

MEMORANDUM

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Subject: Nonclinical Electrophysiological Effects of Ranolazine

Date: 23 October 2003

The sponsor (CV Therapeutics, Inc.) has submitted an amendment to this NDA¹ providing nonclinical study reports to address Pharmacology/Toxicology issues discussed in the DISCIPLINE REVIEW LETTER. Among other things, the sponsor attempts to prove that QT prolongation with ranolazine is not a concern. This memo addresses study reports describing ranolazine's electrophysiological properties in nonclinical studies. Other study reports provided in the amendment were addressed by Dr. Elizabeth Hausner in her memo dated 29 September 2003.

Although some of the evidence provided in this amendment is consistent with ranolazine induced QT prolongation and repolarization disturbances, other evidence suggests antiarrhythmic rather than proarrhythmic potential. Nevertheless, these study results do not alter the previous conclusion (see original memorandum dated 4 September 2003) that the nonclinical electrophysiology findings do not preclude human risk, in large part due to lack of comprehensive information addressing the sensitivity and specificity of the in vitro assays cited. Findings are summarized below.

The sponsor addressed effects of ranolazine, its enantiomers and metabolites on several ionic currents that modulate ventricular repolarization.

- Ranolazine did not inhibit the slowly activating delayed rectifier potassium current (I_{Ks}) through human channels (KvLQT1/minK) expressed in *Xenopus* oocytes. Hence, the sponsor concluded that ranolazine at concentrations up to 900 μ M does not inhibit I_{Ks} . However, these data are not convincing since the *Xenopus* oocyte expression system greatly underestimates potency. The sponsor argued that results of previously submitted studies showing that ranolazine inhibited native I_{Ks} in isolated canine ventricular myocytes were due to current run-down and therefore an artifact of the test system. Given the contradictory study reports and assay limitations, the effects of ranolazine on I_{Ks} are presently unclear.
- Ranolazine enantiomers, like racemic ranolazine, inhibited I_{Kr} and late I_{Na} with similar potencies in canine ventricular myocytes. Additionally, several ranolazine metabolites inhibited late I_{Na} when evaluated at a concentration of 10 μ M. The sponsor argues that late I_{Na} inhibition attenuates ranolazine's effects on action potential duration in M-cells and other ventricular tissue, thereby preventing proarrhythmic activity. However, the torsadogenic drugs terfenadine and cisapride also inhibit late I_{Na} , and terfenadine, like ranolazine, showed similar potencies on I_{Kr} and late I_{Na} . Therefore, inhibition of late I_{Na} does not appear to preclude risk of drug-induced *torsade de pointes*.
- Ranolazine increased the decay of I_{Ca} and therefore inhibited what the sponsor called late I_{Ca} . Although this activity theoretically could shorten action potential duration, the actual significance of this finding is unknown.

¹ Amendment dated 13 September 2003; received by Center on 15 September 2003.

The sponsor addressed proarrhythmic and antiarrhythmic potential of ranolazine in vitro. The relevance of these findings is unknown since the sensitivity of these in vitro models has not been sufficiently well characterized.

- Ranolazine lengthened epicardial monophasic action potential duration in isolated female rabbit hearts. Ranolazine did not increase apex-base dispersion of action potential duration nor induce ventricular arrhythmias. Additionally, ranolazine, at concentrations that inhibit I_{Kr} and late I_{Na} in canine ventricular myocytes, exerted actions consistent with antiarrhythmic activity, since it prevented pause-dependent ventricular arrhythmias induced by positive controls. The specificity of these effects was not evaluated with other QT prolonging drugs that inhibit multiple ionic currents, e.g. terfenadine and cisapride.
- Ranolazine prevented isoproterenol-induced delayed afterdepolarizations in isolated guinea pig ventricular myocytes. This effect is consistent with ranolazine's ability to block β_1 adrenergic receptors at the concentration evaluated.
- Ranolazine lengthened epicardial monophasic action potential duration in isolated guinea pig hearts, while showing effects consistent with antiarrhythmic activity. The sensitivity and specificity of this model has not been thoroughly characterized.
- This sponsor argues that ranolazine lacks proarrhythmic activity since it does not induce early afterdepolarizations, or increase M-cell APD90 and transmural dispersion of repolarization in isolated canine cardiac wedge preparations. Ranolazine was additionally negative for in vitro proarrhythmic effects in this preparation, since *torsade* like arrhythmias did not occur spontaneously and could not be elicited with a single extrastimulus in the drug's presence. Epicardial stimulation was utilized for these studies since stimulation at this site was necessary to capture cisapride's proarrhythmic activity, presumably due to increased transmural dispersion of repolarization at baseline.

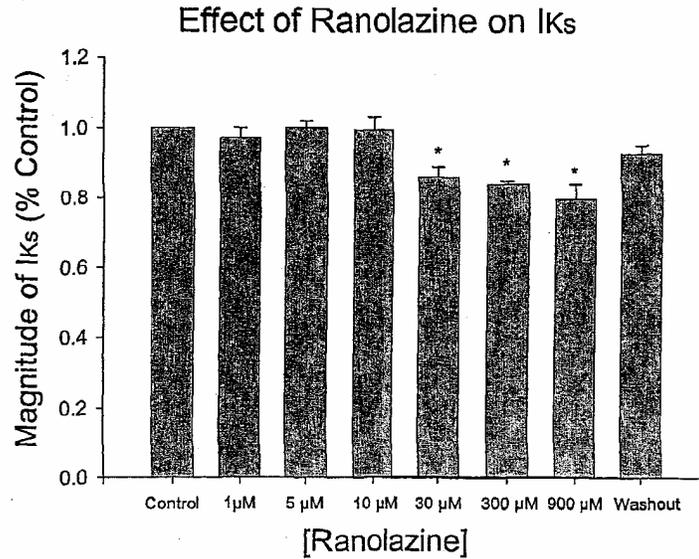
In contrast to the present study results, a previous study showed ranolazine to lengthen M-cell action potential duration and increase transmural dispersion of repolarization, but only in the presence of 2 mM potassium. The lowest potassium concentration evaluated in the present studies was 3 mM. The difference in findings can be explained by the known enhancement of drug-induced I_{Kr} inhibition by hypokalemia.

The individual studies addressed in this memorandum are listed below.

Study Number: Title	Page
CVT303.069-P: Effect of Ranolazine on I_{Ks} in Isolated Canine Left Ventricle Myocytes	3
CVT303.063-P: Effects of Ranolazine Enantiomers on I_{Ks} , I_{Kr} , and Late I_{Na} , and Ranolazine Metabolites on Late I_{Na}	3
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CVT303.069-P: Effect of Ranolazine on I_{Ks} in Isolated Canine Left Ventricle Myocytes

Ranolazine did not inhibit current (I_{Ks}) through human channels (KvLQT1/minK) expressed in *Xenopus* oocytes. Hence, the sponsor concluded that ranolazine at concentrations up to 900 μM does not inhibit I_{Ks} . However, these data do not convincingly show lack of effect of ranolazine on I_{Ks} since the *Xenopus* oocyte expression system greatly underestimates potency.



Effect of Ranolazine on I_{Ks} . Bar graph shows the average change of I_{Ks} tail current under control conditions and after application of increasing concentrations of ranolazine. Bars are mean \pm SEM. * Significantly different at $p < 0.05$ vs. control.

CVT303.063-P: Effects of Ranolazine Enantiomers on I_{Ks} , I_{Kr} , and Late I_{Na} , and Ranolazine Metabolites on Late I_{Na}

Ranolazine enantiomers were evaluated for effects on ionic currents modulating ventricular repolarization in isolated canine ventricular myocytes. Both enantiomers inhibited I_{Kr} and late I_{Na} , but only the S-enantiomer inhibited I_{Ks} , and then only weakly.

Test Substance	IC50 (μM)		
	I_{Kr}	I_{Ks}	Late I_{Na}
R-Ranolazine	28	no inhibition [^]	8
S-Ranolazine	10	>100	5

[^] tested at concentrations up to 100 μM

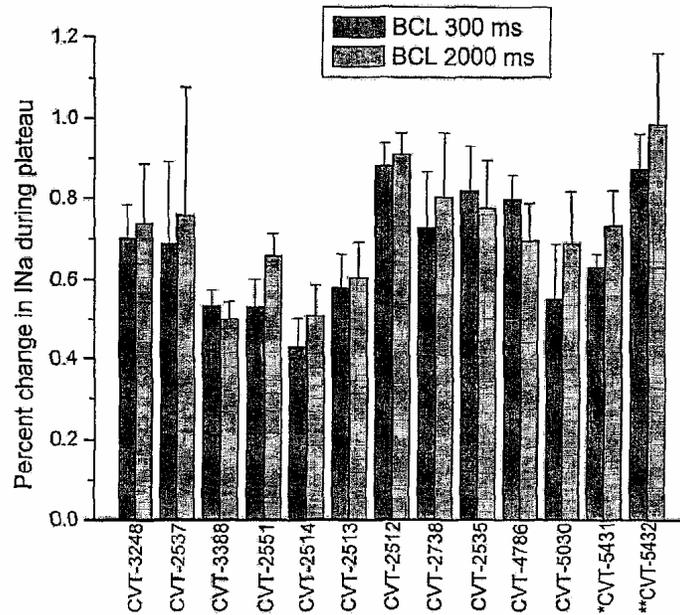
The following table summarizes effects of racemic ranolazine and its enantiomers in the context of positive control drugs. Racemic ranolazine and positive control drugs were not evaluated concurrently. Note that terfenadine and cisapride, both torsadogenic drugs, inhibit both I_{Kr} and late I_{Na} , similar to ranolazine. Furthermore, terfenadine, like ranolazine, is similarly potent on late I_{Na} and I_{Kr} . Therefore, blockade of late I_{Na} does not appear to preclude torsadogenic risk.

Ion Channel Current Inhibition by Ranolazine, Its Enantiomers and Several Comparator Drugs.

	I_{Kr}	I_{Ks}	Late I_{Na}	I_{Ca}	Late I_{Ca}	I_{Na-Ca}	I_{to}
RS-Ranolazine	11	>100	5.9	296	50	91	
R-Ranolazine	28	-	8				
S-Ranolazine	10	>100	5				
Verapamil	3.51	>50	0.33	0.11			
Terfenadine	0.79	-	1.44	1.16			
Risperidone	4.2	>50	13.6	32.5			
Cisapride	0.46	3.5	6.2				
Erythromycin	~80						
HMR 1556	12.6	0.011		27.5			33.9

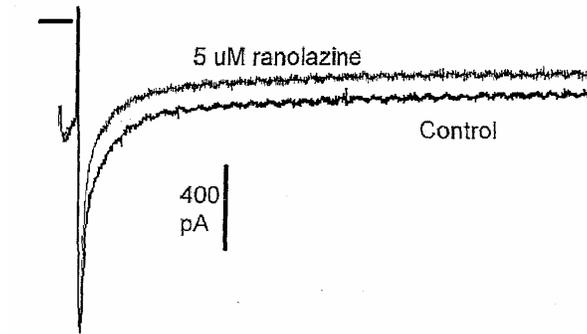
IC_{50} values are shown in μM . All currents were measured in canine ventricular M or epicardial cells.

The following figure illustrates effects of several ranolazine metabolites on late I_{Na} . At a concentration of $10 \mu M$, several ranolazine metabolites inhibited late I_{Na} . Inhibition was independent of basic cycle length (BCL).



CVT303.059-P: Electrophysiologic Effects of Ranolazine on Late I_{Ca} in Isolated Canine Left Ventricular Myocytes

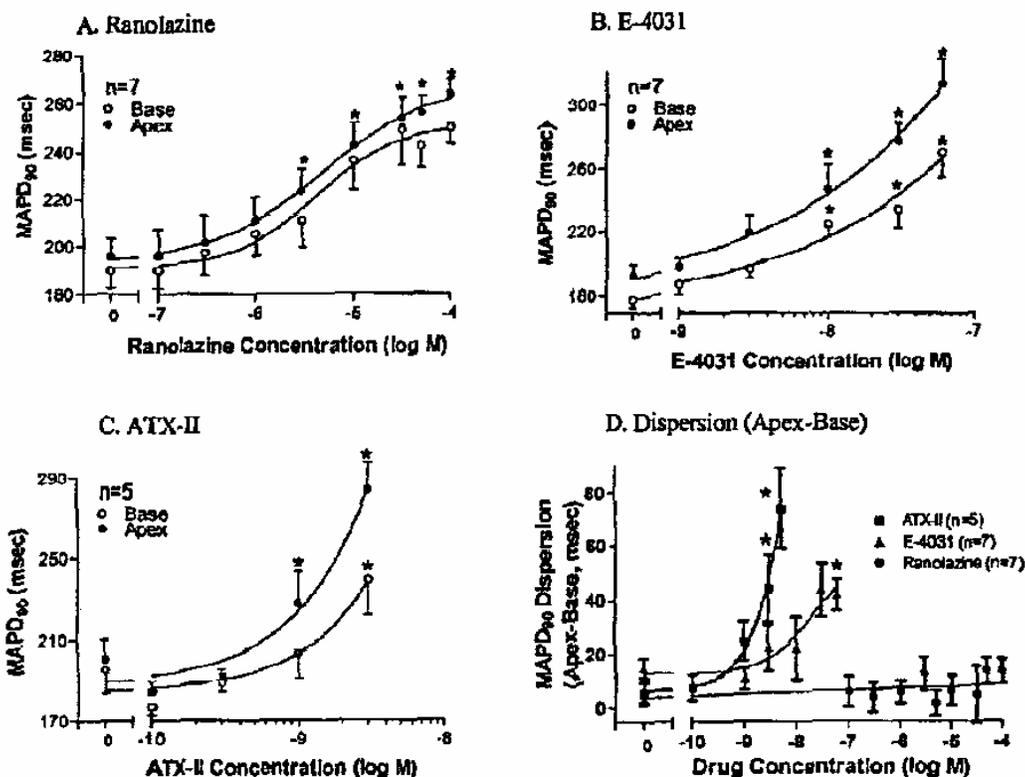
Ranolazine increased the rate of decay of I_{Ca} in isolated left ventricular myocytes. Late I_{Ca} , defined as current measured 300 ms after the start of the test pulse, was inhibited with an IC_{50} of 50 μM . The figure below, which shows the I_{Ca} current trace vs time, illustrates that 5 μM ranolazine inhibited late I_{Ca} while only minimally affecting peak I_{Ca} .



CVT303.065-P: Effects of Ranolazine on Ventricular Repolarization in Isolated Rabbit Hearts

Ranolazine and its enantiomers were evaluated for effects on monophasic action potential duration (MAPD) in isolated female rabbit hearts paced at a constant rate of 1 Hz. Epicardial MAPDs were monitored in base and apex of the heart for determination of spatial dispersion. E-4031, which inhibits I_{Kr} , and ATX-II, which enhances the late I_{Na} , were utilized as concurrent control test substances.

Ranolazine at concentrations of 1-100 μ M increased MAPD in both base and apex in a concentration-related manner. Effects were similar in base and apex, such that the difference between these two sites, or what the sponsor refers to as dispersion, was not altered. Potencies (EC50s) were similar for both sites (4.3 and 4.8 μ M for base and apex, respectively). In comparison, E-4031 and ATX-II increased MAPD and dispersion in a concentration dependent manner. Ranolazine enantiomers also increased MAPD at a single site in a concentration dependent and manner (the site at which MAPD was monitored was not provided). The enantiomers' potencies on MAPD were similar (6.4 and 5.9 M for R and S enantiomers, respectively).



Concentration-response relationships for ranolazine (A), E-4031 (B) and ATX-II (C) to increase the duration of the basal and apical ventricular monophasic action potential (MAPD₉₀) and regional (Apex-Base) differences in MAPD₉₀ prolongation (Dispersion; panel D) in rabbit isolated hearts. Hearts were paced at a rate of 1 Hz. Baseline values for basal and apical MAPD₉₀ were 189±7 and 196±7 msec (n=7) for ranolazine; 178±6 and 191±7 msec (n=7) for E-4031; and 188±15 and 190±10 msec (n=5) for ATX-II treated hearts, respectively. Asterisks indicate values significantly different from those in control of individual group (p<0.05).

Ranolazine, in contrast to E-4031, did not induce ventricular ectopic beats at any concentration evaluated (data not shown). Ranolazine at concentrations of 5 and 10 μ M reduced ventricular ectopic beats induced by E-4031 (data not shown). Additionally, ranolazine at 5 μ M attenuated pause dependent ventricular arrhythmias induced by E-4031 and ATX-II (data not shown). The specificity of this *in vitro* antiarrhythmic effect was not evaluated using other QT prolonging drugs that inhibit multiple ionic currents, e.g. terfenadine or cisapride.

CVT303.070-P: Effects of Ranolazine on Isoproterenol, Forskolin, and Ouabain Induced Delayed Afterdepolarizations and Triggered Activity of Guinea Pig Ventricular Myocytes

Ranolazine at a concentration of 10 μM reduced the amplitude of isoproterenol-induced delayed afterdepolarizations (DADs) and triggered activity in isolated guinea pig ventricular myocytes. Ranolazine did not alter DADs induced by forskolin and ouabain. The effect on isoproterenol-induced DADs is likely due to ranolazine's β_1 adrenergic receptor blockade at the concentration evaluated.

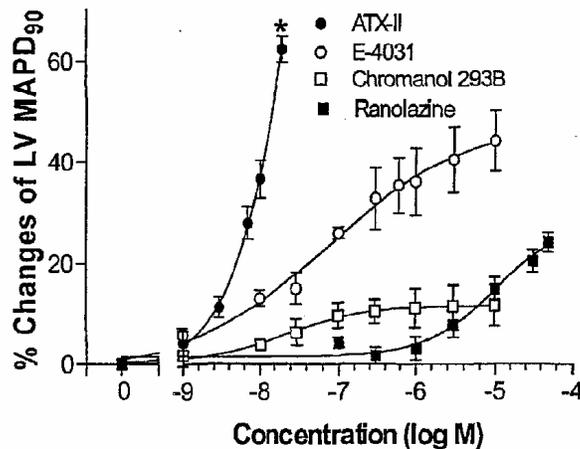
Amplitude of DADs (mV) induced by isoproterenol, forskolin or ouabain before and after addition of ranolazine.

	Isoproterenol (0.1 μM)	Forskolin (3 μM)	Ouabain (20 μM)
Before Ranolazine	11.6 \pm 1.1	9.0 \pm 1.2	10.1 \pm 1.0
After Ranolazine (10 μM)	1.1 \pm 0.5	8.5 \pm 0.9	9.8 \pm 1.4
n	11	6	8
p	< 0.001	0.203	0.840

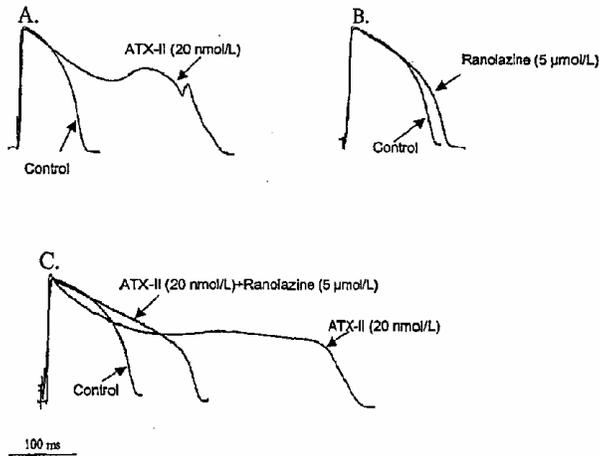
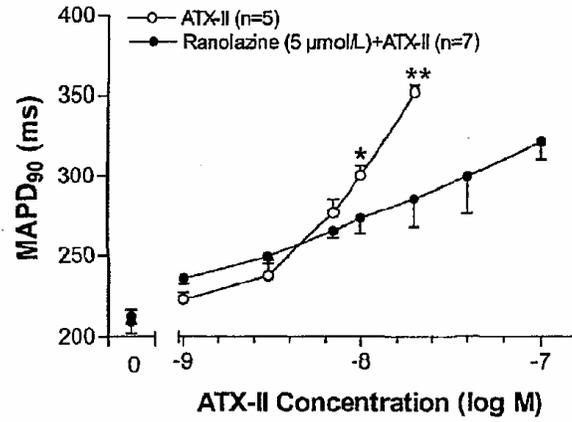
CVT303.061-P: Antiarrhythmic Effects of Ranolazine in a Human LQT Model: The In Vitro Guinea Pig Heart Perfused with the Proarrhythmic Sea Anemone Toxin ATX-II

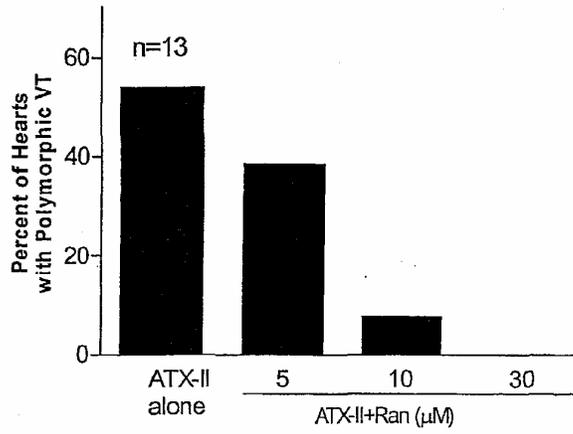
Ranolazine was evaluated for effects on epicardial monophasic action potential duration (MAPD₉₀) in isolated guinea pig hearts (gender not provided) paced at a constant rate of 1.5 Hz. Acute AV block was induced by infusion of N⁶-cyclopentyladenosine, which blocks adenosine receptors. E-4031, which selectively inhibits I_{Kr}, ATX-II, which selectively enhances the late I_{Na}, and chromanol 293, which inhibits I_{Ks}, were utilized as concurrent control test substances. In an additional experiment, rate dependence of ranolazine was compared to that of the positive control test substances.

Ranolazine at concentrations of 1-100 μM lengthened epicardial MAPD₉₀ in a concentration dependent manner, similar to positive control substances. Ranolazine's effects on MAPD₉₀ were independent of pacing cycle length, ranging from 400 to 1000 ms (data not shown). In contrast, E-4031 and ATX-II but not chromanol 293B showed inverse rate dependence, with greater percentage increases at a basic cycle length of 1000 ms than at 400 ms.

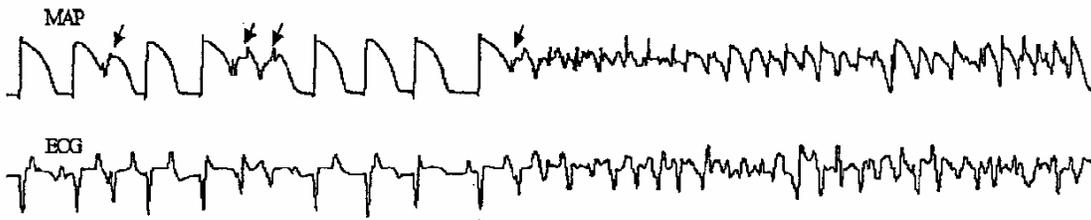


Ranolazine attenuated MAPD lengthening and prevented early afterdepolarizations and polymorphic ventricular tachycardia induced by ATX-II in a concentration related manner. Effects of positive control drugs that inhibit multiple ionic currents (including the late I_{Na}), e.g. terfenadine and cisapride, were not evaluated.

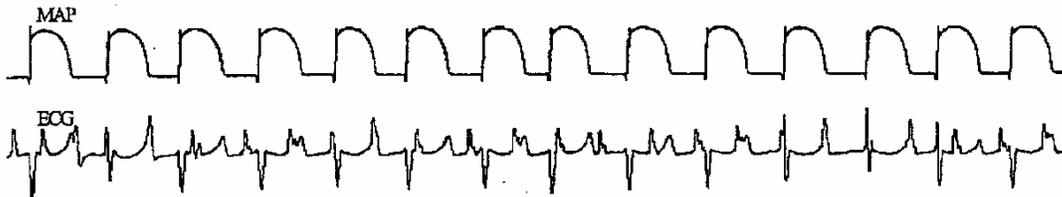




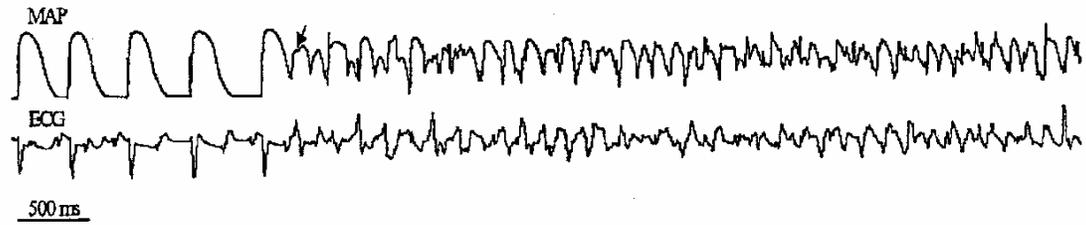
A. ATX-II (20 nmol/L)



B. ATX-II (20 nmol/L)+Ranolazine (5 μmol/L)



C. ATX-II (20 nmol/L) after washout ranolazine



CVT303.068-P: Electrophysiologic Effects of Ranolazine in Arterially Perfused Wedge Preparations from the Canine Left Ventricle: A comparison Between Epicardial and Endocardial Stimulation

Endocardial stimulation appears to sensitize the isolated canine left ventricular wedge preparation to arrhythmias induced by QT prolonging drugs, since cisapride's proarrhythmic effect in this model was captured with epicardial, but not with endocardial stimulation. Ranolazine was previously evaluated using endocardial stimulation; however, effects with epicardial stimulation have not yet been evaluated.

The purpose of the present study was to evaluate the in vitro electrophysiologic effects of ranolazine in canine wedges stimulated from the epicardial surface. Results were compared to those using endocardial stimulation in the same experiment. Both normokalemic (4 mM potassium) and hypokalemic (3 mM potassium) conditions were utilized, as was pacing the preparations at both short and long basic cycle lengths (500 and 2000 ms) to address rate dependence of effects.

With epicardial stimulation and normokalemia, ranolazine at concentrations of 1-100 μM did not lengthen M-cell or epicardial action potential duration (APD90). With epicardial stimulation and hypokalemia, ranolazine at 100 μM lengthened epicardial but not M-cell APD90.

While ranolazine prolonged transmural QT interval and increased Tpeak –Tend in a concentration dependent manner, it did not lengthen M-cell action potential duration or transmural dispersion of repolarization (TDR) under any conditions. Indeed, ranolazine decreased TDR when evaluated with hypokalemia, likely due to a proportionately greater increase in epicardial vs M-cell APD90.

Canine Left Ventricular Wedge: 4 mM [K]_o, BCL=2000 msec, epicardial stimulation

Concentration	Epicardium		M region		QT _{end}	Tpeak-Tend Area	T _{peak} – T _{end}	TDR
	APD50 \pm SE	APD90 \pm SE	APD50 \pm SE	APD90 \pm SE				
control	193.5 \pm 9.7	231.8 \pm 10.0	218.8 \pm 10.6	275.3 \pm 12.0	291.3 \pm 7.5	20.1 \pm 2.3	47.5 \pm 1.6	63.7 \pm 4.0
1 μM	194.4 \pm 8.1	238.2 \pm 9.8	221.0 \pm 2.6	279.5 \pm 7.9	297.4 \pm 7.5	17.2 \pm 2.2	47.4 \pm 2.5	58.6 \pm 5.7
5 μM	204.4 \pm 10.1	245.8 \pm 9.4	226.0 \pm 6.7	290.2 \pm 8.3	303.4 \pm 7.6*	16.3 \pm 2.0	47.1 \pm 2.7	63.7 \pm 4.3
10 μM	202.5 \pm 8.2	252.3 \pm 7.3	224.8 \pm 3.3	292.4 \pm 8.4	311.7 \pm 6.0*	14.7 \pm 2.3	51.8 \pm 3.0	59.9 \pm 6.3
100 μM	179.4 \pm 7.5	244.2 \pm 4.1	193.4 \pm 3.4	285.4 \pm 4.6	330.2 \pm 6.9*	16.3 \pm 3.2	77.4 \pm 8.3*	65.2 \pm 5.9

* p<0.05 vs. control

n=5

Canine Left Ventricular Wedge: 3 mM [K]_o, BCL=2000 msec, epicardial stimulation

Concentration	Epicardium		M region		QT _{end}	Tpeak-Tend Area	T _{peak} – T _{end}	TDR
	APD50 \pm SE	APD90 \pm SE	APD50 \pm SE	APD90 \pm SE				
control	190.1 \pm 10.4	237.7 \pm 10.7	224.9 \pm 13.0	282.1 \pm 13.4	302.6 \pm 12.4	17.8 \pm 3.8	50.9 \pm 2.7	60.6 \pm 1.9
1 μM	199.5 \pm 8.9	245.4 \pm 10.7	228.5 \pm 12.2	290.4 \pm 12.9	310.7 \pm 12.1	18.9 \pm 4.5	60.5 \pm 5.1	62.6 \pm 4.6
5 μM	205.0 \pm 7.4	253.2 \pm 11.0	223.2 \pm 11.4	295.5 \pm 13.6	322.2 \pm 11.2*	15.3 \pm 2.5	56.2 \pm 3.9	63.7 \pm 4.4
10 μM	209.5 \pm 6.5	269.5 \pm 7.8	234.1 \pm 9.5	307.2 \pm 7.3	337.8 \pm 13.0*	15.1 \pm 2.0	61.8 \pm 5.8*	59.3 \pm 4.3
100 μM	192.6 \pm 14.2	294.7 \pm 11.5*	194.4 \pm 10.5	307.8 \pm 8.4	356.3 \pm 18.5†*	12.3 \pm 1.5‡	70.6 \pm 5.6†*	32.4 \pm 8.3*

* p<0.05 vs. control

n=5 (unless otherwise noted) †n=3

With endocardial stimulation, ranolazine at concentrations of 1-100 μM did not lengthen M-cell or epicardial action potential duration (APD90). Effects were independent of potassium concentration. Ranolazine prolonged transmural QT interval in a biphasic manner, with peak effects at 5-10 μM . Ranolazine increased Tpeak – Tend over control values, but only at the highest concentration evaluated. Ranolazine did not significantly lengthen M-cell action potential duration or increase transmural dispersion of repolarization (TDR). Ranolazine's electrophysiologic effects were similar at basic cycle lengths of 500 and 2000 ms (only effects at 2000 ms are shown).

Canine Left Ventricular Wedge: 4 mM [K]_o, BCL=2000 msec, endocardial stimulation

Concentration	Epicardium		M region		QT _{end}	Tpeak-Tend Area	T _{peak} – T _{end}	TDR
	APD50 \pm SE	APD90 \pm SE	APD50 \pm SE	APD90 \pm SE				
control	187.0 \pm 7.3	227.6 \pm 9.4	218.0 \pm 10.2	275.4 \pm 11.6	282.5 \pm 8.4	6.3 \pm 1.5	24.9 \pm 1.9	29.5 \pm 2.1
1 μM	192.4 \pm 6.3	236.6 \pm 8.4	220.0 \pm 1.4	279.4 \pm 7.3	290.2 \pm 8.5	6.4 \pm 2.6	26.0 \pm 2.9	26.4 \pm 2.7
5 μM	198.0 \pm 8.2	241.8 \pm 8.3	223.8 \pm 6.3	288.5 \pm 8.2	301.8 \pm 8.7*	5.8 \pm 2.4	29.1 \pm 3.4	29.4 \pm 5.2
10 μM	199.7 \pm 8.6	249.8 \pm 6.4	225.2 \pm 2.1	292.0 \pm 8.6	307.2 \pm 7.4*	6.0 \pm 2.4	30.8 \pm 2.5	26.0 \pm 4.1
100 μM	171.0 \pm 4.8	238.5 \pm 2.8	192.9 \pm 4.4*	284.8 \pm 4.3	318.8 \pm 1.3†	8.3 \pm 3.2‡	47.1 \pm 3.8‡	28.5 \pm 7.6

* p<0.05 vs. control. n=5 (unless otherwise noted) †n=3 In this and all other tables, measurements are in the following units APD, QT, Tpeak-Tend and TDR are in msec, whereas Tpeak-Tend Area is in mV*msec.)

Canine Left Ventricular Wedge: 3 mM [K]_o, BCL=2000 msec, endocardial stimulation

Concentration	Epicardium		M region		QT _{end}	Tpeak-Tend Area	T _{peak} – T _{end}	TDR
	APD50 \pm SE	APD90 \pm SE	APD50 \pm SE	APD90 \pm SE				
control	186.4 \pm 8.6	234.9 \pm 10.3	228.6 \pm 12.9	285.9 \pm 14.3	293.0 \pm 12.6	5.3 \pm 2.4	33.1 \pm 4.0	29.5 \pm 7.7
1 μM	192.2 \pm 9.2	240.0 \pm 11.0	229.8 \pm 13.9	289.7 \pm 14.6	300.3 \pm 12.8	5.2 \pm 1.7	33.7 \pm 2.7	28.7 \pm 7.2
5 μM	193.6 \pm 9.1	250.6 \pm 10.8	226.5 \pm 11.7	298.4 \pm 13.7	314.4 \pm 11.5*	3.3 \pm 1.0	34.8 \pm 3.0	26.0 \pm 5.4
10 μM	198.9 \pm 7.7	262.1 \pm 8.2	236.4 \pm 8.9	307.9 \pm 7.0	318.8 \pm 8.8	3.9 \pm 1.1	32.6 \pm 1.6	25.0 \pm 5.6
100 μM	181.6 \pm 14.7	285.3 \pm 10.1*	198.4 \pm 12.0	312.2 \pm 9.6	347.7 \pm 16.2†*	3.6 \pm 0.5‡	47.0 \pm 4.8‡	12.9 \pm 3.7

* p<0.05 vs. control n=5 (unless otherwise noted) †n=3

Ranolazine did not induce *torsade de pointes* - type arrhythmias in vitro in canine left ventricular wedges using epicardial stimulation.

Test Substance	Potassium (μM)	Spontaneous Arrhythmia	Stimulation-induced Arrhythmia [^]
Ranolazine (1-100 μM)	4	0/5	0/5
Ranolazine (1-100 μM)	3	0/5	0/5

[^] The sponsor attempted to induce ventricular arrhythmias using a single extrastimulus applied to the epicardial surface at progressively shorter intervals until refractoriness was reached. This methodology was successful in eliciting ventricular arrhythmias in 2 of 6 wedge preparations exposed to cisapride (0.2 μM). Spontaneous arrhythmias were not observed with cisapride. Cisapride's proarrhythmic effects were limited to a single concentration, with slightly higher and lower concentrations yielding no arrhythmias.

Assessing Predictors of Drug-Induced *Torsade de Pointes*

The sponsor provided a manuscript arguing that delayed ventricular repolarization and proarrhythmia are separable, i.e. drugs that do not induce early afterdepolarizations or increase dispersion of repolarization are unlikely to cause TdP, even in the setting of prolonged QT.

Sponsor's Abstract

Torsades de Pointes (TdP) is a malignant polymorphic ventricular tachyarrhythmia that can be caused by drugs that induce electrophysiological changes. Although the number of drugs known to cause TdP has increased in recent years, there is no cell-based assay, *in vitro* heart preparation, or animal model that predicts a drug's potential to induce TdP in humans. Nevertheless, certain electrophysiologic events are known to be associated with the development of TdP. A drug that prolongs action potential duration, induces early afterdepolarizations and ectopic beats, and increases dispersion of ventricular repolarization is very likely to cause TdP. By contrast, a drug that does not induce these changes is unlikely to cause TdP. The exact relationship between prolonged action potential duration, early afterdepolarizations, ectopic beats, increased dispersion of ventricular repolarization, and the development of TdP has not been defined, but the potential of a drug to elicit these events might predict its pro-arrhythmic risk.

The sponsor supports the hypothesis that torsadogenic drugs are always associated with early afterdepolarizations and spatial dispersion of repolarization with data from several *in vitro* models. The sponsor did not provide a comprehensive assessment of the sensitivity and specificity of any single model.