular refractoriness without altering QRS duration. Phenylephrine induced tachyarrhythmias, including TdP and ventricular fibrillation, in sotalol treated dogs.

Limitations of this study design include its acute nature, since chronic but not acute AV block has been shown to promote proarrhythmia by electrical remodeling and downregulation of ion channels, including I_{Kr} (15, 16). Additionally, ranolazine displaces radiolabeled ligand from α -1 adrenergic receptors, suggestive of potential functional antagonism (17). If ranolazine is indeed a functional α -1 adrenergic antagonist at doses administered above, then the in vivo canine model used for this study is inappropriate. Finally, positive control data is quite limited for this model, lessening the regulatory importance of negative findings.

References

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