

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-325

PHARMACOLOGY REVIEW(S)

NDA 22325

PHARMACOLOGY REVIEW OF ORIGINAL 505(b)(2) APPLICATION

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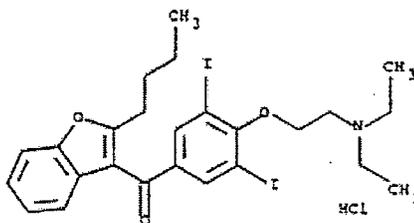
REVIEWER: John Koerner, Ph.D.
Senior Pharmacologist
Division of Cardiovascular and Renal Products

SPONSOR: Prism Pharmaceuticals, Inc.

DRUG

Code Name: PM101 or Captisol-Enabled Amiodarone
General/ Generic Name: Amiodarone HCl
Trade Name: NEXTERONE IV
Empirical Formula: $C_{25}H_{29}I_2NO_3 \cdot HCl$
CAS Number:
Chemical Structure

b(4)



M.W., 681.8

PHARMACOLOGICAL CLASS: Antiarrhythmic agent

PROPOSED USE: Treatment and prophylaxis of frequently occurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy.

FORMULATION AND ROUTE OF ADMINISTRATION: NEXTERONE IV is a sterile clear, colorless to slightly yellow solution visually free from particulates. Each ml of NEXTERONE IV contains 50 mg of amiodarone HCl, 225 mg sulfobutylether beta-cyclodextrin sodium (Captisol) and water for injection. NEXTERONE IV is to be diluted in D5W or normal saline prior to intravenous administration.

PROPOSED DOSING REGIME: _____ 150 mg over 10 minutes is followed by 1mg/min for 6 hours, followed by 0.5 mg/min for the remainder of the 24 hour period.

Related Applications: NDA 20377, CORDARONE IV

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EXECUTIVE SUMMARY

Amiodarone is a marketed drug and the need for a new drug application is dictated by the new dosing formulation and dosing regime. The currently marketed amiodarone (Cordarone IV), the reference listed drug product for this 505(b)(2) application, produces hypotension in patients that is attributed to the co-solvents used in its formulation (polysorbate 80 and benzyl alcohol). The dosage and administration section of the Cordarone IV labeling recommends infusing the product over 10 minutes to minimize the potential for hypotension. The sponsor believes

The sponsor provided nonclinical pharmacology data supporting this distinction. Captisol-Enabled Amiodarone (PM101) at the recommended human dose (2.14 mg/kg over 2 seconds + 0.014 mg/kg/min iv) did not produce hypotension in anesthetized dogs, whereas the positive comparator, Cordarone IV given at a dose of 2.14 mg/kg over 10 minutes + 0.014 mg/kg/min produced hypotension in this study. A 10-fold higher dose of either Captisol-Enabled Amiodarone or Cordarone IV produced hypotension secondary to drug-related reductions in cardiac output and cardiac contractility. This distinction could not be made in conscious telemeterized monkeys, in which both Captisol-Enabled Amiodarone and Cordarone IV given intravenously at a dose of 5 mg/kg over 3 minutes were without effects on blood pressure. In these studies (anesthetized dogs and conscious telemeterized monkeys), neither Captisol-Enabled Amiodarone nor Cordarone IV affected ECGs.

In another study, Captisol-Enabled Amiodarone and Amiodarone IV given intravenously at 2.14 mg/kg over 2 seconds +/- 0.014 mg/kg/min for 20 minutes tested negative for electrophysiological effects in anesthetized open chest dogs. Increasing the bolus dose 10-fold to 21.4 mg/kg or the maintenance dose 50-fold to 0.7 mg/kg/min for 20 minutes yielded electrophysiological effects consistent with depression of AV and sinus nodal function (decreased Wenckebach rate, increased AH and HV intervals, increased sinus nodal recovery time), as well as an increase in atrial effective refractory period. Fatal AV block was observed with both drug products at the 10-fold higher bolus dose, and the 50-fold higher maintenance dose. The LOAEL (bolus dose) for this effect was 21.4 mg/kg over 2 seconds for both drug products. Additionally, both drug products were associated with pacing-induced ventricular tachycardia degenerating into VF. The LOAEL (bolus dose) for this effect was 2.14 mg/kg over 2 seconds for Captisol-Enabled Amiodarone and 21.4 mg/kg over 2 sec for Amiodarone IV, respectively. Intermediate doses were not evaluated; therefore the LOAEL could be lower than the present estimate. This highlighted the potential for life-threatening arrhythmias with rapid administration of either drug product.

The sponsor evaluated Captisol-Enabled Amiodarone and Cordarone IV in a 2 week canine intravenous toxicology study. There were no adverse effects observed at the dose administered (5 mg/kg + 10.3 mg/kg/day for 14 days). The steady state plasma amiodarone concentrations observed in this study were similar between these 2 treatment groups, and therefore independent of the change in formulation.

In no study did the sponsor compare plasma amiodarone concentrations following a 2 sec vs a 10 minute initial dosing regime. Therefore, there is no nonclinical pharmacokinetic data comparing these 2 dosing regimes.

Captisol-Enabled amiodarone produced hemolysis in vitro in human blood, but only at a concentration of 50 mg/ml, which suggest this is not an issue clinically. Captisol-Enabled amiodarone appeared to precipitate in plasma and pH-7.63 buffer, similar to Cordarone IV. The precipitating concentrations were as low as 1.0 mg/ml and 1.5 mg/ml, respectively, for Captisol-Enabled amiodarone and Cordarone IV concentrations. Given similar findings with these 2 formulations, and abundant clinical experience with Cordarone IV, this finding also seems clinically irrelevant.

Recommendation for Additional Nonclinical Studies

This reviewer recommends further nonclinical evaluation of the proarrhythmic potential of the rapid, 2 second, bolus dosing regime of Captisol-Enabled Amiodarone using programmed electrical stimulation to determine if the ventricular tachycardia/fibrillation observed in anesthetized dogs with ventricular pacing is a drug effect.

The rationale for this study follows. Induction of ventricular tachycardia/ventricular fibrillation suggests that at high doses, or rapid administration, amiodarone non-uniformly slows conduction velocity or alters refractoriness, which in turn allows for development of unidirectional block and reentry loops that is revealed by ventricular pacing. If this is a true drug effect, programmed electrical stimulation designed to induce ventricular tachycardia should reveal it.

b(4)

Label Recommendations

The sponsor's proposed label allows for _____

- *Reviewer recommendation: This _____ should be deleted from the proposed label*

b(4)

Section 8. USE IN SPECIAL POPULATIONS

Section 8.1 Pregnancy and Section 8.2 Labor and Delivery

- *Reviewer recommendation: No changes are needed since the wording is identical to the Cordarone IV label.*

Section 12. CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

- *Reviewer recommendation:
The paragraph-*

[

]

- *should be deleted since _____*
- *or the paragraph could be expanded to include the following: "Higher doses produce negative inotropic and hemodynamic effects in animals similar to Cordarone IV."*

b(4)

Section 13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

- *Reviewer recommendation: No changes are needed since the wording is identical to the Cordarone IV label.*

PHARMACOLOGY STUDIES

Study Title: An Examination of the Cardiovascular Effects of PM101, Captisol, and Cordarone IV on Anesthetized Female Beagle Dogs (CorDynamics Study Number 798-0601)

Key Findings: PM101 (2.14 mg/kg) given intravenously as a bolus over 2 seconds to anesthetized female beagle dogs did not affect hemodynamics or heart rate. PM101 given as a bolus over 2 seconds at a 10 fold higher dose (21.4 mg/kg) decreased blood pressure, systemic vascular resistance, cardiac output, left ventricular developed pressure and contractility (+/- LV dP/dt), and heart rate.

Amiodarone IV, given intravenously decreased blood pressure, cardiac output, and left ventricular +/- dP/dt at all dose levels evaluated. The LOEL was 2.14 mg/kg over 10 minutes. Heart rate was altered in a biphasic manner, with elevations seen at 2.14 mg/kg and little to no change observed at 21.4 mg/kg, suggesting reflex tachycardia at the lower dose and direct depression at the higher dose.

PM101 (21.4 mg/kg) and amiodarone (21.4 mg/kg) given over 2 seconds prolonged PR interval.

Study Number: N103

Report Status: Final and quality assured

Study Initiation Date: 13Nov2006

Study Facility: CorDynamics, Inc.
2242 W. Harrison St.
Chicago, IL 60612

GLP Compliance: Yes

Animals: Female Beagle Dogs

Number/dose: 7

Age: 7-13 months

Body weight: 6-12 kg

Drug: PM101

Lot Number: 7041

Vehicle: D5W (5% dextrose in water)

Vehicle: Captisol (lot# CD083.87)

Reference Drug: Amiodarone IV solution (50 mg/ml, lot# 401858)

Vehicle Polysorbate 80/benzyl alcohol

Methods

Female beagle dogs were anesthetized (morphine, α -chloralose) and instrumented for measurement of arterial blood pressure, left ventricular pressure, +/- LV dP/dt, cardiac output, systemic vascular resistance, heart rate and lead II ECGs. ECG parameters monitored were PR, QRS, QT, QTc (Bazett), QTcFredericia, and QTc (van der water) intervals. PM101, amiodarone IV, and vehicle were administered intravenously over a 2 second or 10 minute time period. Each dog received a single treatment and was monitored for 60 minutes prior to sacrifice. Blood samples were taken from dogs given PM101 (2.14 mg/kg over 2 seconds) at 0, 1, 5, 10, 20, 40, 60, 90 and 120 minutes for determination of plasma amiodarone levels. Plasma amiodarone levels were not evaluated in any other treatment groups.

Treatment groups are shown below.

Group	Test Compound	Dose Concentration	Dose (mg/kg)	Volume (mL/kg)	Duration of Dosing	Duration of Experiment (hours)	Number of Female Dogs
1 ^a	D5W	NA	NA	0.043	2 sec.	1	7
2	Captisol	225 mg/mL	NA	0.043	2 sec.	1	7
3	Captisol	225 mg/mL	NA	0.428	2 sec.	1	7
4	PM101	50 mg/mL ^b	2.14	0.043	2 sec.	2 ^c	7
5	PM101	50 mg/mL ^b	21.4	0.428	2 sec.	1	7
6	Amiodarone IV	1.5 mg/mL ^d	2.14	1.43	10 min. ^d	1	7
7	Amiodarone IV	50 mg/mL	2.14	0.043	2 sec.	1	7
8	Amiodarone IV	50 mg/mL	21.4	0.428	2 sec.	1	7
9	Amiodarone IV Excipients ^e	NA	NA	1.43	10 min. ^f	1	7
10	Amiodarone IV Excipients ^e	NA	NA	0.043	2 sec.	1	7
11	Amiodarone IV Excipients ^e	NA	NA	0.428	2 sec.	1	7

^a Sham control was instrumented and dosed with D5W to match-by-volume Group 4 regimen.
^b Contained 225 mg/mL Captisol.
^c 2 hour dosing period enabled extended test compound in plasma bleed points to correlate with possible future studies.
^d 50 mg/mL preparation diluted with D5W to match current human dosing regimen for Amiodarone IV.
^e Amiodarone IV excipient mixture contained 20.2 mg/mL benzyl alcohol (FW 108.14), 100 mg polysorbate 80 (density = 1.064 g/mL), remainder water for injection.
^f Amiodarone IV excipient mixture diluted as in Group 6 with D5W.
Note: Amiodarone IV dosing was with Amiodarone IV Reference Listed Drug (ANDA 75-761; Lot#401858)

Results

All animals survived until scheduled sacrifice.

Bolus (2 sec) administration of D5W and captisol (groups 1, 2, and 3) did not affect hemodynamics.

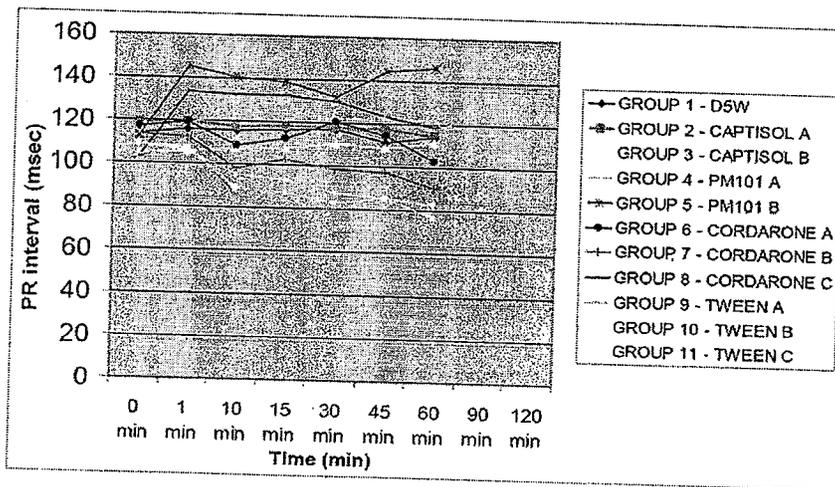
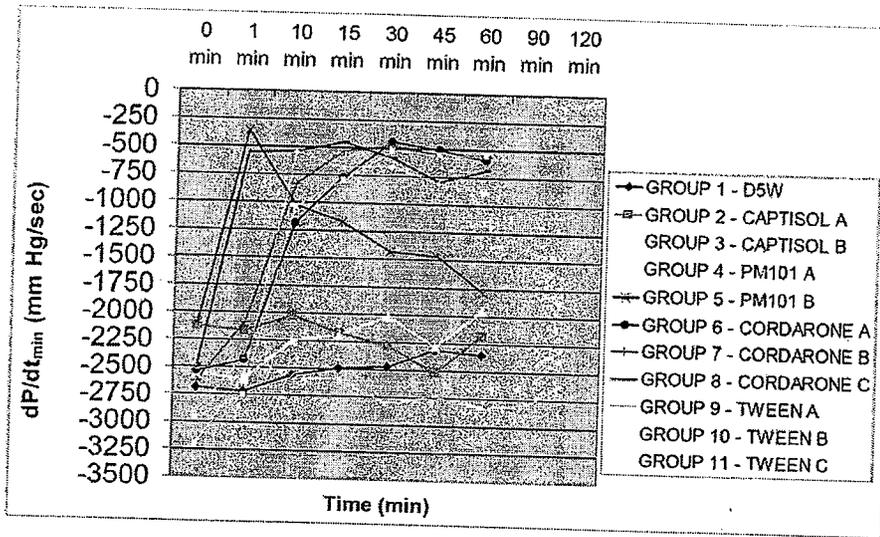
PM101 (2.14 mg/kg) given as a 2 second bolus (group 4) did not affect hemodynamics. PM101 (21.4 mg/kg) given as a 2 second bolus (group 5) decreased mean aortic pressure, systemic vascular resistance, cardiac output, and left ventricular developed pressure and contractility (+/- LV dp/dt) within one minute of administration with rapid recovery of cardiovascular function starting at approximately 10 minutes after dose.

Amiodarone IV at all doses and dose regimens tested (groups 6-8) decreased cardiac output, mean aortic pressure, systemic vascular resistance, and left ventricular contractility (+/- LV dp/dt) within one minute of administration. Systemic and left ventricular pressures in Amiodarone IV-treated animals did not recover during the 60 minutes of the study.

Heart rate was elevated in dogs given Amiodarone IV at 2.14mg/kg (groups 6, 7); this tachycardia is likely reflex given the decrease in blood pressure. Tachycardia was not observed in dogs given Amiodarone IV 21.4mg/kg (group 8), suggesting a direct drug effect to depress heart rate.

Administration of amiodarone IV excipients (groups 9-11), produced effects on cardiovascular parameters similar to those seen in dogs given Amiodarone IV, suggesting that the effects of Amiodarone IV were at least partially due to these excipients.

PM101 (21.4 mg/kg) and amiodarone (21.4 mg/kg) increased PR interval (groups 5 and 8, respectively). No other ECG effects, including effects on QTc were observed in any treatment group (data not shown).



Pharmacokinetic parameters for plasma amiodarone levels determined in dogs given PM101 (2.14 mg/kg over 2 seconds) are shown below. Amiodarone plasma levels peaked at 1 minute following dosing and declined biexponentially with a mean terminal $t_{1/2}$ of 64.1 minutes.

Dose Group	Dose Level (mg/kg)	Gender		C_{max} (ng/mL)	C_0 (ng/mL)	T_{max} (min)	AUC_{0-120} (ng·min/mL)	$AUC_{0-\infty}$ (ng·min/mL)	$t_{1/2}$ (min)	CL (mL/min/kg)	V_z (mL/kg)
4	2.14	F	Mean	13571	21463	1.00	75169	83301	64.1	26.7	2481
			SD	3454	5410	0	17867	19017	5.9	5.5	568
			N	7	7	7	7	7	7	7	7

C_{max} , maximum observed concentration in plasma

C_0 , plasma concentration extrapolated to time zero

T_{max} , time to maximum observed concentration

AUC_{0-120} , area under the plasma concentration-time curve from time 0 to 120 minutes

$AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity

$t_{1/2}$, terminal elimination phase half-life, determined by $\ln(2)/\lambda_z$

CL, total drug clearance.

V_z , volume of distribution

Individual and mean amiodarone concentrations for these same animals are shown below.

			Plasma Amiodarone Concentrations (ng/ml)										
Dose Group	Dose Level (mg/kg)	Gender	Animal	Time After Dosing (Minutes)									
				0	1	5	10	20	40	60	90	120	
4	2.14	F	3	< 25.0	20700	3290	1090	408	211	149	120	109	
			11	< 25.0	11200	1560	549	229	118	91.5	78.9	63.4	
			15	< 25.0	11600	2000	645	284	181	140	113	85.9	
			18	< 25.0	13000	2540	785	322	165	202	136	107	
			21	< 25.0	10600	1470	501	204	129	96.3	88.1	67.0	
			29	< 25.0	13000	2060	592	284	169	123	95.7	87.2	
			39	< 25.0	14900	2370	818	284	149	126	112	96.5	
			Mean	0	13571	2184	711	288	160	133	106	88.0	
			SD	0	3454	624	204	66	32	37	20	17.9	
			CV %	NA	25	29	29	23	20	28	19	20	

Note: Values below the limit of quantitation (< 25.0) were treated as zero in descriptive statistical calculations.

Study Title: **A Six-Hour Examination of the Cardiovascular Effects of PM101 and Cordarone IV on Anesthetized Female Beagle Dogs (CorDynamics Study Number 798-0702)**

Key Findings: PM101 (2.14 mg/kg, iv) given as a bolus over 2 seconds followed by a constant infusion of 0.014 mg/kg/min for 6 hrs did not affect hemodynamics, heart rate or the ECG in anesthetized female beagle dogs.

Amiodarone IV (2.14 mg/kg iv) given over 2 seconds or 10 minutes followed by a constant infusion of 0.014 mg/kg/min for about 6 hrs decreased blood pressure, cardiac output, left ventricular +/- dP/dt, and PR interval, and increased systemic vascular resistance and heart rate. Effects were similar in these 2 dose groups.

Amiodarone IV given as a constant infusion of 0.014 mg/kg/min for 6 hrs produced similar effects as the bolus plus infusion regime, but with a somewhat slower onset.

Study Number: N107

Report Status: Final and quality assured

Study Initiation Date: 7Aug2007

Study Facility: CorDynamics, Inc.
2242 W. Harrison St.
Chicago, IL 60612

GLP Compliance: Yes

Animals: Female Beagle Dogs

Number/dose: 7

Age: 8-17 months

Body weight: 6.8-12.7 kg

Drug: PM101

Lot Number: 7041

Vehicle: D5W (5% dextrose in water)

Vehicle: Captisol (lot# CD083.87)

Reference Drug: Amiodarone IV solution (50 mg/ml, lot# 401858)

Methods

Female beagle dogs were anesthetized (morphine, α -chloralose) and instrumented for measurement of arterial blood pressure, left ventricular pressure, +/- LV dP/dt, cardiac output, systemic vascular resistance, heart rate and lead II ECGs. ECG parameters monitored were PR, QRS, QT, QTc (Bazett), QTcFredericia, and QTc (van der water) intervals. PM101, amiodarone IV, and vehicle were administered intravenously over a 2 second or 10 minute time period. Each dog received a single treatment and monitored until sacrifice 6 hours later.

Treatment groups are shown below.

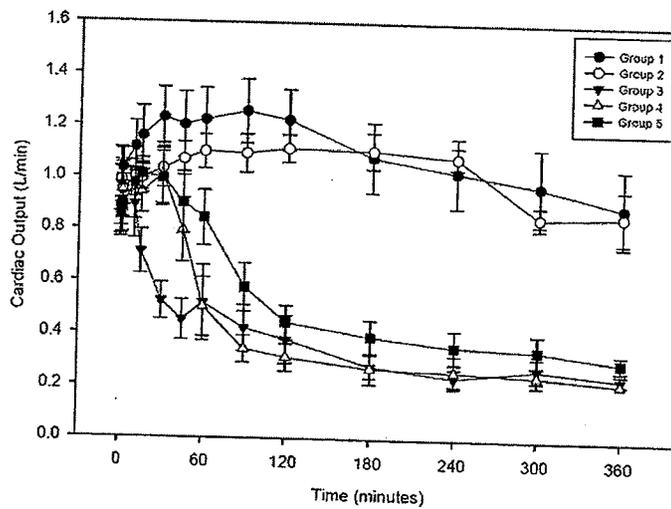
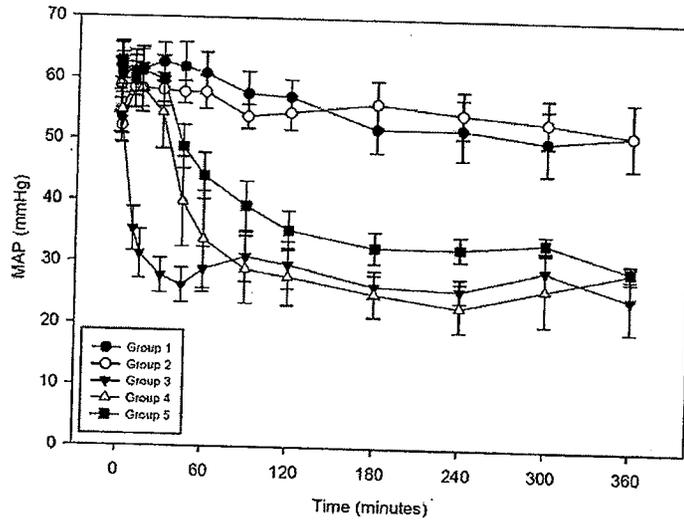
- Group 1. Vehicle (D5W): 0.043 mg/kg iv over 2 seconds + 0.0078 ml/kg/min iv for 6 hrs
- Group 2. PM101: 2.14 mg/kg iv over 2 seconds + 0.014 mg/kg/min iv for 6 hrs
- Group 3. Amiodarone IV: 2.14 mg/kg iv over 10 minutes + 0.014 mg/kg/min iv for 5 hrs 50 min
- Group 4. Amiodarone IV: 2.14 mg/kg iv over 2 seconds + 0.014 mg/kg/min iv for 6 hrs
- Group 5. Amiodarone IV: 0.014 mg/kg/min iv for 6 hrs

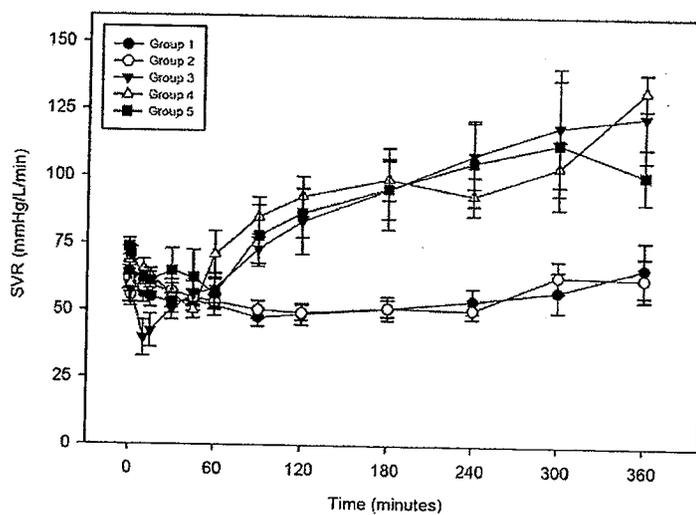
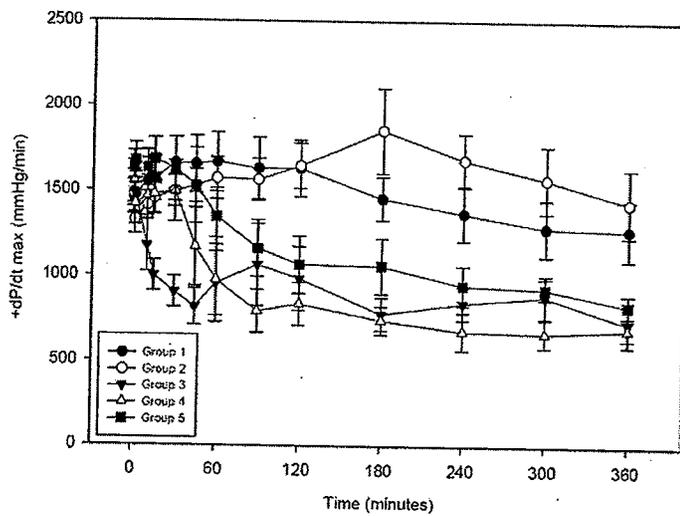
Results

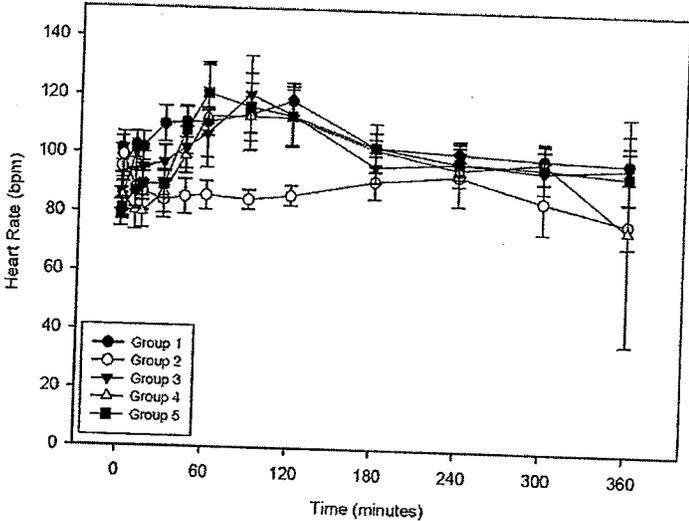
PM101 (2.14 mg/kg, iv) given as a bolus over 2 seconds plus a constant infusion of 0.014 mg/kg/min for 6 hrs did not affect hemodynamics, heart rate or the ECG in anesthetized female beagle dogs.

Amiodarone IV (2.14 mg/kg iv) given over 2 seconds or 10 minutes, followed by a constant infusion of 0.014 mg/kg/min for about 6 hrs decreased blood pressure, cardiac output, left ventricular +/- dP/dt, and PR interval, and increased systemic vascular resistance and heart rate. Effects were similar in these 2 treatment groups.

Amiodarone IV given as a constant infusion of 0.014 mg/kg/min for 6 hrs produced similar effects as the bolus plus infusion regime, but with a somewhat slower onset.







Study Title:

An Examination of the Cardiovascular Electrophysiology Effects of PM101, Captisol and Amiodarone HCl IV Reference Listed Drug in Anesthetized Female Beagle Dogs (CorDynamics Study Number 7 98-07 01)

Key Findings:

PM101 (2.14 mg/kg iv over 2 seconds +/- 0.014 mg/kg/min iv for 20 minutes) tested negative for electrophysiologic effects in anesthetized open chest dogs, as did Captisol.

Amiodarone IV (2.14 mg/kg iv over 2 seconds or 10 minutes +/- 0.014 mg/kg/min iv for 20 minutes) also tested negative for electrophysiologic effects in anesthetized open chest dogs.

Increasing the maintenance doses of PM101 and Amiodarone IV by 50-fold to 0.7 mg/kg/min iv following a 2 second bolus infusion of 2.14 mg/kg decreased Wenckebach rate (both treatment groups) and increased AH and HV intervals (Amiodarone IV).

Increasing the bolus dose of PM101 and Amiodarone IV by 10 fold to 21.4 mg/kg iv increased AH interval, decreased Wenckebach rate, increased atrial effective refractory period, and increased sinus node recovery time.

Fatal AV block was observed in dogs given high doses (bolus or maintenance) of PM101 and Amiodarone IV. The LOAELs for this effect were 21.4 mg/kg iv bolus over 2 seconds and 0.7 mg/kg/min maintenance infusion for both drugs.

Pacing-induced ventricular tachycardia degenerating into VF was observed in dogs given PM101 and Amiodarone IV. The LOAEL for this effect was 2.14 mg/kg iv over 2 seconds for PM101 and 21.4 mg/kg iv over 2 sec for Amiodarone IV, respectively.

Study Number:

N104

Report Status:

Final and quality assured

Study Initiation Date:

28 March 2007

Study Facility:

CorDynamics, Inc.
2242 W. Harrison St.
Chicago, IL 60612

GLP Compliance:

Yes

Animals:

Female beagle dogs

Number/drug

7

treatment group:Age:

8-15 months

Body weight:

5.7-14.4 kg

Drug:

PM101

Lot Number:

7043

Vehicle:

D5W (5% dextrose in water)

Vehicle:

Captisol (lot# CD083.87)

Reference Drug:

Amiodarone IV solution (50 mg/ml, lot# 401858)

Methods

Female beagle dogs were anesthetized (propofol, isoflurane and morphine), the chest was opened, and the animals instrumented for measurement of arterial blood pressure and electrocardiographic parameters: plunge electrodes were implanted for measurement of atrial and ventricular effective refractory periods; a multipolar electrophysiology catheter was positioned distal to the tricuspid valve via the femoral vein to record His bundle electrograms (AH and HV intervals); a catheter was placed into the left ventricle to record left ventricular monophasic action potential duration. Surface ECGs were monitored via electrodes placed on the right arm, left leg and the chest of the animal. PM101, amiodarone IV, and vehicle were administered intravenously over either a 2 second or 10 minute time period, followed in some cases by a constant infusion. Each dog received a single treatment and was monitored for 20 minutes following the initial dosing during which time the following parameters were measured: atrial effective refractory period (AERP), ventricular effective refractory period (VERP), AH interval, HV interval, monophasic action potential duration to 90% repolarization (MAPD90), Wenckebach cycle time, sinus node recovery time (SNRT). Animals were sacrificed following this electrocardiographic evaluation.

Treatment groups are shown below.

Group	Test Compound	Bolus/ Infusion Dose Conc. (mg/mL)	Bolus Dose (mg/kg)	Bolus Volume (mL/kg)	Infusion Volume (mL/kg/min)	Infusion Dosage (mg/kg/min)	Duration of Bolus/ Infusion	Number of Female Dogs
1 ^a	D5W	NA/NA	NA	0.043	0.014	NA	<2 sec./ 20 min.	7
2	Captisol	225/NA	NA	0.043	NA	NA	<2 sec./NA	7
3	Captisol	225/225	NA	0.043	0.014	NA	<2 sec./ 20 min.	7
4	PM101	50 ^b /NA	2.14	0.043	NA	NA	<2 sec./NA	7
5	PM101	50 ^b /50 ^b	2.14	0.043	0.014	0.7	<2 sec./ 20 min.	7
6	Amiodarone IV	1.5 ^c /NA	2.14	1.43	NA	NA	10 min./NA ^c	7
7	Amiodarone IV	50/NA	2.14	0.043	NA	NA	<2 sec./NA	7
8	Amiodarone IV	50/50	2.14	0.043	0.014	0.7	<2 sec./ 20 min.	7
9	Captisol	225/225	NA	0.043	0.0078	NA	<2 sec./ 20 min.	7
10	Captisol	225/NA	NA	0.43	NA	NA	<2 sec./NA	7
11	Captisol	225/225	NA	0.43	0.0078	NA	<2 sec./ 20 min.	7
12	PM101	50 ^b /1.8 ^c	2.14	0.043	0.0078	0.014	<2 sec./ 20 min.	7
13	PM101	50 ^b /NA	2.14	0.43	NA	NA	<2 sec./NA	7
14	PM101	50 ^b /1.8 ^c	2.14	0.43	0.0078	0.014	<2 sec./ 20 min.	7
15	Amiodarone IV	1.5 ^c /1.8 ^c	2.14	1.43	0.0078	0.014	10 min./ 10 min.	7
16	Amiodarone IV	50/1.8 ^c	2.14	0.043	0.0078	0.014	<2 sec./ 20 min.	7
17	Amiodarone IV	50/NA	2.14	0.43	NA	NA	<2 sec./NA	7
18	Amiodarone IV	50/1.8 ^c	2.14	0.43	0.0078	0.014	<2 sec./ 20 min.	7

^a Sham control, instrumented, dosed with D5W to match-by-volume Group 5 regimen.
^b Contained 225 mg/mL Captisol.
^c 50 mg/mL preparation diluted with D5W to match current human dosing regimen for Amiodarone IV.
 NA = Not Applicable

Results

Vehicles tested negative for electrophysiologic effects in anesthetized female dogs.

- D5W and Captisol vehicle groups (Groups 1-3, 9-11)

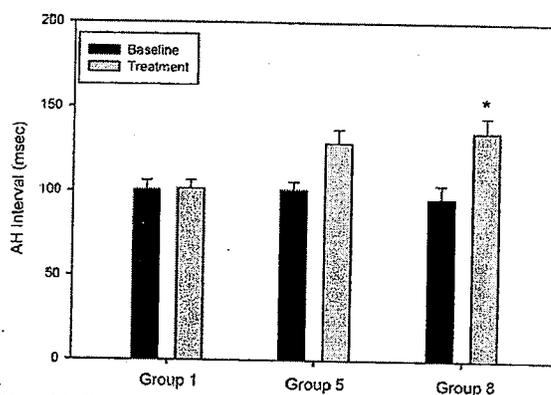
The following drug treatment groups also tested negative for electrophysiologic effects. The total dose of amiodarone given was 2 mg/kg.

- PM101 (2.14 mg/kg iv) given as a 2 second bolus +/- 0.014 mg/kg/min for 20 minutes (Groups 4, 12)
- Amiodarone (2.14 mg/kg iv) given as a 10 minute infusion +/- 0.014 mg/kg/min for 10 min (Groups 6, 15)
- Amiodarone (2.14 mg/kg iv) given as a 2 second bolus +/- 0.014 mg/kg/min for 20 minutes (Groups 7-16)

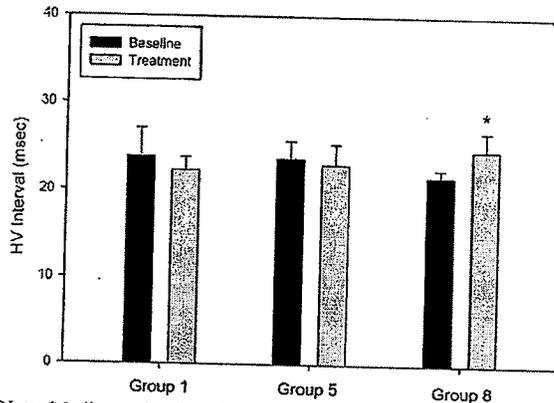
Maintaining the bolus doses of PM 101 and Amiodarone IV at 2.14 mg/kg iv over 2 seconds, but increasing the constant infusion rate to 0.7 mg/kg/min to maintain plasma amiodarone concentration at a constant level similar to C_{max} (shown in a pharmacokinetic simulation) produced the following electrophysiologic effects. The total dose of amiodarone given was 16 mg/kg.

- PM101 (2.14 mg/kg iv) given as a 2 second bolus + 0.7 mg/kg/min for 20 minutes decreased Wenckebach rate (Group 5).
- Amiodarone (2.14 mg/kg iv) given as a 2 second bolus + 0.7 mg/kg/min for 20 minutes decreased Wenckebach rate and increased AH and HV intervals (Group 8).

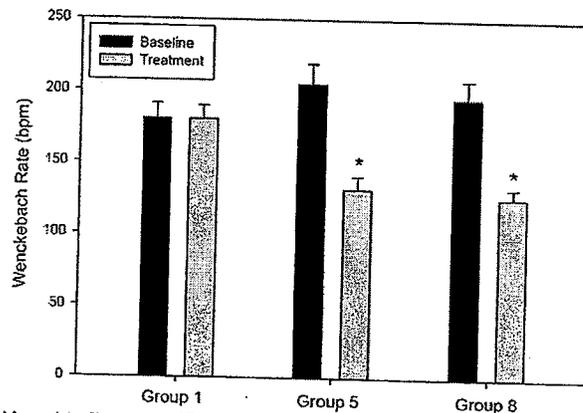
Group 1, D5W
 Group 5, PM 101 (2.14 mg/kg iv over 2 seconds + 0.7 mg/kg/min iv for 20 min)
 Group 8, Amiodarone IV (2.14 mg/kg iv over 2 seconds + 0.7 mg/kg/min iv for 20 min)



Note: * Indicates significantly different % change from baseline compared with Group 1 ($p < 0.05$; ANOVA followed by Dunnett Test). Bars are mean values and vertical lines represent the SEM for 7 dogs per group.



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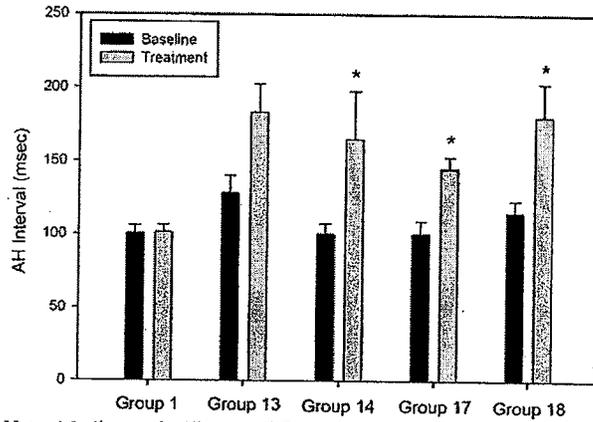


Note: * Indicates significantly different % change from baseline compared with Group 1 ($p < 0.05$; ANOVA followed by Dunnett Test). Bars are mean values and vertical lines represent the SEM for 7 dogs per group.

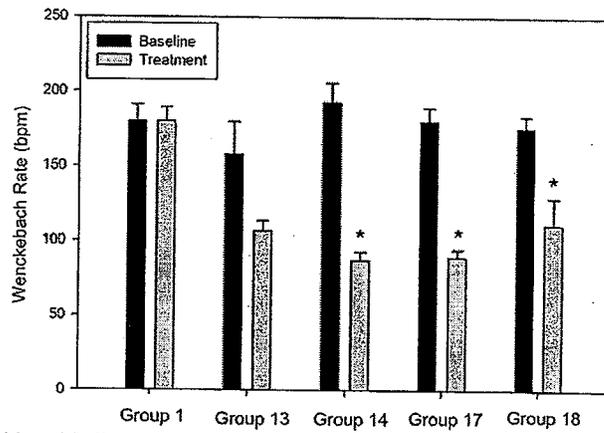
Increasing the bolus doses of Amiodarone IV and PM101 by 10-fold produced the following electrophysiologic effects. The total dose of amiodarone given was 22 mg/kg.

- PM101 (21.4 mg/kg iv over 2 seconds) increased atrial effective refractory period without altering other parameters (Group 13).
- PM101 (21.4 mg/kg iv over 2 seconds) + 0.014 mg/kg/min iv for 20 minutes increased AV interval, atrial effective refractory period and sinus node recovery time, similar to amiodarone IV (Group 14).
- Amiodarone (21.4 mg/kg iv over 2 seconds) +/- 0.014 mg/kg/min iv for 20 minutes increased AV interval, atrial effective refractory period and sinus node recovery time (Groups 17, 18).

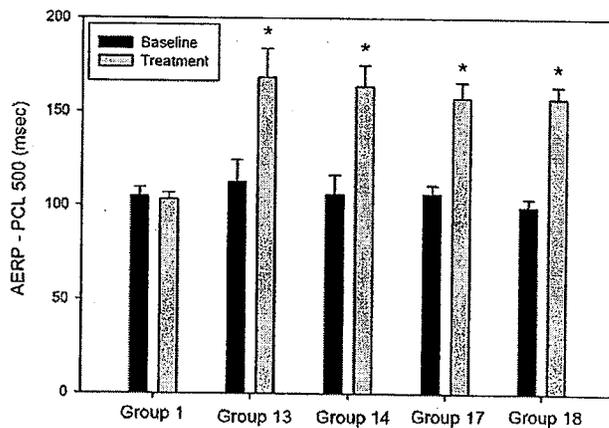
Group 1, D5W
 Group 13, PM101 (21.4 mg/kg iv over 2 seconds)
 Group 14, PM101 (21.4 mg/kg iv over 2 seconds) + 0.014 mg/kg/min iv for 20 minutes
 Group 17, Amiodarone IV (21.4 mg/kg iv over 2 seconds)
 Group 18, Amiodarone IV (21.4 mg/kg iv over 2 seconds) + 0.014 mg/kg/min iv for 20 minutes



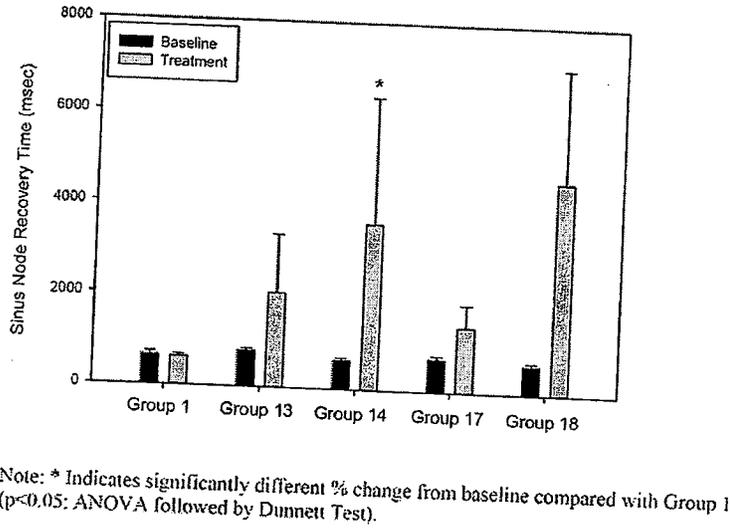
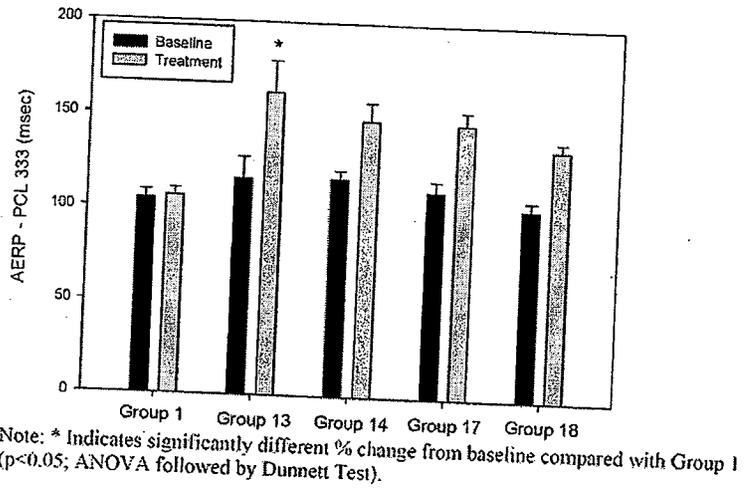
Note: * Indicates significantly different % change from baseline compared with Group 1 (p<0.05; ANOVA followed by Dunnett Test.). Bars are mean values and vertical lines represent the SEM for 7 dogs per group.



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Electrophysiological effects of PM101 and Amiodarone IV in anesthetized dogs are summarized below.

Group	Drug	Bolus Dose		Maintenance Dose		Wenckebach Rate (bpm)	AH Interval (ms)	HV Interval (ms)	Sinus Node Recovery Time (ms)	AERP (ms)	VERP (ms)
		(mg/kg)	Duration	(mg/kg/min)	Duration						
1	D5W	-	2 sec	-	20 min						
2	Captisol	-	2 sec	-	20 min						
3	Captisol	-	2 sec	-	20 min						
9	Captisol	-	2 sec	-	20 min						
10	Captisol	-	2 sec	-	20 min						
11	Captisol	-	2 sec	-	20 min						
4	PM101	2.14	2 sec	0	NA						
12	PM101	2.14	2 sec	0.014	20 min						
5	PM101	2.14	2 sec	0.7	20 min	decr					
13	PM101	21.4	2 sec	0	NA						
14	PM101	21.4	2 sec	0.014	20 min	decr	incr		incr	incr	
6	Amiodarone IV	2.14	10 min	0	NA						
15	Amiodarone IV	2.14	10 min	0.014	10 min						
7	Amiodarone IV	2.14	2 sec	0	NA						
16	Amiodarone IV	2.14	2 sec	0.014	20 min						
8	Amiodarone IV	2.14	2 sec	0.7	20 min	decr	incr	incr			
17	Amiodarone IV	21.4	2 sec	0	NA	decr	incr				
18	Amiodarone IV	21.4	2 sec	0.014	20 min	decr	incr		incr	incr	

AERP, Atrial effective refractory period
 VERP, Ventricular effective refractory period

Twelve dogs died on-study or were sacrificed in extremis as shown below. The sponsor's narratives for the deaths (*italics*) and reviewer's comment follow. Given the similar findings in both PM101 and Amiodarone IV dosing groups, this reviewer attributes deaths to administration of amiodarone at the doses given.

Amiodarone Dose (Group #)	Pacing-induced VF (number of events)	Fatal AV Block (number of events)	Severe Hypotension (presence)
<i>2mg/kg</i>			
PM101 - Group 4	1		no
<i>16mg/kg</i>			
PM101 - Group 5	1		yes
PM101 - Group 5		1	yes
Amiodarone IV - Group 8		1	yes
<i>22mg/kg</i>			
PM101 - Group 13	1		yes
PM101 - Group 13		1	yes
PM101 - Group 14	1		yes
PM101 - Group 14		1	yes
(Amiodarone IV) - Group 17	1		yes
(Amiodarone IV) - Group 17		1	yes
(Amiodarone IV) - Group 18	1		yes
(Amiodarone IV) - Group 18		1	yes

Notes: Severe Hypotension = Diastolic arterial pressure < 20 mmHg

Group 4 – Intended human-equivalent dosing regimen of PM101 (2.14 mg/kg over 2 seconds i.e. ~2 mg/kg)
 During programmed electrical stimulation to interrogate refractoriness following the administration of PM101, one dog in this group experienced an extrastimulus-induced ventricular tachycardia that rapidly degraded into ventricular fibrillation. Cardioversion was not attempted. Prior to this event, the dog was normotensive and was not in acute cardiovascular jeopardy. Based on the cardiovascular condition of the animal and the temporal association with a short cycle length ventricular extrastimulus, the relationship of VT/VF to test article exposure was questionable.

Reviewer comment: Given similar findings in animals given higher doses of PM101 and Amiodarone IV, and the lack of a reasonable alternative explanation, this adverse finding is attributed to amiodarone administration at this dose level.

Groups 5 and 8 – Plasma Cmax holding regimen of PM101 or Amiodarone IV (2.14 mg/kg over 2 seconds + 0.7 mg/kg/min for 20 minutes, i.e. intended bolus dose plus 50 times the maintenance dose; total dose ~16 mg/kg)
 Three dogs from these regimens were affected, two animals in Group 5 (PM101) and one animal in Group 8 (Amiodarone IV). During high-rate cardiac pacing, one dog in Group 5 experienced spontaneous conversion to ventricular tachycardia that rapidly degraded into ventricular fibrillation. Prior to the initiation of this pacing cycle, the dog was extremely hypotensive and was in acute cardiovascular jeopardy concomitant with the Cmax holding infusion regimen of PM101. Thus, cardioversion was not attempted. It is believed that the extreme hypotension (and presumably reduced oxygen state of the myocardium) served as a vulnerable substrate for arrhythmogenesis in the presence of high-rate cardiac pacing. One dog each in Groups 5 and 8 experienced progressive atrioventricular rhythm disturbances culminating in complete AV block during the Cmax holding infusion regimen of PM101. The resultant cardiac dysfunction in the presence of severe hypotension resulted in the animal being declared in extremis.

Reviewer comment: While induction of ventricular tachycardia degenerating into ventricular fibrillation by high rate pacing is confounded by hypotension, the relationship of this severe ventricular arrhythmia to a direct drug effect on the heart cannot be eliminated. Fatal AV block appears to be induced by a high maintenance dose (LOAEL, 0.7 mg/kg/min) of either drug product. The LOAEL might be lower than this estimate since intermediate dose levels were not examined.

Groups 13, 14, 17, and 18 – 10-fold human-equivalent regimen bolus dose of PM101 or Amiodarone IV (21.4 mg/kg over 2 seconds + 0.014 mg/kg/min for 20 minutes, i.e. ~22 mg/kg)
Eight dogs from these regimens were affected, two animals each in Groups 13 and 14 (PM101) and two animals each in Groups 17 and 18 (Amiodarone IV). During high-rate cardiac pacing, one dog each in Groups 13, 14, 16, and 17 experienced spontaneous conversion to ventricular tachycardia that rapidly degraded into ventricular fibrillation. Prior to the initiation of this pacing cycle, the dog was extremely hypotensive and was in acute cardiovascular jeopardy concomitant with the extended infusion regimen of PM101. Thus, cardioversion was not attempted. It is believed that the extreme hypotension (and presumably reduced oxygen state of the myocardium) associated with PM101 administration served as a vulnerable substrate for arrhythmogenesis in the presence of high-rate cardiac pacing. One dog each in Groups 13, 14, 17, and 18 experienced progressive atrioventricular rhythm disturbances culminating in complete AV block during the PM101 infusion. The resultant cardiac dysfunction in the presence of severe hypotension resulted in the animal being declared in extremis.

Reviewer comment: While induction of ventricular tachycardia degenerating into ventricular fibrillation by high rate pacing is confounded by hypotension, the relationship of this severe ventricular arrhythmia to a direct drug effect on the heart cannot be eliminated. Fatal AV block is seen in animals given a high bolus dose of either drug product (LOAEL, 21.1 mg/kg over 2 seconds). The LOAEL might be lower than this estimate since intermediate dose levels were not examined.

Study Title: **A Crossover, Single-Dose Intravenous Infusion Comparison Study of Captisol-Enabled™ Amiodarone, Cordarone® and a Benzyl Alcohol-Free Amiodarone Formulation in a Male Cynomolgus Monkey Telemetry Model**

Key Findings: Captisol-Enabled Amiodarone (5 mg/kg, iv over 3 min) did not affect hemodynamics, heart rate or the ECG in telemeterized monkeys.

Cordarone and benzyl alcohol free amiodarone given at the same dose (5 mg/kg, iv over 3 min) also did not affect hemodynamics, heart rate or the ECG in telemeterized monkeys.

Study Number: 1548-166

Report Status: Final and quality assured

Study Initiation Date: 31 March 2003

Study Facility: { } b(4)

GLP Compliance: Yes

Animals: Male Cynomolgus monkeys

Number/dose: 3

Age: 4.5-6.2 yrs

Body weight: 3.5-4.3 kg

Drugs: Amiodarone in captisol (50 mg amiodarone/ml, 225 mg captisol/ml (lot no. not provided).

Cordarone (50 mg amiodarone/ml, 100 mg Tween-80/ml, and 20.2 mg benzyl alcohol/ml)

Benzyl alcohol-free amiodarone (50 mg amiodarone/ml, 100 mg Tween-80/ml)

Vehicle 5% Dextrose in sterile water for injection (D5W)

Methods

Conscious male cynomolgus monkeys instrumented with a telemetry transmitter for monitoring blood pressure, heart rate and an ECG were given amiodarone-captisol, Cordarone or benzyl alcohol-free amiodarone (5 mg amiodarone/kg iv over 3 minutes) in a crossover design, with 3 days between each treatment. Animals were monitored for clinical signs, hemodynamics and ECG for 6 hours after drug administration.

Results

No clinical signs or changes in electrocardiographic activity and blood pressure were produced by any of the drug treatments administered.

Observations/Measurements:

Mortality and clinical findings	Daily																																												
Body weight	Weekly																																												
Food consumption	Weekly																																												
ECG evaluation	Once pre-dose, Day 14, and near the end of the recovery period																																												
Ophthalmic Examination	Once during the predose phase, on Day 15, and near the end of the recovery phase.																																												
Clinical Pathology	Blood samples were taken for hematology, clinical chemistry and coagulation parameters twice predose and once prior to sacrifice.																																												
	<p>Hematology</p> <table border="0"> <tr> <td>red blood cell (erythrocyte) count</td> <td>platelet count</td> </tr> <tr> <td>hemoglobin</td> <td>white blood cell (leukocyte) count</td> </tr> <tr> <td>hematocrit</td> <td>differential blood cell count</td> </tr> <tr> <td>mean corpuscular volume</td> <td>blood smear</td> </tr> <tr> <td>mean corpuscular hemoglobin</td> <td>reticulocyte count</td> </tr> <tr> <td>mean corpuscular hemoglobin concentration</td> <td></td> </tr> </table> <p>Coagulation</p> <table border="0"> <tr> <td>prothrombin time</td> <td>activated partial thromboplastin time</td> </tr> </table> <p>Clinical Chemistry</p> <table border="0"> <tr> <td>glucose</td> <td>alanine aminotransferase</td> </tr> <tr> <td>urea nitrogen</td> <td>alkaline phosphatase</td> </tr> <tr> <td>creatinine</td> <td>gamma glutamyltransferase</td> </tr> <tr> <td>total protein</td> <td>aspartate aminotransferase</td> </tr> <tr> <td>albumin</td> <td>calcium</td> </tr> <tr> <td>globulin</td> <td>inorganic phosphorus</td> </tr> <tr> <td>albumin/globulin ratio</td> <td>sodium</td> </tr> <tr> <td>cholesterol</td> <td>potassium</td> </tr> <tr> <td>total bilirubin</td> <td>chloride</td> </tr> </table> <p>Urinalysis</p> <table border="0"> <tr> <td>appearance (clarity and color)</td> <td>ketones</td> </tr> <tr> <td>volume</td> <td>bilirubin</td> </tr> <tr> <td>specific gravity</td> <td>blood</td> </tr> <tr> <td>pH</td> <td>microscopic examination of sediment</td> </tr> <tr> <td>protein</td> <td>urobilinogen</td> </tr> <tr> <td>glucose</td> <td></td> </tr> </table>	red blood cell (erythrocyte) count	platelet count	hemoglobin	white blood cell (leukocyte) count	hematocrit	differential blood cell count	mean corpuscular volume	blood smear	mean corpuscular hemoglobin	reticulocyte count	mean corpuscular hemoglobin concentration		prothrombin time	activated partial thromboplastin time	glucose	alanine aminotransferase	urea nitrogen	alkaline phosphatase	creatinine	gamma glutamyltransferase	total protein	aspartate aminotransferase	albumin	calcium	globulin	inorganic phosphorus	albumin/globulin ratio	sodium	cholesterol	potassium	total bilirubin	chloride	appearance (clarity and color)	ketones	volume	bilirubin	specific gravity	blood	pH	microscopic examination of sediment	protein	urobilinogen	glucose	
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Plasma Drug Levels	<p>Blood samples were taken from all animals for determination of plasma amiodarone levels.</p> <ul style="list-style-type: none"> • Predose and at 5 and 10 minutes after administration of the loading dose. • 1, 3, and 6 hours after initiation of the initial infusion; Group 2 was not bled at these time points because dosing was terminated on Day 1. • 24, 48, 96, 168, 240, and 336 hours after initiation of the maintenance infusion. <p>• Recovery animals were bled at 24, 48, 96, and 168 hours after the end of the maintenance infusion.</p>																																												
Sacrifice	<p>End of treatment period: On Day 16, three animals/sex/group in Group 1, two males and three females in Group 2, and three males and two females in Group 3 were sacrificed and necropsied.</p> <p>Recovery period: On Day 8, all remaining animals were sacrificed and necropsied.</p>																																												

Necropsy	All (scheduled and unscheduled sacrifice) animals were necropsied. Tissues and organs were evaluated macroscopically.																																														
Organ weights	The following organs from all animals were weighed. <table style="width: 100%; border: none;"> <tr> <td style="width: 50%;">adrenal (2)</td> <td style="width: 50%;">pituitary gland</td> </tr> <tr> <td>brain</td> <td>prostate</td> </tr> <tr> <td>epididymis (2)</td> <td>salivary gland [mandibular (2)]</td> </tr> <tr> <td>heart</td> <td>spleen</td> </tr> <tr> <td>kidney (2)</td> <td>testis (2)</td> </tr> <tr> <td>liver with gallbladder (drained)</td> <td>thymus</td> </tr> <tr> <td>lung</td> <td>thyroid (2 lobes) with parathyroid</td> </tr> <tr> <td>ovary (2)</td> <td>uterus</td> </tr> </table>	adrenal (2)	pituitary gland	brain	prostate	epididymis (2)	salivary gland [mandibular (2)]	heart	spleen	kidney (2)	testis (2)	liver with gallbladder (drained)	thymus	lung	thyroid (2 lobes) with parathyroid	ovary (2)	uterus																														
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Drug-Related Findings

Mortality: Two animals were sacrificed on-study due to technical issues.

- Male H46029 in the Cordarone IV generic group was sacrificed on Dosing Phase Day 6 due to accidental removal of the needle resulting in a bloody discharge from the needle hole and swelling of the tissue at the port site.
- Female H46053 in the PM101 IV group was sacrificed on Dosing Phase Day 11 due to the rupture of a swelling on the right shoulder.
- Macroscopic observations associated with these two unscheduled sacrifices included thickened skin and gelatinous appearance at the catheter site in Male H46029, and skin abrasion and thickened subcutaneous tissue in Female H46053.
- These observations were due to inflammation involving the catheter and consisted of edema, chronic-active inflammation, and hemorrhage. These deaths are not considered treatment-related.

Clinical Findings: During the dosing phase, clinical signs were unremarkable in the control males. Control Female H46041 had clinical signs of vomitus (cloudy, foamy, and white) and abnormal feces (mucooid and/or nonformed feces) that may be due to the stress during dosing. On Dosing Phase Day 1 treatment-related clinical signs in the Cordarone IV generic group included hypoactivity, swollen ears, paws, muzzle, and periorbital region, and red skin in the ears. On the advice of the staff veterinarian, dosing was terminated in this group. These clinical signs were interpreted to be likely due to the release of histamine induced by Polysorbate 80 in the Cordarone IV generic formulation. Animals were treated with diphenhydramine hydrochloride [Benadryl®, 50 mg/mL, approximately 1.5

mg/kg IV and 1.5 mg/kg IM (intramuscular)] and prednisolone (Solu-Delta-Cortef®, 10 mg/mL, approximately 5 mg/kg IV). Dosing was reinstated the following day (Dosing Phase Day 2) at the maintenance infusion rate for the remainder of the Dosing Phase per the protocol. An additional dose of Benadryl® (3 mg/kg IM) was administered to this group on Day 2 prior to initiation of dosing. During the remainder of the phase, starting on Day 2, no remarkable clinical signs of toxicity were observed in Cordarone IV generic group. No treatment-related clinical signs were noted in the PM101 IV group during or after administration of PM101 IV. No remarkable clinical signs were seen during recovery in any of the groups.

Body Weight: No drug related findings

Food Consumption: No drug related findings

Ophthalmic Findings: No drug related findings

ECG Findings: No drug related findings

Clinical Chemistry: No drug related findings

Coagulation: No drug related findings

Organ Weights: No drug related findings

Macroscopic Findings: No drug related findings

Histopathology Findings: No drug related findings

Plasma Amiodarone Levels: Plasma toxicokinetic parameters are shown for male and female dogs given PM101 and Cordarone. Plasma exposures were similar between male and female dogs. Although mean steady state amiodarone concentrations appeared higher in PM101 than in Cordarone IV treated animals. The sponsor did not compare plasma drug levels statistically.

Summary of Toxicokinetic Parameters of Amiodarone in Dog Plasma

Dose Group	Group Designation	Gender	Animal Number	C _{ss} (ng/mL)	CL (L/kg/hr)	t _{1/2} (hr)	λ _z (1/hr)	V _z (L/kg)
2	Cordarone IV	M	Mean	272	1.62	NA	NA	NA
			SD	45	0.30	NA	NA	NA
			N	5	5	0	0	0
		F	Mean	223	2.02	NA	NA	NA
			SD	54	0.51	NA	NA	NA
			N	5	5	0	0	0
3	PM101 IV	M	Mean	455	0.956	57.3	0.0123	70.7
			SD	58	0.133	NA	NA	NA
			N	5	5	2	2	2
		F	Mean	380	1.14	65.8	0.0105	97.2
			SD	37	0.12	NA	NA	NA
			N	5	5	1	1	1

Note: Group 2 received a 10 minute infusion and then dosing was stopped. Dosing resumed on Day 2 with the maintenance infusion. Group 3 received a bolus loading dose, a 6-hour post initiation infusion, and the maintenance infusion. Due to the break in dosing for Group 2, the different dosing regimens prior to the initiation of maintenance infusion, and the very long half-life of amiodarone, the comparison of Groups 2 and 3 needs to be approached cautiously.

Study Title: **Hemolytic Potential and Plasma Compatibility Testing with PM101**

Key Findings: The NOAELs for hemolysis were 25 mg/ml and 1.8 mg/ml for PM101 and Cordarone IV, respectively.

The NOAELs for plasma compatibility were <1.0 and 1.5 mg/ml for PM101 and Cordarone IV. Amiodarone likely precipitates at pH values greater than its pKa of 5.6, which accounts for the findings in plasma.

Study Number: N101

Report Status: Final and quality assured

Study Initiation Date: 06 December 2006

Study Facility: (b)(4)

GLP Compliance: Yes

Tissue: Human blood from a fasted donor

Variables Evaluated: Hemolysis and plasma compatibility

Drug: PM101

Lot Number: 7043

Reference Drug: Cordarone IV

Lot Number: 402554

Vehicle: D5W

Methods

Hemolytic potential was examined by incubating test substance at concentrations of 50, 25, 12.5, 1.8, 1.5 and 1.0 mg/ml with 0.5 ml of whole blood for 45 minutes at 37 degrees C, and measuring hemoglobin levels in the supernatant plasma of each sample. A positive test is defined by a supernatant hemoglobin concentration that is \geq 500 mg/dL greater than the concurrent vehicle control.

Plasma compatibility was examined by mixing test substance at concentrations of 50, 25, 12.5, 1.8, 1.5 and 1.0 mg/ml with 0.5 ml of plasma. Changes in color or clarity relative to a concurrent negative control plasma sample, and the presence of flocculation, precipitation, or coagulation are indicative of plasma incompatibility. The sample is examined microscopically to further characterize any differences.

Results

The NOEL for hemolysis was 25 mg/ml for PM101 and 1.8 mg/ml for Cordarone IV.

Mixture	Hemoglobin ^a (mg/dL)	Test Result ^b	Tube No.
Human blood plus:			
Vehicle			
Human Plasma	58	Negative	1
1% Saponin	2	Not applicable	2
Test Article (PM101)	6155	Positive	3
50 mg/mL	3047	Positive	4
25 mg/mL	500	Negative	5
12.5 mg/mL	143	Negative	6
1.8 mg/mL	10	Negative	7
1.5 mg/mL	12	Negative	8
1.0 mg/mL	15	Negative	9
Test Article (Cordarone IV)			
50 mg/mL	6386	Positive	10
25 mg/mL	4678	Positive	11
12.5 mg/mL	548	Positive	12
1.8 mg/mL	11	Negative	13
1.5 mg/mL	11	Negative	14
1.0 mg/mL	18	Negative	15

^a Hemoglobin concentration of the mixture supernatants.

^b Negative = No hemolysis; Positive = Hemolysis.

The NOEL for plasma incompatibility was less than 1.0 mg/ml for PM101 and 1.5 mg/ml for Cordarone IV. The test results for PM101 were less pronounced at 1.5 and 1.0 mg/ml than for higher concentrations.

Mixture	Test Result	Tube No.
Human plasma and		
Vehicle		
Macro	NC	2
Micro	NA	
PM101 (50 mg/mL)		3
Macro	Cloudy, opaque	
Micro	Precipitate	
PM101 (25 mg/mL)		4
Macro	Cloudy, opaque	
Micro	Precipitate	
PM101 (12.5 mg/mL)		5
Macro	Cloudy, opaque	
Micro	Precipitate	
PM101 (1.8 mg/mL)		6
Macro	Cloudy, opaque	
Micro	Precipitate	
PM101 (1.5 mg/mL)		7
Macro	Slightly cloudy	
Micro	Precipitate	
PM101 (1.0 mg/mL)		8
Macro	Hazy	
Micro	Precipitate	

Macro = Macroscopic Observations.

Micro = Microscopic Observations.

NA = Not Applicable.

NC = No Change.

Mixture	Test Result	Tube No.
Human plasma and Cordarone IV (50 mg/ml.) Macro	Cloudy, opaque Precipitate	9
Micro		
Cordarone IV (25 mg/ml.) Macro	Cloudy, opaque Precipitate	10
Micro		
Cordarone IV (12.5 mg/ml.) Macro	Cloudy Precipitate	11
Micro		
Cordarone IV (1.8 mg/ml.) Macro	Slightly cloudy Precipitate	12
Micro		
Cordarone IV (1.5 mg/ml.) Macro	NC	13
Micro		
Cordarone IV (1.0 mg/ml.) Macro	NC	14
Micro		

Macro = Macroscopic Observations.
 Micro = Microscopic Observations.
 NA = Not Applicable.
 NC = No Change.

PM101 and Cordarone IV at concentrations as low as 1.0 mg/ml in isotonic Sorenson's buffer, pH 7.63, showed cloudy precipitates similar to those seen in plasma. The sponsor argued that the precipitate was occurring at pH values above amiodarone's pKa of 5.6. Therefore, the precipitate seen in plasma is considered to be amiodarone.

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/s/

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11/12/2008 05:07:01 PM
PHARMACOLOGIST

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