

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-325

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/Serial Number: 22-325
Drug Name: NEXTERONE™ IV (amiodarone HCl)
Indication(s): Ventricular Fibrillation and Hemodynamically Unstable
Ventricular Tachycardia
Applicant: Prism Pharmaceuticals, Inc.
Date(s): February 21, 2008
Review Priority: Standard

Biometrics Division: Biometrics I (HFD-710)
Statistical Reviewer: Fanhui Kong
Concurring Reviewers: H.M. James Hung

Medical Division: Division of Cardiovascular and Renal Products
Clinical Team: Robert Fiorentino, Norman Stockbridge
Project Manager: Russell Fortney

Keywords: MITT, PP, T-test, Systolic Blood Pressure (SBP)

Table of Contents

1. INTRODUCTION.....	3
1.1 OVERVIEW.....	3
1.2 DATA SOURCES.....	4
2. STATISTICAL EVALUATION.....	4
2.1 EVALUATION OF PHARMACODYNAMICS.....	4
2.2 EVALUATION OF SAFETY.....	6
3. SUMMARY AND CONCLUSIONS.....	6

1. INTRODUCTION

1.1 Overview

PM101 is a novel formulation of amiodarone complexed with Captisol in water for injection. In PM101, Captisol acts to improve the aqueous solubility of amiodarone at least 10^4 fold. The PM101 formulation represents a potential advance over current formulations of Amiodarone IV because it does not contain polysorbate 80 or benzyl alcohol.

b(4)

The current submission consists of two clinical studies, Study 101 and Study 102, which are developed for PM101. The first study (Study 101) was a bioequivalence study of PM101 compared to Amiodarone IV Reference Listed Drug. It will not be reviewed here. Study 102 was a phase II study to assess the blood pressure effects of PM101 and to provide support

b(4)

The primary objective of Study 102 was to compare the effect of PM101 administered as an immediate intravenous (I.V.) bolus push versus placebo on systolic blood pressure (SBP). The primary endpoint was the change in systolic blood pressure from baseline to the lowest value (peak reduction) within 15 minutes after the start of study drug administration. Secondary objectives included evaluation of change from baseline in heart rate (HR) and the change from baseline to the lowest value in mean arterial pressure (MAP) and diastolic blood pressure (DBP).

Approximately 342 healthy male and female (non-pregnant, non-breast-feeding) volunteers 18 to 55 years of age were randomized in a 2:2:1:1 ratio to four arms; 114 to PM101, 113 to placebo, 57 to Amiodarone I.V. (10 minute loading infusion), and 58 to Amiodarone I.V. (15 second loading infusion). Four subjects did not take study drug and were excluded from the pharmacodynamic (PD) and safety analyses, which included 338 subjects; 323 subjects completed the study.

As described by the sponsor, subjects entered the clinic on Day -2. In the morning of Day -1 (approximately 25 hours prior to dose administration), continuous 24-hour Holter monitoring was started. On Day 1, approximately 1 hour prior to dose administration, the baseline Holter monitoring period ended, and a second 24-hour period (the "on treatment" period) began. Subjects fasted for approximately 10 hours prior to study drug administration. Pharmacodynamics—BP and HR—were assessed at specified times on Day 1 and Day 2. Subjects were discharged from the clinic on Day 2 following the final safety assessments.

The primary PD endpoint was the change in SBP from baseline to the lowest value (peak reduction) within 15 minutes of study drug administration in the per protocol (PP) population, which included all randomized subjects who were compliant with study medication administration without major protocol deviations and completed the assessments of the primary efficacy endpoint during the first 15 minutes post-dose. Four subjects did not take study drug and were excluded from the PD and safety analyses, which included 338 subjects; 323 subjects completed the study.

The study was conducted between July 3, 2007 and November 2, 2007 in Montreal, Canada.

It was not clear when the protocol and the statistical analysis plan were approved and finalized. These documents were not submitted to FDA for review.

1.2 Data Sources

The Clinical Study Reports and SAS transport data sets for the studies were provided in electronic form in \\CDSESUB1\EVSPROD\NDA022325\0000.

2. STATISTICAL EVALUATION

2.1 Evaluation of Pharmacodynamics

The primary PD endpoint was the change in SBP from baseline to the lowest value (peak reduction) within 15 minutes of study drug administration in the per protocol (PP) population. The primary efficacy analyses were not performed in this study. The peak reduction from baseline SBP was the lowest post-dose value observed within the first 15 minutes. The observed value and change from baseline to the lowest value were summarized by treatment group using descriptive statistics. The change from baseline was analyzed using an ANOVA model. The ANOVA model included an effect for treatment. The mean difference (PM101-placebo) and the lower limit of its 90% CI were presented. No formal statistical tests were performed for comparisons between Amiodarone I.V. and other groups.

Non-inferiority of PM101 compared to placebo for the primary endpoint was prospectively defined as a SBP decrease of 5 mmHg from baseline to the lowest value within 15 minutes after the drug administration in the PM101 group compared to placebo. That is, if the lower limit of the 90% confidence interval (CI) of the difference between placebo and PM101 (PM101-placebo) in SBP (change from baseline to the lowest value within 15 minutes after the start of study drug) was greater than -5 mmHg, PM101 would be considered non-inferior to placebo for the primary endpoint. A sensitivity analysis was performed using the modified intention-to-treat (MITT) population to support the primary analysis.

Secondary objectives included evaluation of change from baseline in HR and change from baseline in MAP and DBP.

Analysis of the primary endpoint in this study as indicated in Table 3.1 shows that the change from baseline was comparable between placebo and PM101 (-4.25 ± 4.24 vs. -4.83 ± 5.01 mmHg, respectively), with a mean difference of -0.57 mmHg, indicating that PM101 was non-inferior (lower limit of 90% CI was -1.64). These results were supported by secondary analyses in the MITT population, see Table 3.2 for the results. In fact, both the lowest 95% CI limit and the lowest 95% CI limit are given. The two-sided 95% CI is used to determine the non-inferiority of PM 101. For a non-inferiority test with a fixed margin, using such a lower bound will protect the non-inferiority conclusion of the treatment with an error rate of no more than 0.025. The lowest change from baseline in SBP for both Amiodarone I.V. groups (-4.81 ± 4.83 and -4.80 ± 5.89 mmHg for the 10 minute and 15 second loading dose groups, respectively) was comparable to those seen in the placebo and PM101 groups.

**Table 3.1: Systolic Blood Pressure from Baseline to 15 Minutes Post-Dose:
Study 102 -- PP Population**

Parameter, mmHg	Placebo (N=111)	PM101 (N=104)	Amiodarone I.V. 10 min (N=54)	Amiodarone I.V. 15 sec (N=54)
Mean SBP at Baseline	108.16	106.92	107.14	107.89
Mean Lowest SBP within 15 Minutes Post-Dose	103.91	102.10	102.33	103.09
Mean Change from Baseline to Lowest SBP with 15 Minutes Post-Dose	-4.25	-4.83	-4.81	-4.80
Standard Deviation	4.42	5.01	4.83	5.89
Minimum, Maximum	-22.0, 5.0	-25.0, 3.5	-21.0, 5.0	-24.0, 6.5
Mean Difference, PM101 - Plbo		-0.57		
Lower Limit of 90% CI of Mean Difference		-1.64		
Lower Limit of 95% CI of Mean Difference		-1.84		

Source: Reviewer.

**Table 3.2: Systolic Blood Pressure from Baseline to 15 Minutes Post-Dose:
Study 102 -- MITT Population**

Parameter, mmHg	Placebo (N=112)	PM101 (N=112)	Amiodarone I.V. 10 min (N=57)	Amiodarone I.V. 15 sec (N=57)
Mean SBP at Baseline	108.16	106.91	107.53	107.54
Mean Lowest SBP within 15 Minutes Post-Dose	103.85	102.08	102.49	102.65
Mean Change from Baseline to Lowest SBP with 15 Minutes Post-Dose	-4.31	-4.83	-5.04	-4.89
Standard Deviation	4.45	6.10	5.11	5.76
Minimum, Maximum	-22.0, 5.0	-38.5, 14.5	-21.0, 5.0	-24.0, 6.5
Mean Difference, PM101 - Plbo		-0.51		
Lower Limit of 90% CI of Mean Difference		-1.69		
Lower Limit of 95% CI of Mean Difference		-1.92		

Source: Reviewer.

2.2 Evaluation of Safety

Not available.

3. SUMMARY AND CONCLUSIONS

In this submission, the sponsor conducted 2 pivotal studies, Study 101 and Study 102. The former was a bioequivalence study and is not reviewed here. Study 102 was conducted between July 3, 2007 and November 2, 2007 in Montreal, Canada. The primary objective of the study was to compare the effect of PM101 administered as an immediate intravenous (I.V.) bolus push versus placebo on systolic blood pressure.

Analysis of the primary endpoint in this study showed that the change from baseline was comparable between placebo and PM101, with PM101 being non-inferior to placebo.

C:\Data\My Documents\NDA Review\NDA 2005\22325

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Fanhui Kong
6/10/2008 06:12:41 PM
BIOMETRICS

James Hung
6/11/2008 04:24:29 PM
BIOMETRICS