

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**22-325**

**MEDICAL REVIEW(S)**



## DIVISION OF CARDIO-RENAL DRUG PRODUCTS

### Divisional Memo

**NDA:** 22-325 (Nexterone; amiodarone for ventricular arrhythmias)  
**Sponsor:** Prism Pharmaceuticals  
**Review date:** 22 December 2008

**Reviewer:** N. Stockbridge, M.D., Ph.D., HFD-110

**Distribution:** NDA 22-325  
HFD-110/Fortney/Hicks

This memo conveys the Division's decision to approve a new intravenous formulation of amiodarone for treatment of life-threatening ventricular arrhythmias.

This application has been the subject of reviews of CMC (Shiromani; 24 September and 10 December 2008), microbiology (Riley; 20 November 2008), pharmacology (Koerner; 12 November 2008), biopharmaceutics (Dorantes; 18 December 2008), clinical studies (Fiorentino; 24 November 2008) and statistics (Kong; 10 October 2008).

Most issues have been addressed in Dr. Hicks's CDTL memo (25 November 2008). I summarize very briefly.

The Nexterone captisol-based formulation was intended \_\_\_\_\_

b(4)

\_\_\_\_\_ The sponsor used a non-inferiority design to compare, in normal volunteers, blood pressure responses to usual bolus infusions of 150 mg as Nexterone over 2 s, Cordarone over 15 s, Cordarone over 10 min, and placebo. Nexterone was similar to Cordarone (95% CI of -1.8 mmHg), but the two infusions of Cordarone were also indistinguishable, so the study lacked assay sensitivity, perhaps because it was conducted in normal volunteers. Adverse events were similar in active treatment groups.

A study in anesthetized dogs suggested less blood pressure effects with captisol-containing Nexterone than with Cordarone, but \_\_\_\_\_

b(4)

Relative bioavailability was assessed (and considered adequate) in a 2-period crossover study with an (inadequate!) 42-day washout. Such a study is not ordinarily required of an intravenous drug. However, amiodarone is not in solution, and the Division has required a study to show that its kinetics are similar to those of the reference drug.

The Microbiology review notes that \_\_\_\_\_

b(4)

\_\_\_\_\_ Therefore, the limit applicable to Cordarone is sufficient here.

As a result, Nexterone can be approved with labeling that is very similar to Cordarone's.

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

/s/

-----  
Norman Stockbridge  
12/22/2008 07:48:04 AM  
MEDICAL OFFICER

## CLINICAL REVIEW

Application Type NDA  
Submission Number 022325

Letter Date February 21, 2008  
Stamp Date February 25, 2008  
PDUFA Goal Date December 25, 2008

Reviewer Name Robert P. Fiorentino, MD, MPH  
Review Completion Date October 01, 2008

Established Name Amiodarone IV  
(Proposed) Trade Name Nexterone IV  
Therapeutic Class Antiarrhythmic agent  
Applicant Prism Pharmaceuticals

Priority Designation Standard

Formulation Intravenous  
Dosing Regimen Bolus, Infusion  
Indication Initiation of treatment and prophylaxis of  
frequently recurring ventricular fibrillation  
and hemodynamically unstable ventricular  
tachycardia  
Intended Population Patients refractory to other therapy

**Table of Contents**

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>6</b>
1.1	Recommendation on Regulatory Action.....	6
1.2	Risk Benefit Assessment .....	6
1.3	Recommendations for Postmarketing Risk Management Activities .....	7
1.4	Recommendations for other Post Marketing Study Commitments .....	7
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND.....</b>	<b>7</b>
2.1	Product Information.....	7
2.2	Currently Available Treatments for Proposed Indications .....	8
2.3	Availability of Proposed Active Ingredient in the United States .....	8
2.4	Important Safety Issues With Consideration to Related Drugs .....	9
2.5	Summary of Presubmission Regulatory Activity Related to Submission.....	10
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES .....</b>	<b>10</b>
3.1	Submission Quality and Integrity .....	10
3.2	Compliance with Good Clinical Practices.....	10
3.3	Financial Disclosures.....	11
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....</b>	<b>11</b>
4.1	Chemistry Manufacturing and Controls .....	11
4.2	Clinical Microbiology.....	11
4.3	Preclinical Pharmacology/Toxicology.....	11
4.4	Clinical Pharmacology .....	11
4.4.1	Mechanism of Action.....	11
4.4.2	Pharmacodynamics.....	12
4.4.3	Pharmacokinetics .....	12
<b>5</b>	<b>SOURCES OF CLINICAL DATA .....</b>	<b>13</b>
5.1	Table of Studies.....	13
5.2	Review Strategy.....	14
5.3	Discussion of Individual Studies .....	14
<b>6</b>	<b>REVIEW OF PRIMARY PHARMACODYNAMIC (PD) ENDPOINT .....</b>	<b>19</b>
<b>7</b>	<b>REVIEW OF SAFETY .....</b>	<b>20</b>
7.1	Methods and Findings .....	20
7.1.1	Clinical Studies Used to Evaluate Safety.....	20
7.1.2	Adequacy of Data .....	20
7.1.3	Pooling Data Across Studies to Estimate and Compare Incidence .....	20
7.2	Adequacy of Safety Assessments .....	20
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	20
7.2.2	Explorations for Dose Response.....	22
7.2.3	Special Animal and/or In Vitro Testing .....	22
7.2.4	Routine Clinical Testing .....	22
7.2.5	Metabolic, Clearance, and Interaction Workup .....	22
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class .....	23
7.3	Major Safety Results .....	23
7.3.1	Deaths .....	23
7.3.2	Nonfatal Serious Adverse Events .....	23
7.3.3	Dropouts and/or Discontinuations .....	23
7.3.4	Significant Adverse Events.....	32
7.4	Supportive Safety Results.....	32

Clinical Review  
 Robert P. Fiorentino, MD, MPH  
 NDA 022325  
 Nexterone® Amiodarone HCl IV

7.4.1	Common Adverse Events .....	32
7.4.2	Laboratory Findings.....	39
7.4.3	Vital Signs .....	40
7.4.4	Electrocardiograms (ECGs).....	46
7.4.5	Special Safety Studies.....	47
7.4.6	Immunogenicity .....	47
7.5	Other Safety Explorations .....	47
7.5.1	Dose Dependency for Adverse Events.....	47
7.5.2	Time Dependency for Adverse Events .....	47
7.5.3	Drug-Demographic Interactions .....	48
7.5.4	Drug-Disease Interactions.....	51
7.5.5	Drug-Drug Interactions.....	51
7.6	Additional Safety Explorations.....	51
7.6.1	Human Carcinogenicity .....	51
7.6.2	Human Reproduction and Pregnancy Data .....	51
7.6.3	Pediatrics and Effect on Growth .....	52
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound .....	52
7.7	Additional Submissions .....	52
<b>8</b>	<b>POSTMARKETING EXPERIENCE.....</b>	<b>52</b>
<b>9</b>	<b>APPENDICES .....</b>	<b>54</b>
9.1	Literature Review/References .....	54
9.2	Labeling Recommendations .....	55
9.3	Advisory Committee Meeting .....	56
9.4	Detailed Overview of Clinical Protocols.....	56
9.5	Additional Tables & Figures Referenced in Review .....	68

**INDEX OF TABLES**

Table 1.	Table of Studies .....	13
Table 2.	Study 102 Treatment Assignments .....	15
Table 3.	Study 102, Systolic Blood Pressure Change from Baseline to Lowest Value within 15 minutes Post-Dose (PP Population).....	19
Table 4.	Study 102, Systolic Blood Pressure from Baseline to 15 Minutes Post-Dose: MITT Population	19
Table 5.	Study 101, Demographic and Baseline Characteristics (Safety Population) .....	21
Table 6.	Study 102, Demographic and Baseline Characteristics (Safety Population) .....	21
Table 7.	Study 101, Subject Disposition.....	24
Table 8.	Study 101, Discontinued Subjects (All Randomized Subjects Population).....	25
Table 9.	Study 102, Subject Disposition, All Randomized Population .....	28
Table 10.	Study 102, Subjects Excluded from the Per Protocol Population.....	28
Table 11.	Study 102, Blood pressure changes for per-protocol excluded subject (available data).....	29
Table 12.	Study 102, Discontinued Subjects from All Randomized Subjects.....	30
Table 13.	Study 102, Protocol Deviations by Arm .....	31
Table 14.	Study 102, Commonly Reported Protocol Deviations.....	31
Table 15.	Subjects with Severe Adverse Events.....	32
Table 16.	Study 101 Adverse Events .....	33
Table 17.	Study 101 Treatment-Emergent Adverse Events in >3% of the Population for Either Treatment Group (Safety Population) .....	33
Table 18.	Study 101, Treatment-Emergent, Treatment-Related Infusion Site AEs.....	34
Table 19.	Study 102, Treatment Emergent AEs .....	35

Table 20. Study 102, Safety Population, Treatment Emergent AE's (%).....	36
Table 21. Study 102, All Treatment-Emergent Adverse Events (Safety Population) by System Organ Class.....	37
Table 22. Study 102, Injection site reactions by time.....	38
Table 23. Study 102, Safety Population (%).....	39
Table 24. Study 102, Abnormal Lab values for Subject 001-291.....	40
Table 25. Proportion of subjects with $\geq 10$ mm drop in Systolic Blood Pressure Across Timepoints (Study 102 Safety Population).....	42
Table 26. Proportion of subjects with $\geq 20$ mm drop in Systolic Blood Pressure Across Timepoints.....	42
Table 27. Study 102, Subjects with Treatment-Emergent Holter Monitoring Abnormalities (MITT Population).....	47
Table 28. Study 102, Summary of Injection Site Reaction Observations... <b>Error! Bookmark not defined.</b>	
Table 29. Treatment Emergent Adverse Events by Sex.....	49
Table 30. AERS Analysis, Amiodarone IV.....	53
Table 31. Study 102, Subjects that discontinued due to adverse events.....	68
Table 32. Study 102, Subjects not included in one of the defined analysis populations.....	69
Table 33. Study 102, SAFETY POPULATION, ALL TREATMENT EMERGENT AE's.....	69

**INDEX OF FIGURES**

Figure 1. Molecular structure of Amiodarone HCl.....	7
Figure 2. Mean Plasma Concentrations of Amiodarone in PM 101 I.V. and Amiodarone I.V. (Semi-Log Scale).....	12
Figure 3. Mean Plasma Concentrations of Desethylamiodarone in PM 101 I.V. and Amiodarone I.V. (Semi-Log Scale).....	13
Figure 4. Study 102, Study Design Schematic.....	17
Figure 5. Study 102, Study Assessments and Procedures.....	18
Figure 6. Change in Systolic Blood Pressure from Baseline.....	41
Figure 7. Change in Heart Rate From Baseline (Study 102, Safety Population), T=0 to T=20 minutes....	43
Figure 8: Scatterplots of Change in HR vs. concurrent change in SBP.....	44
Figure 9. Mean Change in Blood Pressure for Subjects with increase in HR $\geq 10$ bpm.....	45
Figure 10. Mean change in heart rate associated with $\geq 10$ mmHg drop in recorded SBP.....	45
Figure 11. Study 102, Holter Monitoring, Safety Population.....	46
Figure 12. Change in heart rate from baseline by Sex (Study 102 Safety Population).....	50
Figure 13. Change in SBP over time by Sex, PM101 I.V. arm.....	51
Figure 14. Proposed Labeling with Recommended Deletion.....	56
Figure 15. Study 101, Study Design Schematic.....	57
Figure 16. Study 101, Pharmacokinetic and Safety Measurements and Flow Chart.....	60
Figure 17. Study 101 Pharmacokinetic Parameters.....	62
Figure 18. Study 102 Flowchart.....	64
Figure 19. Study 102 Assessments and Procedures.....	66

Clinical Review  
Robert P. Fiorentino, MD, MPH  
NDA 022325  
Nexterone® Amiodarone HCl IV

**LIST OF COMMON ABBREVIATIONS USED IN TEXT:**

---

AE	adverse event
AF, afib	atrial fibrillation
BP	blood pressure
bpm	beats per minute
DBP	diastolic blood pressure
ECG	electrocardiogram
HR	heart rate
IV	intravenous
SAE	serious adverse event
SBP	systolic blood pressure
PM101 IV	Study name for formulation of amiodarone containing Captisol

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

I recommend approval of Nexterone IV for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapy, as follows:

- Initial Loading Dose: 150 mg/100 mL (in D5W or Normal Saline) infused over 10 minutes
- Followed by: 1 mg/min for 6 hours
- Followed by: 0.5 mg/min for 18 hours

In the event of breakthrough episodes of VF or hemodynamically unstable VT, a repeat loading dose may be administered.

I do not recommend approval of Nexterone IV as a \_\_\_\_\_ the sponsor has submitted a pharmacodynamic study (Study 102) that was intended \_\_\_\_\_

b(4)

\_\_\_\_\_ The primary endpoint of this study was the change in systolic blood pressure from baseline to the lowest value through 15 minutes post-dose. The primary comparison was to the placebo arm, however, additional subjects were also randomized to one of two other active controls arms that included an amiodarone 10 minute rapid IV load or a 15 second rapid IV load.

b(4)

b(4)

### 1.2 Risk Benefit Assessment

Although efficacy was not assessed in this NDA, the ability of this formulation to terminate cardiac arrhythmias is anticipated to be equivalent to other generic amiodarone formulations,

assuming bioequivalence. Given identical dosage and administration as specified in the label, the risks of this formulation would be anticipated to be similar to other generic forms of intravenous amiodarone. However, as noted above.

b(4)

### 1.3 Recommendations for Postmarketing Risk Management Activities

Postmarketing risk management activities are not recommended for this NDA.

### 1.4 Recommendations for other Post Marketing Study Commitments

Postmarketing study commitments have not been proposed and none are recommended.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Nexterone IV is an alternative generic formulation of intravenous amiodarone to the Reference Listed Drug, Cordarone IV. Nexterone is a new formulation of amiodarone containing 50 mg/mL of amiodarone hydrochloride, 3.77 mg/mL of citric acid monohydrate, 2.10 mg/mL of trisodium citrate dehydrate, and 225 mg/mL of Captisol® in water for injection. Nexterone is unique compared to the other Amiodarone IV Reference Listed Drug the amiodarone hydrochloride is dissolved using polysorbate 80 and benzyl alcohol as cosolvents.

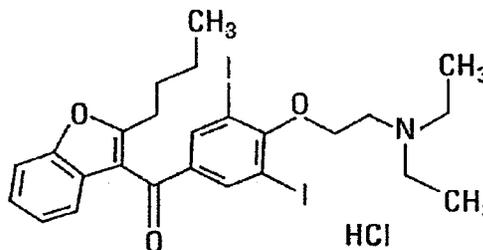


Figure 1. Molecular structure of Amiodarone HCl

Amiodarone is considered a Class III antiarrhythmic agent that blocks potassium channels, thereby prolonging cardiac repolarization, action potential duration and the refractory period. Amiodarone can also block sodium channels, calcium channels and adrenergic receptors. Amiodarone, unlike other Class III drugs, has little proarrhythmic activity.

As noted in the currently approved label, Amiodarone IV has been associated with severe hypotension in some patients with hemodynamically unstable ventricular tachycardia. The sponsor believes this hypotension is due to the cosolvents (polysorbate 80 and benzyl alcohol) in currently marketed generic Amiodarone IV formulations.

b(4)

Proposed Indication and Usage Statement

The sponsor proposes the following indication for Nexterone IV:

“NEXTERONE IV is indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients who are refractory to other therapy. NEXTERONE IV also can be used to treat patients with VT/VF for whom oral amiodarone is indicated, but who are unable to take oral medication. During or after treatment with NEXTERONE IV, patients may be transferred to oral amiodarone therapy.”

**2.2 Currently Available Treatments for Proposed Indications**

Both ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) are considered “malignant” or potentially lethal arrhythmias.

Based on current ACLS guidelines<sup>1</sup> amiodarone is the antiarrhythmic drug of choice (class IIb level of evidence) for persistent VF or pulseless VT if standard (non-antiarrhythmic) resuscitative measures are ineffective, including electrical defibrillation or cardioversion. Amiodarone has supplanted IV lidocaine in the current guidelines and has also been advocated for treatment of VT/VF refractory to lidocaine after acute myocardial infarction. Implantable cardiac defibrillators (ICDs) have also become a mainstay in preventing potentially fatal ventricular arrhythmias in patients at risk. Amiodarone is used adjunctively for prevention of ventricular arrhythmias in patients with ICDs.

Amiodarone is not indicated for *nonsustained* or *hemodynamically tolerated* arrhythmias, such as ventricular premature beats (VPB), nonsustained VT (NSVT) and accelerated idioventricular rhythms (AIVR).

**2.3 Availability of Proposed Active Ingredient in the United States**

Multiple generic formulations of IV amiodarone formulations have been approved in the United States. The oral formulation of amiodarone HCl was first approved in December of 1985 (NDA 018972)<sup>2</sup> and the IV formulation of amiodarone was first approved in August 1995 (NDA 020377).

---

<sup>1</sup> ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). Zipes DP, et al. J Am Coll Cardiol. 2006 Sep 5;48(5):e247-346.

<sup>2</sup> [http://www.fda.gov/cder/foi/nda/pre96/18-972\\_Cardarone.htm](http://www.fda.gov/cder/foi/nda/pre96/18-972_Cardarone.htm)

Clinical Review  
Robert P. Fiorentino, MD, MPH  
NDA 022325  
Nexterone® Amiodarone HCl IV

---

As noted previously, the IV formulation has been approved for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy. Amiodarone HCl Injection also can be used to treat patients with VT/VF for whom oral amiodarone is indicated, but who are unable to take oral medication.

#### Adverse Events and FDA Warnings

Notable adverse effects of IV amiodarone include sinus bradycardia or arrest, AV nodal blockade, liver function abnormalities, hypotension and phlebitis. Rare cases of fulminant hepatitis and acute respiratory distress syndrome have been reported. However, many of the adverse events seen with long term oral administration are generally not observed in the acute setting with IV treatment. The adverse events seen in chronic oral treatment include pulmonary toxicity (chronic interstitial pneumonitis being most common), thyroid dysfunction, corneal microdeposits, optic neuropathy, bluish-gray discoloration of skin, and various gastrointestinal side effects.

An FDA alert was issued in May of 2005 and stated the following:

FDA ALERT [05/2005] –Pulmonary toxicity, Hepatic Injury, and Worsened Arrhythmia. Amiodarone may cause potentially fatal toxicities, including pulmonary toxicity, hepatic injury, and worsened arrhythmia. Amiodarone should only be used to treat adults with life-threatening ventricular arrhythmias when other treatments are ineffective or have not been tolerated.

#### Off-label Uses

Despite the current indications, IV amiodarone is used “off-label” to treat a variety of supraventricular tachyarrhythmias, including atrial fibrillation (AF) in the acute setting.<sup>3</sup> IV amiodarone is used to control ventricular rate during AF, to maintain sinus rhythm after cardioversion and to maintain perioperative sinus rhythm following cardiac surgery. The quality of published data supporting these uses is variable. It should be noted that amiodarone IV has not been conclusively shown to effectively convert AF to sinus rhythm.

Although the label for oral amiodarone contains a boxed warning due to the above adverse events and known off-label use, the intravenous amiodarone label currently does not contain this boxed warning.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

Amiodarone is a Vaughan Williams class III antiarrhythmic drug, which also includes ibutilide, dofetilide, sotalol, and azimilide. All of these drugs block potassium channels, thereby prolonging repolarization, the action potential duration and the refractory period. These changes are manifested on an ECG by prolongation of the QT interval, providing the substrate for torsade

---

<sup>3</sup> Goldschlager N, Epstein AE, Naccarelli GV et al. A practical guide for clinicians who treat patients with amiodarone: 2007. Heart Rhythm. 2007 Sep;4(9):1250-9. Epub 2007 Jul 20.

de pointes. However, amiodarone is an exception to the class, with little proarrhythmic activity, related to its unique pharmacology and differences in its selectivity for the different channel types.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

### Preapproval Meetings:

- To reach agreement with the Agency on the submission of the IND, the sponsor had a meeting with the Division on January 6, 2006. The following relevant comments were communicated to the sponsor:
  - The development program must convince the Division that \_\_\_\_\_
  - \_\_\_\_\_

b(4)

At the pre-NDA meeting held on November 20, 2007 the Division agreed that there is no need for a Summary of Clinical Efficacy, an Integrated Summary of Efficacy, Summary of Clinical Safety, or an Integrated Summary of Safety (ISS).

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

The quality of the submission, with respect to organization, format and accessibility of files/datasets was acceptable to this reviewer and sufficient to complete my review.

### 3.2 Compliance with Good Clinical Practices

The protocol and informed consent form were reviewed and approved by an Institutional Review Board (IRB) prior to the screening or enrollment of study participants. The study was conducted in accordance with the Harmonized Tripartite Guidelines for Good Clinical Practice (GCP) issued by the International Conference on Harmonization (ICH) and with the local laws and regulations for the use of investigational therapeutic agents. The investigator was informed that regulatory authorities, including the United States (US) Food and Drug Administration (FDA) and representatives of the sponsor, could inspect the study documents and subject records at any time. Participation in the study was voluntary. Subjects were informed verbally and in writing regarding the objectives, procedures, and risks of study participation and allowed to ask questions. Each subject signed an informed consent form (ICF) written in the subject's usual language and was provided with a copy.

### **3.3 Financial Disclosures**

Sponsor states that none of the investigators that participated in support of this application held any of the disclosable financial arrangements with Prism Pharmaceuticals, Inc., as defined in 21 CFR 54.2(a)(b)(c) and (f). In this reviewer's opinion, the financial disclosures did not raise concerns about the integrity of the studies or data within this NDA.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

Please see final Chemistry review for full details. However, CMC has identified a manufacturing impurity that is expected to be present in all amiodarone formulations (oral and intravenous).

\_\_\_\_\_ This is a new issue despite the drug being approved in generic form for many years.

b(4)

The CMC review dated July 30, 2008 states:

“This NDA in its present form cannot be recommended for approval from a CMC perspective. The approval of this application, from a CMC perspective, depends on the applicant's response to the FDA IR letter sent to the applicant on 15-Sep-2008. Additionally, the overall Compliance and Microbiology recommendations have not been received at this time.”

### **4.2 Clinical Microbiology**

Microbiology recommendations have not been received at the time this review was completed.

### **4.3 Preclinical Pharmacology/Toxicology**

Pharmacology/Toxicology recommendations have not been received at the time this review was completed.

### **4.4 Clinical Pharmacology**

Clinical Pharmacology recommendations have not been received at the time this review was completed.

#### **4.4.1 Mechanism of Action**

Amiodarone is generally considered a class III antiarrhythmic drug, but it possesses electrophysiologic characteristics of all four Vaughan Williams classes. Like class I drugs, amiodarone blocks sodium channels at rapid pacing frequencies, and like class II drugs, it exerts

a noncompetitive antisymphathetic action. One of its main effects, with prolonged administration, is to lengthen the cardiac action potential, a class III effect. The negative chronotropic effect of amiodarone in nodal tissues is similar to the effect of class IV drugs. In addition to blocking sodium channels, amiodarone blocks myocardial potassium channels, which contributes to slowing of conduction and prolongation of refractoriness. The antisymphathetic action and the block of calcium and potassium channels are responsible for the negative dromotropic effects on the sinus node and for the slowing of conduction and prolongation of refractoriness in the atrioventricular (AV) node. The vasodilatory action of amiodarone can decrease cardiac workload and consequently myocardial oxygen consumption.

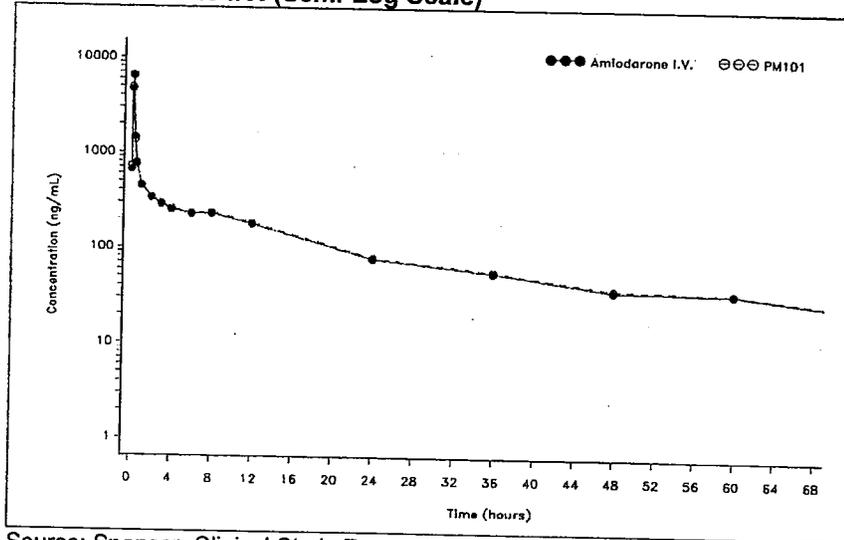
#### 4.4.2 Pharmacodynamics

As per the current label, intravenous amiodarone has been reported to produce negative inotropic and vasodilatory effects in animals and humans. In clinical studies of patients with refractory VF or hemodynamically unstable VT, treatment-emergent, drug-related hypotension occurred in 288 of 1836 patients (16%) treated with amiodarone. No correlations were seen between the baseline ejection fraction and the occurrence of clinically significant hypotension during infusion of intravenous amiodarone.

#### 4.4.3 Pharmacokinetics

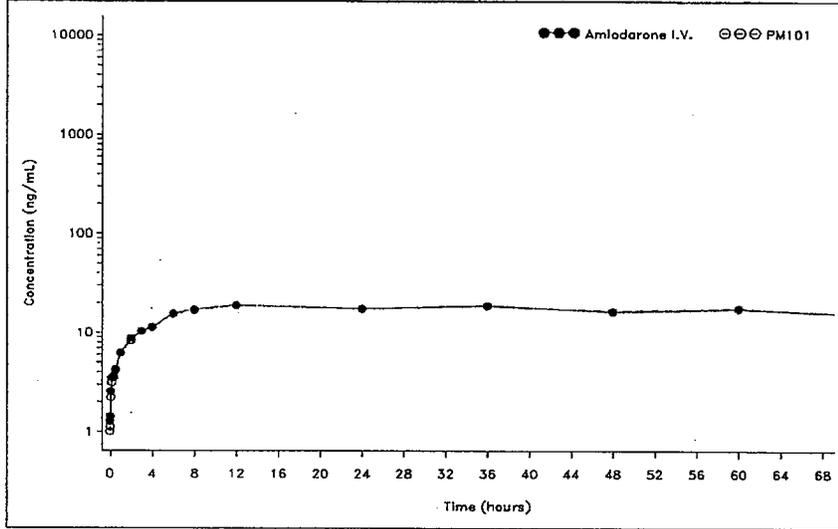
Plasma concentrations of PM101 IV (the study name for Nexterone IV) and Amiodarone IV in Study 101 are shown below for both amiodarone and its predominant active metabolite, desethylamiodarone, suggesting bioequivalence of the two formulations.

**Figure 2. Mean Plasma Concentrations of Amiodarone in PM 101 I.V. and Amiodarone I.V. (Semi-Log Scale)**



Source: Sponsor, Clinical Study Report 101, page 47.

**Figure 3. Mean Plasma Concentrations of Desethylamiodarone in PM 101 I.V. and Amiodarone I.V. (Semi-Log Scale)**



Source: Sponsor, Clinical Study Report 101, page 48

## 5 Sources of Clinical Data

The sponsor provided data from two studies, a bioequivalence study (Study 101) and a pharmacodynamic study (Study 102).

### 5.1 Table of Studies

**Table 1. Table of Studies**

Study ID	Description	N subjects	Endpoint	Investigational Drug	Control	Outcome
101	A randomized, single-center, double-blind, 2-period crossover study to evaluate the relative bioavailability of PM101 I.V. and Amiodarone I.V.	88 subjects (58M, 30F)	Pharmacokinetic bioequivalence measurements ( $C_{max}$ , $T_{max}$ , UAC, $T_{1/2}$ , etc.)	Nexterone 150mg IV infused over 10 minutes	Amiodarone 150mg IV infused over 10 minutes.	Nexterone IV bioequivalent to generic Amiodarone IV
102	A randomized, double-blind, double-dummy, placebo-controlled trial to determine the relative effect of PM101 I.V. versus placebo	342 randomized 323 completed (189M, 149F)	Change from baseline in systolic blood pressure to the lowest value within 15 minutes of the start of the infusion	Nexterone IV 2-second bolus	Placebo (D5W)	Nexterone IV non-inferior to placebo.

Clinical Review  
 Robert P. Fiorentino, MD, MPH  
 NDA 022325  
 Nexterone® Amiodarone HCl IV

	on hemodynamics in healthy adult volunteers					
--	---	--	--	--	--	--

Source: Reviewer

## 5.2 Review Strategy

Available clinical data from Studies 101 and 102 were reviewed, with particular focus on Study 102 since this study specifically evaluated the Nexterone IV bolus formulation with respect to hemodynamic measurements. Vitals signs data from both of these studies were not pooled as these studies had different treatment and assessment schedules. Data analyses were performed by JMP and/or STATA 10 software programs.

## 5.3 Discussion of Individual Studies

### **STUDY 101**

*(Please refer to the separate Clinical Pharmacology review of Study 101 and to Appendix 9.4 of this review for more detailed overview of study protocol.)*

Study 101 was designed as a bioequivalence study comparing a 10-minute infusion of PM101 (the Nexterone formulation) with a 10-minute infusion of generic IV amiodarone. Eighty-eight healthy subjects were randomized in a 1:1 ratio to one of two treatment sequences: Sequence "AB" (PM101 on Day 1 of Period 1 and Amiodarone IV on Day 1 of Period 2) or Sequence "BA" (Amiodarone IV on Day 1 of Period 1 and PM101 on Day 1 of Period 2). Subjects in both treatment groups received 150 mg of amiodarone at a rate of 10 mL/min for 10 minutes.

The two (crossover) periods of each treatment sequence were separated by a washout period of approximately 42 days.

Blood samples for the assessment of pharmacokinetic parameters were collected within 30 minutes prior to dose administration and 1, 5, 10, 20 and 30 minutes, and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after the start of the study drug infusion. The pharmacokinetic parameters were estimated from concentrations of amiodarone and the major metabolite, desethylamiodarone, in plasma samples.

Safety information collected for Study 101 included assessments of adverse events (AEs), clinical laboratory data, vital signs measurements, physical examinations, and electrocardiogram (ECG) measurements. Blood pressure and heart rate were obtained approximately 10 minutes prior to the start of the study drug infusion and approximately 10, 30, and 60 minutes after the start of the study drug infusion. During the study, blood pressure and pulse were measured after the subject was in a semi-reclined position for 5 minutes.

Study 101 demonstrated bioequivalence between PM101 (Nexterone) IV and generic amiodarone.

**STUDY 102**

*(Refer to Appendix 9.4 for more detailed overview of Study protocol)*

Study 102 was a randomized, double-blind, double-dummy, placebo-controlled trial to determine the relative effect of a PM101 (Nexterone) I.V. bolus versus placebo on hemodynamics in healthy adult volunteers. The primary objective of the study was to compare the effect of PM101 administered as an immediate intravenous bolus versus placebo on systolic blood pressure. Secondary objectives included evaluation of change from baseline in heart rate and change from baseline to the lowest value in mean arterial pressure and diastolic pressure.

The primary endpoint was the change in systolic blood pressure from Baseline to the lowest value (peak reduction) after the start of study drug administration through 15 minutes post-dose.

The baseline blood pressure measurement for each subject was calculated as the average of the last 2 observations prior to the first dose of study medication administration. The baseline HR measurement for each subject was calculated as the average of the last 4 observations prior to the first dose of study medication administration.

Key Eligibility Criteria

- Healthy male or female 18 to 55 years of age
- BMI 18-35 kg/m<sup>2</sup>
- No significant disease or abnormal laboratory values
- Normal 12-lead electrocardiogram, without any clinically significant abnormalities of rate, rhythm or conduction
- Nonsmoker

Procedures

Subjects were screened within 21 days of dosing. On Day 1, subjects were randomized in a 2:2:1:1 ratio to the Placebo, PM101 (Nexterone) IV, Amiodarone I.V. 10 minute loading infusion, or Amiodarone I.V. 15 second loading infusion groups, respectively, as shown in Table 2. Randomization continued until 342 subjects had been randomized.

Note that Arm A and Arm B were used in the primary pharmacodynamic endpoint analysis.

**Table 2. Study 102 Treatment Assignments**

Treatment Group	Study Drug	Regimen
A	Placebo I.V. (D5W)	D5W immediate intravenous bolus (< 2 seconds) then D5W intravenous infusion for 6 hours then D5W intravenous infusion for 18 hours
B	PM101 (Nexterone) I.V. 2 Second Bolus	150 mg immediate intravenous bolus (<2 seconds) then 1 mg/minute intravenous infusion for 6 hours then

Clinical Review  
 Robert P. Fiorentino, MD, MPH  
 NDA 022325  
 Nexterone® Amiodarone HCl IV

		0.5 mg/min intravenous infusion for 18 hours
C	Amiodarone I.V. Reference Listed Drug (10 minute Loading Dose)	150 mg/100 mL intravenous infusion over <u>10 min</u> at 10 mL/min then 1 mg/minute intravenous infusion for 6 hours then 0.5mg/min intravenous infusion for 18 hours
D	Amiodarone I.V. Reference Listed Drug (15 Second Loading Dose)	150 mg intravenous infusion over <u>15 seconds</u> then 1 mg/minute intravenous infusion for 6 hours then 0.5 mg/min intravenous infusion for 18 hours

*Summary of Treatment Schedule*

On the morning of Day -1 (~ 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.

Blood pressure measurements were made by automatic cuff every 10 minutes starting at 60 minutes prior to study drug administration to obtain stabilized baseline measurements. In an effort to minimize “white-coat” blood pressure effects, sham maneuvers were implemented. This included a simulated administration of study drugs at 21 minutes prior to study drug administration, in a manner that duplicated the actual administration at T=0. Blood pressure measurements were conducted every 3 minutes until dosing and heart rate measurements were conducted every 1 minute until dosing.

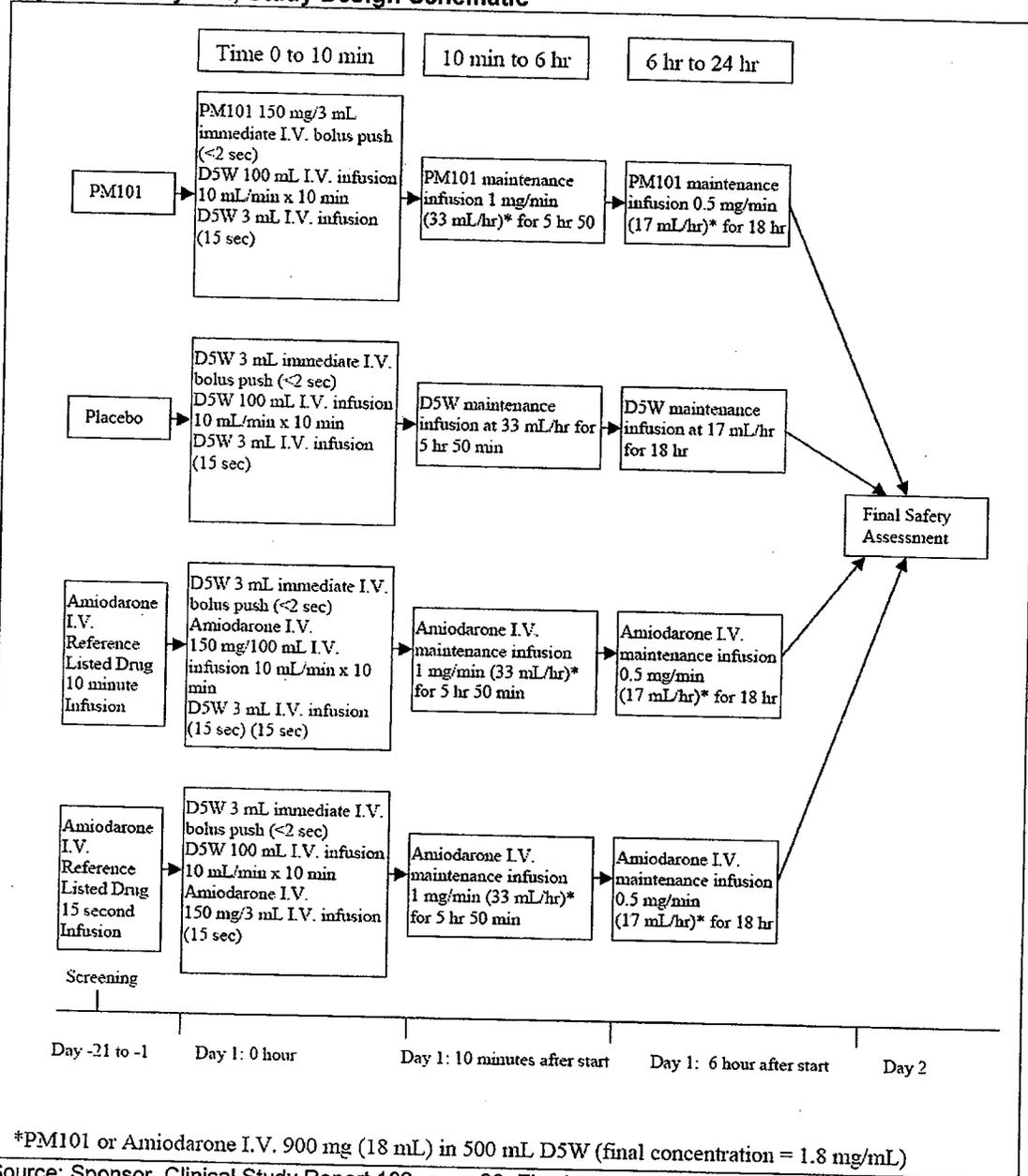
At T=0 (time zero), three scenarios occurred that preserved blinding in a manner that depended on randomization assignment:

1. The D5W bottle was replaced by an infusion bottle containing Amiodarone I.V. 150 mg/100 mL or matching placebo and infused at a rate of 10 mL/min for 10 minutes.
2. An immediate bolus push injection (<2 seconds) of PM101 150 mg/3 mL or placebo-D5W was administered through a side port.
3. A 15 second injection of Amiodarone I.V. (150 mg/3 mL) or matching placebo was administered through a side port.

At T = 10 minutes, the D5W bottle was replaced with a bottle of PM101 1.8 mg/mL, OR Amiodarone I.V. 1.8mg/ml OR placebo-D5W and infused at a rate of 1.0 mg/min for 5 hours and 50 minutes.

At T = 6 hours, the flow rate of the D5W bottle containing PM101 1.8 mg/mL, OR Amiodarone I.V. 1.8mg/mL, OR placebo-D5W was changed to a rate of 0.5 mg/min for the next 18 hours.

**Figure 4. Study 102, Study Design Schematic**



Blood pressure (BP) was assessed every 3 minutes for the first 60 minutes following dosing, then every hour until 12 hours following dose initiation. A final BP measurement was conducted at 24 hours post dose.

Heart rate (HR) was assessed every 1 minute for the first 60 minutes after dosing and then every hour until 12 hours after dosing. A final HR measurement was conducted at 24 hours post dose.

Subjects were discharged from the clinic on Day 2 following final safety assessments as diagramed in the figure below.

**Figure 5. Study 102, Study Assessments and Procedures**

STUDY PHASE	Screen	Treatment Period			
	1	2			
VISIT NUMBER	1	2			
DAY	-21	-2	-1	1	2
Medical History	X				
Informed Consent	X				
Assess Eligibility	X		X	X	
Physical Examination	X				X [A]
12-lead ECG	X	X			
Holter monitoring			X [B]	X [B]	X [B]
Clinical Lab Tests	X	X			X
Vital Signs	X				X
Body Weight	X				
Serum Pregnancy Test	X	X			
Urine Drug Screen	X	X			
Clinic Admission		X			
Randomization				[C]	
Medication Dose				[D]	[D]
BP Measurement				[E]	[E]
Heart Rate				[F]	[F]
Telemetry				[G]	[G]
Assessment of AEs				X	X
Clinic Discharge					X

[A] Abbreviated physical examination prior to clinic discharge  
 [B] Continuous 24-hour Holter monitoring from -25 to -1 hours (baseline), and -1 to 23 hours post dose (on treatment).  
 [C] After verification of eligibility  
 [D] According to the randomization schedule, combination of bolus/loading infusion + maintenance infusions  
 [E] BP Measurements at -60, -50, -40, -30, -21, -18, -15, -12, -9, -6, -3 and 0 minutes pre-dose; every 3 minutes for 60 minutes, then once hourly until 12 hours, and at 24 hours post-dose (from T = 0).  
 [F] Heart rate measurements at -60, -50, -40, -30, -21, -20, -19, -18, -17, -16, -15, -14, -13, -12, -11, -10, -9, -8, -7, -6, -5, -4, -3, -2, -1 and 0 minutes, pre-dose; every 1 minute for the first 60 minutes, then once hourly until 12 hours, and at 24 hours post-dose. (from T = 0).  
 [G] Continuous monitoring via telemetry from approximately 60 minutes pre-dose until 2 hours after stopping the maintenance infusion.

Source: Sponsor, Clinical Study Report 102, page 39, Table 1.

## 6 Review of Primary Pharmacodynamic (PD) Endpoint

As noted previously, because the sponsor did not submit data on administration of Nexterone in a diseased patient population that would be at risk for hemodynamically unstable VT or persistent VF, there is no efficacy data for review.

However, the results of the primary pharmacodynamic (PD) endpoint for Study 102 are provided in Table 3. Analysis of the primary PD endpoint in this study showed that the change from baseline was comparable between placebo and PM101, with PM101 being non-inferior to placebo. The FDA statistical reviewer has confirmed these results (see separate review).

**Table 3. Study 102, Systolic Blood Pressure Change from Baseline to Lowest Value within 15 minutes Post-Dose (PP Population)**

	Change from Baseline (mmHg)		Treatment Effect (vs. Placebo) <sup>a</sup>	
	Placebo (N=111)	PM101 (N=104)	Mean Difference	Lower Limit of 90% CI
Mean (SD)	-4.25 ± 4.424	-4.83 ± 5.009	-0.57	-1.64
Median	-3.50	-4.00		
Min, max	-22.0, 5.0	-25.0, 3.5		

<sup>a</sup> The mean difference (PM101-Placebo) and lower limit of 90% CI of difference are calculated from an ANOVA model with effect for treatment. If the lower limit of 90% CI > -5, PM101 is considered non-inferior to Placebo.

Source: Sponsor, Clinical Study Report 102, page 56, Table 5.

Additional analyses using the modified intent-to-treat population are shown in Table 4.

**Table 4. Study 102, Systolic Blood Pressure from Baseline to 15 Minutes Post-Dose: 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: FDA statistical reviewer, Fanhui Kong.

*REVIEWER COMMENT: The above modified ITT analysis is helpful as a sensitivity analysis for those subjects excluded from the primary, per-protocol analysis population. Non-inferiority appears to be preserved. Dropouts and discontinuations will be discussed separately in section 7.3.3 of this review.*

## **7 Review of Safety**

### **Safety Summary**

#### **7.1 Methods and Findings**

##### **7.1.1 Clinical Studies Used to Evaluate Safety**

Study 102 provided the primary clinical safety data and was specifically designed to evaluate acute changes in hemodynamics across treatments arms. Therefore, vital sign assessments were conducted more frequently in Study 102 compared to study 101, which was a bioequivalence study that was not designed to evaluate acute hemodynamic changes. Nevertheless, clinical data from study 101 was reviewed for any significant adverse events.

##### **7.1.2 Adequacy of Data**

Review of the dataset for coding of adverse events from verbatim terms through higher level coded terms did not raise concerns regarding the appropriateness of coding. Subjects who were discontinued or withdrew appeared to have accurate coding of AE terms across these datasets.

##### **7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence**

Data from studies 101 and 102 were not formally pooled and analyzed, due to the disparate rates of treatment administrations and formulations of study drugs between the two studies, as well as the incompatible assessment schedules based on different timelines.

However, adverse event data for both studies were reviewed.

#### **7.2 Adequacy of Safety Assessments**

##### **7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations**

Baseline demographics of target populations in Study 101 and Study 102 are tabulated in **Table 5** and **Table 6**, respectively.

**Table 5. Study 101, Demographic and Baseline Characteristics (Safety Population)**

Parameter	Sequence AB (N=44)	Sequence BA (N=44)	Overall (N=88)
Sex – n (%)			
Male	29 (65.9)	29 (65.9)	58 (65.9)
Female	15 (34.1)	15 (34.1)	30 (34.1)
Race – n (%)			
White	42 (95.5)	36 (81.8)	78 (88.6)
Black/African American	1 (2.3)	5 (11.4)	6 (6.8)
Asian	1 (2.3)	1 (2.3)	2 (2.3)
American Indian/Alaska Native	0 (0.0)	2 (4.5)	2 (2.3)
Ethnicity – n (%)			
Hispanic/Latino	5 (11.4)	9 (20.5)	14 (15.9)
Not Hispanic/Latino	39 (88.6)	35 (79.5)	74 (84.1)
Age (years)			
Mean (SD)	35.9 (12.00)	38.8 (11.84)	37.4 (11.94)
Minimum-maximum	18-59	18-58	18-59
Height (cm)			
Mean (SD)	170.56 (9.337)	170.20 (8.776)	170.38 (9.011)
Minimum-maximum	151.0-186.0	149.0-184.0	149.0-186.0
Weight (kg)			
Mean (SD)	72.80 (11.211)	73.48 (12.133)	73.14 (11.619)
Minimum-maximum	51.5-96.3	47.3-98.9	47.3-98.9
BMI (body mass index)			
Mean (SD)	24.99 (2.979)	25.28 (3.098)	25.13 (3.025)
Minimum-maximum	19.1-30.9	18.6-33.4	18.6-33.4

Sequence: AB=PM101 I.V./Amiodarone I.V.; BA=Amiodarone I.V./PM101 I.V.

Source: Sponsor, reproduced by reviewer from Clinical Study Report.

**Table 6. Study 102, Demographic and Baseline Characteristics (Safety Population)**

Parameter	Placebo (N=112)	PM101 (N=112)	Amiodarone I.V. (10 min loading infusion group) (N=57)	Amiodarone I.V. (15 sec loading infusion group) (N=57)	Total (N=338)
Age (years)					
Mean (SD)	35.5 ± 9.83	36.5 ± 10.98	36.7 ± 9.26	34.4 ± 8.62	35.9 ± 9.94
Sex – n (%)					
Male	63 (56.3%)	63 (56.3%)	32 (56.1%)	31 (54.4%)	189 (55.9%)
Female	49 (43.8%)	49 (43.8%)	25 (43.9%)	26 (45.6%)	149 (44.1%)
Ethnicity – n (%)					
Hispanic/Latino	23 (20.5%)	25 (22.3%)	9 (15.8%)	15 (26.3%)	72 (21.3%)
Not Hispanic/Latino	89 (79.5%)	87 (77.7%)	48 (84.2%)	42 (73.7%)	266(78.7%)
Race – n (%)					
White	105 (93.8%)	105 (93.8%)	53 (93.0%)	50 (87.7%)	313 (92.6%)
Black/African American	6 (5.4%)	5 (4.5%)	2 (3.5%)	7 (12.3%)	20 (5.9%)
Asian	1 (0.9%)	2 (1.8%)	2 (3.5%)	0	5 (1.5%)

Clinical Review  
 Robert P. Fiorentino, MD, MPH  
 NDA 022325  
 Nexterone® Amiodarone HCl IV

Height (cm)					
Mean (SD)	168.4 ± 9.07	167.6 ± 9.52	167.0 ± 8.63	168.6 ± 7.56	167.9 ± 8.90
Weight (kg)					
Mean (SD)	73.0 ± 12.43	72.2 ± 13.74	70.7 ± 12.27	73.0 ± 13.14	72.4 ± 12.94
BMI					
Mean (SD)	25.7 ± 3.21	25.5 ± 2.89	25.2 ± 3.05	25.6 ± 3.57	25.5 ± 3.13
BMI = body mass index.					

Source: Sponsor, reproduced from Clinical Study Report.

Across treatment arms, subjects appear to be similar in baseline characteristics. There do not appear to be significant imbalances in baseline demographics.

As bioequivalence and pharmacodynamic studies, both Study 101 and Study 102 evaluated the appropriate doses and durations of exposure in the above population.

### 7.2.2 Explorations for Dose Response

Study 102 was specifically designed to evaluate a more rapid *rate* of the loading dose administration (2 second bolus) compared to that currently approved for IV amiodarone (10 minute infusion). However, total doses of amiodarone administered did not vary between treatment arms; therefore dose response analyses were not performed for this generic amiodarone formulation.

### 7.2.3 Special Animal and/or In Vitro Testing

Proof of concept studies were performed in animals but no specific animal testing was otherwise performed for this generic formulation of amiodarone. Preclinical testing was adequate to explore the hemodynamic changes attributable to amiodarone and was appropriate based on drug's pharmacology.

### 7.2.4 Routine Clinical Testing

Studies 101 and 102 were performed in controlled study environments in a contract research clinic. The assessment of vital signs, collection of laboratory samples and elicitation of adverse event data appears to have been appropriately performed. Assessment of systolic blood pressure by automated cuff, although potentially imprecise, is an accepted means of determining blood pressure in light of more invasive options (e.g., pressure transduction via arterial cannulization.)

### 7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolism, clearance and interaction of amiodarone have been previously described in this generic compound's label. A brief summary of available data is provided below.

Amiodarone is metabolized to desethylamiodarone by the cytochrome P450 (CYP450) enzyme group, specifically cytochromes P450 3A4 (CYP3A4) and CYP2C8. The CYP3A4 isoenzyme is present in both the liver and intestines. Amiodarone is an inhibitor of CYP3A4 and p-

glycoprotein. Therefore, amiodarone has the potential for interactions with drugs or substances that may be substrates, inhibitors or inducers of CYP3A4 and substrates of p-glycoprotein. Only a limited number of *in vivo* drug-drug interactions with amiodarone have been reported, chiefly with the oral formulation. In view of the long and variable half-life of amiodarone, potential for drug interactions exists not only with concomitant medication but also with drugs administered after discontinuation of amiodarone.

Since amiodarone is a substrate for CYP3A4 and CYP2C8, drugs/substances that inhibit these isoenzymes may decrease the metabolism and increase serum concentration of amiodarone. Such drugs are listed in the currently approved label.

### **7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class**

Amiodarone has a unique adverse event profile when taken orally over an extended period of time; however, adverse events related to the first rapid loading infusion have been appropriately evaluated in Study 102, including evaluation of hemodynamic changes.

## **7.3 Major Safety Results**

### **7.3.1 Deaths**

There were no deaths reported in Study 101 or Study 102.

### **7.3.2 Nonfatal Serious Adverse Events**

There were no nonfatal Serious Adverse Events reported in Study 101 or Study 102.

### **7.3.3 Dropouts and/or Discontinuations**

Dropouts and discontinuations for Studies 101 and 102 are discussed separately below.

Clinical Review  
 Robert P. Fiorentino, MD, MPH  
 NDA 022325  
 Nexterone® Amiodarone HCl IV  
STUDY 101

**Table 7. Study 101, Subject Disposition**

Parameter/Category	Sequence AB (N=44)		Sequence BA (N=44)		Overall (N=88)	
	PM101 I.V. (N=44)	Amiodarone I.V. (N=43)	Amiodarone I.V. (N=44)	PM101 I.V. (N=38)	Amiodarone I.V. (N=87)	PM101 I.V. (N=82)
<b>Number of Subjects</b>						
Randomized to Sequence	44		44		88	
Took Study Drug During Treatment Period	44 (100.0%)	43 (100.0%)	44 (100.0%)	38 (100.0%)	87 (100.0%)	82 (100.0%)
Completed Treatment Period	43 (97.7%)	41 (95.3%)	38 (86.4%)	37 (97.4%)	79 (90.8%)	80 (97.6%)
Discontinued Treatment Period Early	1 (2.3%)	2 (4.7%)	6 (13.6%)	1 (2.6%)	8 (9.2%)	2 (2.4%)
<b>Primary Reason for Discontinuation</b>						
Adverse Event	0	2 (4.7%)	2 (4.5%)	1 (2.6%)	4 (4.6%)	1 (1.2%)
Protocol Violation	0	0	0	0	0	0
Withdrawal Consent	0	0	3 (6.8%)	0	3 (3.4%)	0
Lost to Follow-up	0	0	0	0	0	0
Sponsor's Request	0	0	0	0	0	0
Principal Investigator Decision	0	0	0	0	0	0
Other	1 (2.3%)	0	1 (2.3%)	0	1 (1.1%)	1 (1.2%)
<b>Safety Population [1]</b>	44 (100.0%)	43 (100.0%)	44 (100.0%)	38 (100.0%)	87 (100.0%)	82 (100.0%)

Note: Sequence: AB = PM101 I.V./Amiodarone I.V., BA = Amiodarone I.V./PM101 I.V.  
 Percentages were based on the number of subjects who took any study drug in each treatment group or combined.  
 [1] All randomized subjects who took any amount of study drug. Subjects were grouped based on treatment received.

Source: Sponsor, Clinical Study Report, page 77, Table 14.1.1

Electronic Case Report Forms (eCRFs) and adverse event data were reviewed for all subjects that were discontinued in Study 101. Table 8 summarizes the reasons for discontinuation and the adverse events for each discontinued subject.

**Table 8. Study 101, Discontinued Subjects (All Randomized Subjects Population)**

Treatment Sequence (First/Second)	Subject ID	Age/Sex	Listed Reason for Discontinuation	CRF Review of AEs
Amiodarone I.V./PM101 I.V.	001-008	24, F	Adverse event(s)	Sinus tachycardia: experienced sinus tachycardia prior to the start of infusion and was later withdrawn from the study for sinus tachycardia that occurred intermittently for 31 hours after the start of infusion.
Amiodarone I.V./PM101 I.V.	001-011	45, M	Withdrew Consent	"Subject withdrew himself due to his job requirement."
Amiodarone I.V./PM101 I.V.	001-016	56, F	Other: Vein infiltration during the dosing.	Non-contributory
Amiodarone I.V./PM101 I.V.	001-026	23, F	Adverse event(s)	Infusion site reaction during infusion of PM101; resolved.
Amiodarone I.V./PM101 I.V.	001-028	39, M	Withdrew Consent	"Subject said that he will not show up for the second period due to the fact that his wife is dead."
Amiodarone I.V./PM101 I.V.	001-034	53, M	Withdrew Consent	The subject withdrew himself for personal reasons.
Amiodarone I.V./PM101 I.V.	001-068	48, F	Adverse event(s)	Dyspnea, hot flush
PM101 I.V./Amiodarone I.V.	001-037	19, F	Adverse event(s)	Abdominal pain, chest discomfort, feeling cold, hypoesthesia, dyspnea, while receiving Amiodarone IV
PM101 I.V./Amiodarone I.V.	001-047	31, F	Adverse event(s)	Chest discomfort while receiving Amiodarone IV
PM101 I.V./Amiodarone I.V.	001-085	29, M	Other: OPIATES POSITIVE	

Source: Reviewer.

Narratives of subjects (sponsor's) who discontinued due to an adverse event are provided below:

**Subject 001-008**, 24yo white female, history of childhood heart murmur. Had tachycardia prior to infusion of first dose of amiodarone IV and then dizziness for 13 hours and tachycardia until the following day (>24 hrs). Subject withdrew and did not receive PM101 IV in period 2.

**Subject 001-026**, a 23-year-old white female, was randomized to Amiodarone I.V. treatment in Period 1 and received her infusion. During Period 2, the subject received an infusion of PM101 I.V. At 3 minutes after the start of the infusion, the subject developed redness on the infusion arm. The investigator believed this indicated an allergic reaction and PM101 I.V. was stopped shortly thereafter. No treatment was given, and the event resolved without sequelae after 34 minutes. The subject withdrew from the study as a result of the adverse event.

**Subject 001-037**, a 19-year-old White female, was randomized to PM101 I.V. treatment in Period 1 and received her first infusion of study drug. 5 minutes after the start of the infusion, the subject reported feeling hot. The infusion was continued, and feeling hot resolved without treatment after 10 minutes. The subject was noted to have intermittent redness of about 1 cm at the infusion site. Two days later, the subject reported mild palpitations at 10:30 a.m. that resolved within 1 hour.

During Period 2 of the study, the subject received an infusion of Amiodarone I.V. At 2 minutes after the start of infusion, the subject developed erythema on both arms and reported she was having difficulty breathing. Amiodarone I.V. was stopped and D5W was started. Dyspnea and erythema both resolved within 2 to 3 minutes. The subject was noted to have infusion site bruising at 4 hours after the start of infusion and pain at 10 hours after the start of infusion. In addition to the events described above, the subject experienced a constellation of adverse events following study drug infusion, including palpitations, abdominal distension, abdominal pain, diarrhea, oral hypoesthesia, nausea, chest discomfort, fatigue, feeling cold, and hypoesthesia. The subject withdrew from the study as a result of the adverse events.

**Subject 001-047**, a 31-year-old White female, was randomized to PM101 I.V. treatment during Period 1 and received her first infusion with no complications noted. During Period 2, the subject received an infusion of Amiodarone I.V. At 2 minutes after the start of the infusion, the subject experienced chest pressure, a burning sensation in her chest, and difficulty breathing. Study drug infusion was stopped. All three events resolved without sequelae within 3 minutes of onset. 20 minutes after start of infusion, the subject reported pain and a sensation of swelling in her left foot. No treatment was given for either event, and both events resolved within 1 day. Later that same day, the subject developed sweating that resolved after 2.5 hours. The subject subsequently discontinued from the study as a result of the adverse events.

**Subject 001-068**: a 46-year-old White female was randomized to Amiodarone I.V. treatment during Period 1. At 1 minute after the start of the infusion, the subject reported difficulty with breathing and hot flush. Amiodarone I.V. was stopped. Dyspnea and hot flush both resolved without sequelae within 1 minute. Later that same day, the subject developed redness on her thighs and on her back. Erythema of the back resolved the next day; the outcome of the erythema on the thighs was unresolved at the time the subject withdrew from the study.

*REVIEWER COMMENT: Formal comparisons of adverse event rates are limited by the relatively small number of subjects in Study 101. However, there does not appear to be an increased rate of adverse events leading to subject discontinuations in the PM101 arm, nor does there appear to be a specific AE that is disproportionately represented in the PM101 arm. Adverse events that include hot flashes and infusion site reactions are not unexpected AEs.*

### STUDY 102

A total of 342 subjects were randomized and enrolled in the study and 338 subjects received study drug; 112 subjects received placebo, 112 subjects received PM101 2 second IV bolus, 57 subjects received Amiodarone I.V. 10 minute loading infusion, and 57 subjects received Amiodarone I.V. 15 second loading infusion.

A summary of the four subjects who were randomized but did not receive study medication is provided below:

1. Subject 001-011 (placebo): withdrawn at -55 minutes due to nausea
2. Subject 001-103 (placebo): withdrawn at -50 minutes due to abnormal pre-dose laboratory results for hemoglobin and hematocrit that were provided to the investigator after IV insertion that were deemed a violation of exclusion criteria [protocol violation]
3. Subject 001-054 (PM101): withdrawn due to vasovagal reaction (consisting of the combined adverse events of pulse rate decreased, dizziness, blood pressure decreased, sinus bradycardia transitioning to junctional rhythm) while receiving I.V. D5W and before study drug.

4. Subject 001-053 (Amiodarone I.V. 15 second loading infusion): withdrawn due to vasovagal reaction (consisting of the combined adverse events of sweating, nausea, bradycardia until brief asystole, weak pulse, weakness, blood pressure decreased, junctional rhythm) while receiving I.V. D5W and before study drug.

An additional 15 subjects (4.4%) discontinued from the study; 6 (5.4%) in the PM101 group, 3 (5.3%) in the Amiodarone I.V. 10 minute loading infusion group, and 6 (10.5%) in the Amiodarone I.V. 15 second loading infusion group.

Most of these discontinuations (11/15) were due to adverse events, which occurred in 4 (3.6%), 1 (1.8%), and 6 (10.5%) subjects in the PM101, Amiodarone I.V. 10 minute loading, and Amiodarone 15 second loading groups, respectively.

### Subject Disposition

The three study populations described throughout the analyses are defined below:

**Safety Population:** All randomized subjects who took any amount of study drug. Subjects were grouped based on treatment received.

**Modified Intent-to-Treat Population:** All randomized subjects who took any amount of study drug, together with a Baseline and one on therapy assessment of systolic blood pressure. Subjects were grouped based on randomization schedule.

**Per-Protocol Population:** All randomized subjects who took any amount of study drug, 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 (scheduled time points). Subjects were grouped based on randomization schedule.

The disposition of subjects in the All Randomized population is displayed in **Table 9**.

Clinical Review  
 Robert P. Fiorentino, MD, MPH  
 NDA 022325  
 Nexterone® Amiodarone HCl IV

**Table 9. Study 102, Subject Disposition, All Randomized Population**

Parameter/Category	Placebo (N=114)	PM101 I.V. (N=113)	Amiodarone I.V. 10 min (N=57)	Amiodarone I.V. 15 sec (N=58)	Total (N=342)
<b>Number of Subjects</b>					
Randomized	114	113	57	58	342
Took Study Drug	112 (100.0%)	112 (100.0%)	57 (100.0%)	57 (100.0%)	338 (100.0%)
Completed Study	112 (100.0%)	106 (94.6%)	54 (94.7%)	51 (88.5%)	323 (95.6%)
Discontinued Study	0	6 ( 5.4%)	2 ( 3.3%)	6 ( 10.5%)	15 ( 4.4%)
<b>Primary Reason for Discontinuation</b>					
Adverse Event	0	4 ( 3.6%)	1 ( 1.8%)	6 ( 10.5%)	11 ( 3.3%)
Protocol Violation	0	0	0	0	0
Withdrawal Consent	0	1 ( 0.9%)	1 ( 1.8%)	0	2 ( 0.6%)
Lost to Follow-up	0	0	0	0	0
Sponsor's Request	0	0	0	0	0
Principal Investigator Decision	0	0	0	0	0
Other	0	1 ( 0.9%)	1 ( 1.8%)	0	2 ( 0.6%)
<b>Safety Population [1]</b>	112 (100.0%)	112 (100.0%)	57 (100.0%)	57 (100.0%)	338 (100.0%)
<b>Modified Intent-to-Treat Population [2]</b>	112 (100.0%)	112 (100.0%)	57 (100.0%)	57 (100.0%)	338 (100.0%)
<b>Per-Protocol Population [3]</b>	111 ( 99.1%)	104 ( 92.9%)	54 ( 94.7%)	54 ( 94.7%)	323 ( 95.6%)

Percentages were based on the number of subjects who took any study drug in each treatment group or combined.  
 [1]: All randomized subjects who took any amount of study drug. Subjects were grouped based on treatment received.  
 [2]: All randomized subjects who took any amount of study drug, together with a Baseline and one on therapy assessment of systolic blood pressure. Subjects were grouped based on randomization schedule.  
 [3]: All randomized subjects who took any amount of study drug, 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 (scheduled time points). Subjects were grouped based on randomization schedule.

Source: Sponsor, Clinical Study Report, page 101, Table 14.1.1.

A tabulation of subjects excluded from each of the above three study populations is provided in **Appendix 9.5**.

Subjects Excluded from Per-Protocol Population

The per-protocol population was pre-specified for the primary PD analysis in Study 102. Subjects excluded from the per-protocol population and the reason for the exclusion is provided in **Table 10**.

**Table 10. Study 102, Subjects Excluded from the Per Protocol Population**

Parameter	Placebo (N=112)	PM101 (N=112)	Amiodarone I.V. (10 min loading infusion group) (N=57)	Amiodarone I.V. (15 sec loading infusion group) (N=57)
Missing BP measurements from T0 to T15	001-114	001-018 001-101 001-186 001-199 001-209 001-240 001-302	001-159 001-245	001-005 001-200 001-289
Dosing error		001-042		
Exclusion criterion			001-100	
<b>Total subjects excluded</b>	<b>1</b>	<b>8</b>	<b>3</b>	<b>3</b>

Source: Reproduced from sponsor.

There was a comparatively higher numbers of subjects (8) excluded from the per-protocol analysis in the PM101 arm due to missing blood pressures between T=0 to T=15.

In order to evaluate the impact of the excluded subjects on the primary analysis, a summary of recorded blood pressure changes over the analysis period (T=0 to T=15min) is shown in Table 11 below. Note that these data represent blood pressure readings that were available from the vital signs dataset (VS.xpt):

**Table 11. Study 102, Blood pressure changes for per-protocol excluded subject (available data)**

Subject ID	Lowest available SBP change from baseline from T= 0 to 15min	Mean change in SBP from baseline from T=0 to 15min
001-018	-2.5 (0 min)	17.42
001-101	-3.0 (0 min)	5.67
001-186	-2.5 (9min)	5.58
001-199	-38.5 (6min)	-13.92
001-209	-2.0 (3 min)	1.50
001-240	-3.5 (15min)	0.80
001-302	-0.5 (6 min)	-0.75

SBP = systolic blood pressure. Source: Reviewer.

Note the substantial drop in SBP in subject 001-199 recorded at 6 minutes. Since Subject 001-199 had a BP measurement that was missing at the T=15 minute timepoint, he was excluded from the per protocol population. However, as demonstrated by the statistical reviewer, inclusion of these subjects (including Subject 001-199) in the modified ITT analysis did not change the conclusion of non-inferiority of PM101 IV compared to placebo (see Section 6).

#### Discontinued Subjects

The following table summarizes the sponsor's reason for all study discontinuations as well as this reviewer's summary of case report forms and subject narratives. Note that in the PM101 arm; only one subject (001-054) was excluded from the safety population because they did not receive the study drug.

Clinical Review  
 Robert P. Fiorentino, MD, MPH  
 NDA 022325  
 Nexterone® Amiodarone HCl IV

**Table 12. Study 102, Discontinued Subjects from All Randomized Subjects**

Treatment Group	Subject ID	Listed Reason for Discontinuation	CRF Review Notes
Placebo	001-011	AE	Nausea prior to T=0. Not treated (see above)
Placebo	001-103	Protocol violation	(see above)
PM101 I.V.	001-018	AE	Subject started dosing and experienced generalized hot flushes followed by dizziness and difficulty breathing. The medication was stopped.
PM101 I.V.	001-054	AE*	*Vasovagal reaction (see above) before receiving study drug
PM101 I.V.	001-068	AE	Adverse event: superficial phlebitis at infusion site
PM101 I.V.	001-139	AE	Stopped infusion due to pain. Redness, pain and induration of the vein at catheter site.
PM101 I.V.	001-160	AE	Pain over infusion site and vein with induration and redness.
PM101 I.V.	001-187	Other: Due to failed catheter attempts and no evidence of any unused good veins	
PM101 I.V.	001-242	Withdrew consent	The subject refused to remain in the study. Unrelated AE term: "Sensation of heat (lower body)"
Amiodarone IV 10min	001-113	AE	Superficial phlebitis, infusion site right arm
Amiodarone IV 10min	001-284	Tubing problems, medication not infused completely	
Amiodarone IV 10min	001-295	Withdrew consent	Nausea. Subject no longer wanted study drug and it was discontinued.
Amiodarone IV 15sec	001-028	AE	Superficial phlebitis
Amiodarone IV 15sec	001-053	AE*	Vasovagal reaction (withdrew before receiving study drug)*
Amiodarone IV 15sec	001-154	AE	Infusion stopped because subject had pain at infusion site and right hand swelling
Amiodarone IV 15sec	001-157	AE	Arm was swollen, redness at infusion site, subject complained of pain. Nausea following catheter insertion and decreased pulse rate.
Amiodarone IV 15sec	001-175	AE	Superficial phlebitis. Sinus bradycardia, not clinically significant.
Amiodarone IV 15sec	001-218	AE	Superficial phlebitis infusion site left arm. Additional AE term: Blood pressure decreased.
Amiodarone IV 15sec	001-247	AE	Superficial phlebitis. Subject is recorded as an early termination due to infusion site issues.

Source: Reviewer

*REVIEWER COMMENT: In the PM101 arm and the Amiodarone IV 15 second loading dose arm, a larger proportion of discontinued subjects had adverse events associated with infusion site reactions, including phlebitis. It is clear that both of these AEs were due to study drug and possibly the result of the rapid rate of administration investigated in these arms.*

Protocol Deviations

**Table 13. Study 102, Protocol Deviations by Arm (Safety Population)**

Arm	Number of Subjects w/ $\geq 1$ protocol deviation (% safety population)
PM101 I.V. (n=112)	38 (34%)
Placebo (n=112)	28 (25%)
Amiodarone I.V. 15 sec (n=57)	25 (44%)
Amiodarone I.V. 10 min (n=57)	18 (32%)

Source: Reviewer

On review of the datasets, the most commonly reported deviations ( $\geq 1$ ) for the PM101 IV arm are tabulated along with the frequency of occurrence:

**Table 14. Study 102, Commonly Reported Protocol Deviations**

Number of Occurrences	Reported Deviation
7	To be included in the PP population post-dose BP measurements must be taken every 3 minutes for the 1st 15 minutes (T0 to T15).
6	Blood pressure will be measured at -60, -50, -40, -30, -21, -18, -15, -12, -09, -06, -03 and 0 mins; and post-dose every 3 minutes for the 1st 60 minutes, hourly from 2-12 hours and at 24 hours.
6	Subject will sit in a semi-recumbent position from approximately 60 minutes pre- to 60 minutes post-dose.
4	Post study procedures did not require a urine pregnancy test.
4	The subjects will be encouraged to drink at least 2L of water within 24 hours after the start of dosing in order to assure that they are well hydrated.
2	Subjects will remain in a semi-recumbent position from 60 mins pre- to 60 mins post-dose. All other BP and HR measurements will be obtained after the subject has been sitting for 5 minutes.

Source: Reviewer

Although the type of protocol deviations were similar across all arms, the other 3 arms had the deviation defined as "Subject will sit in a semi-recumbent position from approximately 60 minutes pre- to 60 minutes post-dose" as the most frequently occurring deviation.

*REVIEWER COMMENT: In my view, it is very unlikely that these deviations would have influenced the outcome of the trial. As shown previously in the modified intention to treat analysis (shown previously), including available vital signs data for subjects that otherwise were excluded from the per-protocol population because of protocol deviations, did not alter the study outcome.*

### 7.3.4 Significant Adverse Events

There were no marked hematological or other lab abnormalities that met the criteria for a serious adverse event. Adverse events that led to discontinuations were discussed previously and were primarily infusion-site reactions. Hemodynamic changes are discussed separately below.

#### Severe Adverse Events

There was one subject in Study 101 and one subject in Study 102 that had a “severe” adverse event.

**Table 15. Subjects with Severe Adverse Events**

Study	Subject ID	Treatment	AE Terms	Narrative Summary
101 (Bioequivalence study)	001-068	Amiodarone IV  (Amiodarone / PM101 IV sequence)	Difficulty to breathe, hot flushes	Subject receiving Amiodarone IV at time of AE. Developed redness on leg, shivering, given Benadryl 50mg oral. Resolved, subject discontinued from study. Narrative provided above in Section 7.3.3.
102 (PK / PD study)	001-187	PM101 IV	Superficial phlebitis infusion site	34 year old white female developed infusion site phlebitis rated as severe.

Source: Reviewer.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Treatment emergent AEs were defined as those AEs that began on or after the date/time of study medication administration or increased in severity or intensity on or after the date/time of study medication administration. Drug related AEs included those AEs that were reported by the Investigator to have had a reasonable possibility that the AE was related to study medication.

#### Study 101

For Study 101, Table 16 summarizes adverse events in both treatment groups.

Clinical Review  
 Robert P. Fiorentino, MD, MPH  
 NDA 022325  
 Nexterone® Amiodarone HCl IV

**Table 16. Study 101 Adverse Events**

	Number of Subjects n(%)					
	Sequence AB (N=44)		Sequence BA (N=44)		Overall (N=88)	
	PM101 I.V. (N=44)	Amiodarone I.V. (n=43)	Amiodarone I.V. (n=44)	PM101 I.V. (N=38)	Amiodarone I.V. (N=87)	PM101 I.V. (n=82)
<b>At Least :</b>						
1 AE	20 (45.5)	12 (27.9)	23 (52.3)	19 (50.0)	35 (40.2)	39 (47.6)
1 treatment-related AE	13 (29.5)	11 (25.6)	17 (38.6)	16 (42.1)	28 (32.2)	29 (35.4)
1 SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1 AE leading to premature discontinuation of study drug	0 (0.0)	2 (4.7)	1 (2.3)	1 (2.6)	3 (3.4)	1 (1.2)

Treatment-related AEs were AEs that were possibly or probably related to study drug.  
 Source: Sponsor.

*REVIEWER COMMENT: The number of adverse events in this study is generally comparable across treatment arms, except for what appears to be a lower number of subjects with ≥ 1 AE in the Amiodarone IV arm of sequence AB.*

Specific adverse events for Study 101 are tabulated below.

**Table 17. Study 101 Treatment-Emergent Adverse Events in >3% of the Population for Either Treatment Group (Safety Population)**

System Organ Class Preferred Term	PM101 I.V. (N=82) n(%) <sup>a</sup>	Amiodarone I.V. (N=87) n(%) <sup>a</sup>
<b>Subjects with at least 1 AE</b>	39 (47.6)	35 (40.2)
<b>Gastrointestinal disorders</b>	7 (8.5)	6 (6.9)
Nausea	3 (3.7)	2 (2.3)
Abdominal pain	0 (0.0)	3 (3.4)
Flatulence	3 (3.7)	0 (0.0)
<b>General disorders and administration site conditions</b>	16 (19.5)	17 (19.5)
Catheter site pain	5 (6.1)	2 (2.3)
Feeling hot	5 (6.1)	1 (1.1)
Infusion site pain	3 (3.7)	3 (3.4)
Infusion site erythema	3 (3.7)	2 (2.3)
Chest discomfort	0 (0.0)	3 (3.4)
Fatigue	0 (0.0)	3 (3.4)
Feeling cold	0 (0.0)	3 (3.4)
<b>Investigations</b>	4 (4.9)	4 (4.6)
Blood pressure decreased	3 (3.7)	1 (1.1)
<b>Musculoskeletal and connective tissue disorder</b>	7 (8.5)	5 (5.7)
Back pain	4 (4.9)	1 (1.1)
Pain in extremity	0 (0.0)	3 (3.4)
<b>Nervous system disorder</b>	10 (12.2)	14 (16.1)
Headache	5 (6.1)	7 (8.0)
Somnolence	4 (4.9)	2 (2.3)
Dizziness	3 (3.7)	2 (2.3)

Clinical Review  
 Robert P. Fiorentino, MD, MPH  
 NDA 022325  
 Nexterone® Amiodarone HCl IV

System Organ Class Preferred Term	PM101 I.V. (N=82) n(%) <sup>a</sup>	Amiodarone I.V. (N=87) n(%) <sup>a</sup>
Hypoesthesia	0 (0.0)	4 (4.6)
<b>Respiratory, thoracic and mediastinal disorders</b>	4 (4.9)	8 (9.2)
Dyspnea	1 (1.2)	4 (4.6)
<b>Skin and subcutaneous tissue disorder</b>	3 (3.7)	7 (8.0)
Dermatitis contact	1 (1.2)	3 (3.4)
Erythema	0 (0.0)	3 (3.4)
<b>Vascular disorders</b>	3 (3.7)	3 (3.4)
Hot flush	2 (2.4)	3 (3.4)

<sup>a</sup> A subject was counted once if the subject reported one or more events in each system organ class/preferred term.

Source: Reproduced from Sponsor.

As noted above, a higher percentage of subjects had  $\geq 1$  AE in the PM101 group compared to the Amiodarone IV group (47.6% vs. 40.2%). Of note is the higher rate of “catheter site pain” (6.1% vs. 2.3%) and “feeling hot” (6.1% vs. 1.1%) in the PM101 vs. Amiodarone groups.

Sponsor has provided a tabulation of infusion site AEs that included infusion site erythema, hemorrhage, pain, warmth, reaction, and induration AEs and included AEs reported spontaneously by subjects and AEs noted by the clinic staff during visual evaluation of the infusion site and questioning of the subject approximately 1 and 24 hours after the start of the infusion.

**Table 18. Study 101, Treatment-Emergent, Treatment-Related Infusion Site AEs**

	Sequence AB (n=44)		Sequence BA (n=44)		Overall (n=88)	
	PM101 IV (n=44)	Amiodarone IV (n=43)	Amiodarone IV (n=44)	PM101 IV (n=38)	Amiodarone IV (n=87)	PM101 IV (n=82)
Infusion Site AEs	8 (9.1%)	2 (4.7%)	6 (13.6%)	4 (10.5)	8 (9.2%)	8 (9.8)

Source: Sponsor.

*REVIEWER COMMENT: In this study, the rates of infusion site AEs were similar overall between the amiodarone and PM101 groups.*

### Study 102

A total of 342 subjects were enrolled in the study and 338 subjects comprising the safety population received study medication. All 112 subjects in the PM101 group received a dose of 150 mg amiodarone during the first 10 minutes of infusion (mean dose of  $1024.82 \pm 97.538$  mg during the entire study).

Clinical Review  
 Robert P. Fiorentino, MD, MPH  
 NDA 022325  
 Nexterone® Amiodarone HCl IV

In **Table 19**, note the higher rates of adverse events in the Amiodarone IV 15 second loading dose arm compared to the PM101 IV 2 second bolus and Amiodarone IV 10 minute loading dose arm. Assessment is complicated by a high rate of treatment-related AEs in the placebo arm.

**Table 19. Study 102, Treatment Emergent AEs**

<b>Overall Summary of Treatment-Emergent Adverse Events (Safety Population), N (%)</b>				
	<b>Placebo (N=112)</b>	<b>PM101 IV (2 sec loading dose) (N=112)</b>	<b>Amiodarone I.V. (10 min loading infusion group) (N=57)</b>	<b>Amiodarone I.V. (15 sec loading infusion group) (N=57)</b>
Subjects with ≥ 1 AE	42 (37.5%)	91 (81.3%)	45 (78.9%)	54 (94.7%)
Subjects with ≥ 1 treatment-related AE <sup>a</sup>	34 (30.4%)	88 (78.6%)	40 (70.2%)	54 (94.7%)
Subjects with ≥ 1 SAE	0	0	0	0
Subjects with ≥ 1 AE leading to premature discontinuation of study medication	0	4 (3.6%)	1 (1.8%)	6 (10.5%)
Note: Only treatment-emergent AEs were tabulated.				
<sup>a</sup> Treatment-related AE was an AE probably or possibly related to study drug.				

Source: Study sponsor.

In descending frequency, **Table 20** displays AE terms represented by >1% in the PM101 IV arm, against rates in the same AE category in different arms. The most common adverse event terms in the PM101 arm were “feeling hot,” “infusion site pain” and “infusion site phlebitis.” Note the higher frequency of “feeling hot” in the rapid infusions of PM101 2 second bolus and Amiodarone 15 sec arms.

Clinical Review  
 Robert P. Fiorentino, MD, MPH  
 NDA 022325  
 Nexterone® Amiodarone HCl IV

**Table 20. Study 102, Safety Population, Treatment Emergent AE's (%)**

Adverse Event Term	PM101 I.V. (n=112)	Amiodarone I.V. 15 sec (n=57)	Amiodarone I.V. 10 min (n=57)	Placebo (n=112)
FEELING HOT	37.5%	40.4%	5.3%	3.6%
INFUSION SITE PAIN	33.9%	40.4%	33.3%	15.2%
INFUSION SITE PHLEBITIS	22.3%	38.6%	28.1%	0%
HEADACHE	8.0%	7.0%	12.3%	11.6%
INFUSION SITE ERYTHEMA	8.0%	22.8%	12.3%	1.8%
DIZZINESS	7.1%	3.5%	0%	1.8%
FEELING COLD	5.4%	5.3%	0%	0.9%
INFUSION SITE INDURATION	5.4%	10.5%	7.0%	3.6%
INFUSION SITE SWELLING	5.4%	10.5%	7.0%	0.9%
HOT FLUSH	3.6%	14%	1.8%	0%
ABDOMINAL PAIN	1.8%	3.5%	0%	1.8%
BLOOD PRESSURE DECREASED	1.8%	0%	0%	0%
BURNING SENSATION	1.8%	1.8%	0%	0%
INFUSION SITE BRUISING	1.8%	0%	3.5%	0.9%
INFUSION SITE REACTION	1.8%	3.5%	5.3%	0%
INJECTION SITE PRURITUS	1.8%	0%	1.8%	0%
MUSCLE SPASMS	1.8%	0%	0%	0.9%
NAUSEA	1.8%	8.8%	8.8%	3.6%
PAIN IN EXTREMITY	1.8%	1.8%	3.5%	0.9%

Source: Clinical reviewer.

A complete listing of all Treatment Emergent AEs in Study 102 is provided in **Section 9.5**.

*REVIEWER COMMENT: It's important to note that in each of these arms, the rate of infusion also differs. Therefore, the distribution and rate of adverse events are likely to be a function of both the formulation itself as well as the rate of infusion.*

**Table 21. Study 102, All Treatment-Emergent Adverse Events (Safety Population) by System Organ Class**

System Organ Class Preferred Term	n (%) <sup>a</sup>			
	Placebo (N=112)	PM101 (N=112)	Amiodarone I.V. (10 min loading infusion group) (N=57)	Amiodarone I.V. (15 sec loading infusion group) (N=57)
<b>Subjects with ≥ 1 AE</b>	<b>42 (37.5%)</b>	<b>91 (81.3%)</b>	<b>45 (78.9%)</b>	<b>54 (94.7%)</b>
Cardiac disorders	0	2 (1.8%)	0	2 (3.5%)
Eye disorders	0	0	1 (1.8%)	1 (1.8%)
Gastrointestinal disorders	7 (6.3%)	4 (3.6%)	6 (10.5%)	7 (12.3%)
General disorders and administration site conditions	28 (25.0%)	86 (76.8%)	40 (70.2%)	48 (84.2%)
Infections and infestations	1 (0.9%)	0	0	0
Injury, poisoning and procedural complications	1 (0.9%)	0	1 (1.8%)	0
Investigations	2 (1.8%)	5 (4.5%)	0	0
Metabolism and nutrition disorders	0	1 (0.9%)	0	0
Musculoskeletal and connective tissue disorders	4 (3.6%)	8 (7.1%)	2 (3.5%)	5 (8.8%)
Nervous system disorders	16 (14.3%)	18 (16.1%)	8 (14.0%)	13 (22.8%)
Disturbance in attention	0	0	0	2 (3.5%)
Psychiatric disorders	0	0	1 (1.8%)	2 (3.5%)
Renal and urinary disorders	0	1 (0.9%)	0	1 (1.8%)
Reproductive system and breast disorders	2 (1.8%)	2 (1.8%)	2 (3.5%)	3 (5.3%)
Respiratory, thoracic and mediastinal disorders	2 (1.8%)	3 (2.7%)	1 (1.8%)	3 (5.3%)
Skin and subcutaneous tissue disorders	2 (1.8%)	2 (1.8%)	2 (3.5%)	3 (5.3%)
Vascular disorders	0	5 (4.5%)	1 (1.8%)	8 (14.0%)

<sup>a</sup> A subject was counted once if the subject reported one or more events in each system organ class/ preferred term.

Source: Sponsor, reproduced by reviewer.

Note the most frequent organ class represented above is “General Disorders and Administration Site Conditions,” which is accounted for predominantly by the high number of infusion site related AEs. Additional analyses were performed by the sponsor to further evaluate infusion site adverse events. Infusion site AEs included AE preferred terms with the words “infusion site” or “injection site” and included AEs reported spontaneously by subjects as well as AEs noted by the clinic staff. In addition, for this study, the AE title “infusion site phlebitis” was used in the presence of at least 2 of the following signs: Palpable cord, Induration, Pain, Warmth or Redness and/or symptoms along the course of the infusion vein for a significant period of time (more than 24 hours) and according to the clinical judgment of the medical investigator.

**Table 22. Study 102, Injection site reactions by time.**

	n (%) <sup>a</sup>			
	Placebo (N=112)	PM101 (N=112)	Amiodarone I.V. (10 min loading infusion group) (N=57)	Amiodarone I.V. (15 sec loading infusion group) (N=57)
<b>5 minutes</b>				
Yes	0	3 (2.7%)	0	0
No	112 (100.0%)	108 (97.3%)	57 (100.0%)	57 (100.0%)
Total	112	111	57	57
<b>60 minutes</b>				
Yes	0	7 (6.4%)	1 (1.8%)	0
No	112 (100.0%)	103 (93.6%)	55 (98.2%)	57 (100.0%)
Total	112	110	56	57
<b>24 hours</b>				
Yes	5 (4.5%)	33 (29.5%)	22 (38.6%)	28 (50.0%)
No	107 (95.5%)	79 (70.5%)	35 (61.4%)	28 (50.0%)
Total	112	112	57	56

<sup>a</sup> A subject was counted once if the subject reported one or more event in each system organ class/preferred term.

Source: Sponsor, Clinical Study Report, page 84, Table 17

Evident in Table 22 is the comparatively higher number of infusion site reactions in the PM101 arm in the first hour.

Although the sponsor has tabulated treatment emergent adverse events in the safety population, this reviewer noted that the term "BLOOD PRESSURE DECREASED" is a relatively frequent AE in the overall safety population (that is, not limited to *treatment emergent* AEs). This was curious given that this is an infrequent adverse event in the treatment emergent population, as displayed previously in Table 20. Non-treatment emergent AE's are shown in Table 23.

Clinical Review  
 Robert P. Fiorentino, MD, MPH  
 NDA 022325  
 Nexterone® Amiodarone HCl IV

**Table 23. Study 102, Safety Population (%)**

Adverse Event (Preferred Term)	PM101 I.V. (n=112)	Amiodarone I.V. 15 sec (n=57)	Amiodarone I.V. 10 min (n=57)	Placebo (n=112)
FEELING HOT	41.1	47.4	8.8	6.3
INFUSION SITE PAIN	38.4	40.4	38.6	17.9
INFUSION SITE PHLEBITIS	23.2	38.6	29.8	.
<b>BLOOD PRESSURE DECREASED</b>	<b>20.5</b>	<b>15.8</b>	<b>10.5</b>	<b>8.9</b>
HEADACHE	14.3	10.5	15.8	14.3
DIZZINESS	11.6	14	7	4.5
INFUSION SITE ERYTHEMA	8	22.8	12.3	.
FEELING COLD	6.3	5.3	.	4.5
INFUSION SITE INDURATION	5.4	10.5	7	3.6
INFUSION SITE SWELLING	5.4	10.5	7	.
HOT FLUSH	3.6	14	3.5	.
NAUSEA	3.6	14	14	7.1
ABDOMINAL PAIN	.	3.5	.	.

Source: Reviewer.

At the FDA's request, the sponsor provided an explanation via email for the relatively high rate of the term, "BLOOD PRESSURE DECREASED," in the non-treatment-emergent patient population (email dated Thursday, August 07, 2008):

The definition for "Investigation: Blood Pressure Decreased" for the clinic where this study was conducted is initiated when a single blood pressure reading has either the systolic or diastolic pressure below 90/50. In the event of such an observation a follow up reading is done within 20 minutes and if in the follow up reading the systolic or diastolic pressure remains below 90/50, and there is a meaningful change from baseline in the opinion of the investigator, then it is confirmed as an AE. If the follow up reading is above 90/50 or the investigator does not believe that there was a meaningful change from baseline then the AE is not confirmed. Please note that in the pre-dose timeframe since there was no actual baseline (baseline is defined at T0) the AE was opened and confirmed by the blood pressure number alone with no clinical interpretation of whether or not it was a meaningful change.

Review of the vital sign data and adverse events appears to support the sponsor's conclusion and suggests that significant drops in blood pressure due to treatments were not miscounted or missed. Review of vital sign data is further discussed below in section 7.4.3.

## 7.4.2 Laboratory Findings

### Study 101

Blood chemistry, hematology, and urinalysis were obtained during screening, on check-in to the clinic for each treatment period (Day -1), and at the conclusion of Period 2 (or early termination).

Laboratory datasets and separate analyses performed by the sponsor were reviewed. There were no clinically significant changes in mean laboratory values evident in this study over the

timelines above. Relatively small and clinically insignificant changes above or below standardized cut-off values for individual subjects did not appear treatment related.

### **Study 102**

Blood chemistry, hematology, and urinalysis were obtained during screening, upon admission to the clinic, and before discharge from the clinic. A review of mean changes in laboratory values in each arm over time as well as individual changes revealed a significant increase in ALT, AST and LDH in Subject 001-291, who received PM101 IV:

**Table 24. Study 102, Abnormal Lab values for Subject 001-291**

TEST	SCREENING	DAY -2	DAY 2	Normal Range
ALT	13	22	68	0-41 U/L
AST	18	53	166	0-38 U/L
LDH	119	197	232	135-225 U/L

Source: Reviewer

Laboratory assessments after the Day 2 timepoint were not mandated by the protocol and were not submitted by the sponsor. No substantial adverse events or other significant laboratory values are notable in this subject during enrollment in the trial.

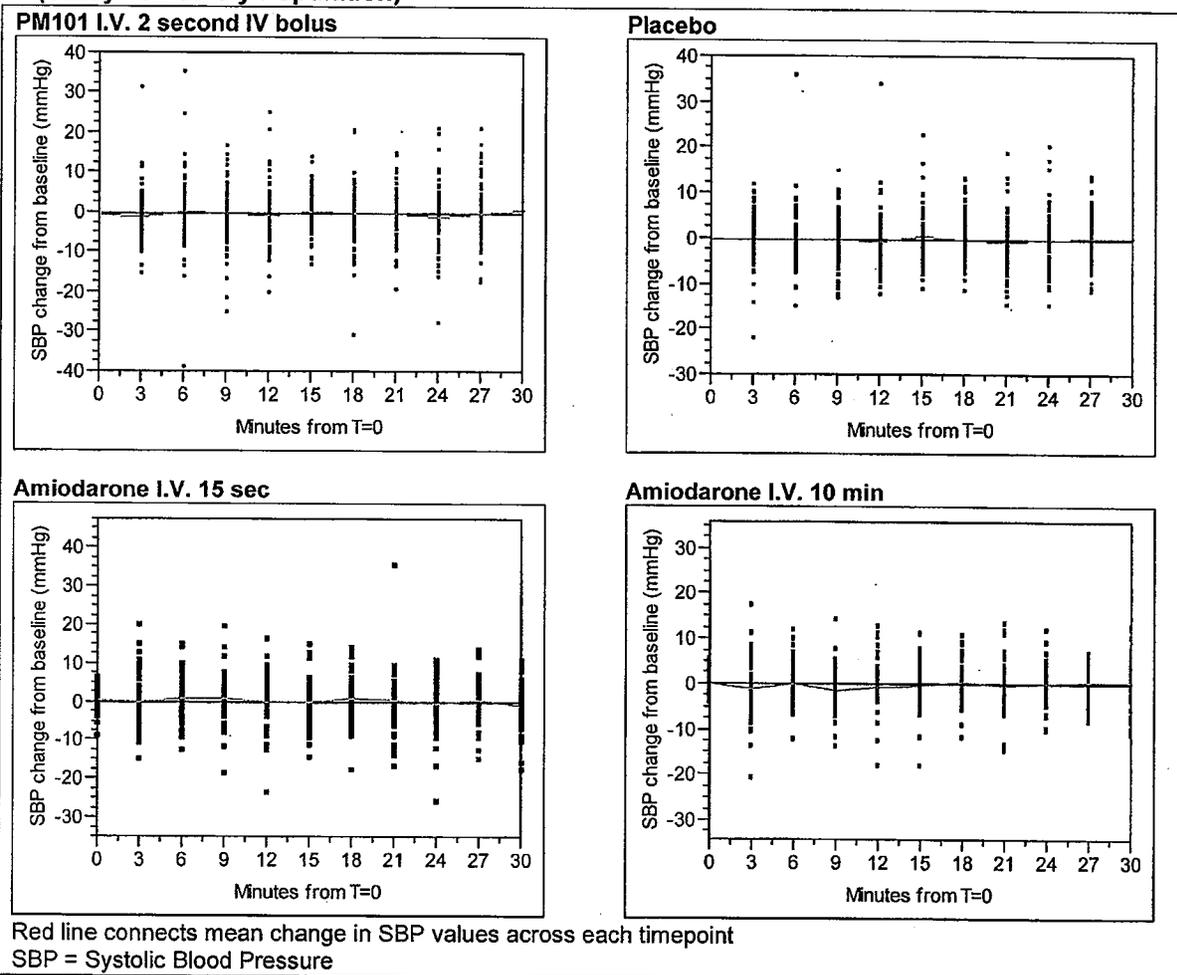
### **7.4.3 Vital Signs**

Unlike Study 101, Study 102 was specifically designed to assess vitals signs during the rapid loading dose phase of administration of study drug. Analyses below are derived from the Study 102 datasets.

#### **Blood Pressure**

No appreciable mean difference in blood pressure change from baseline was observed in any of the four arms of Study 102. Figure 6 below plots a line (red) connecting mean change in systolic blood pressure in the first 30 minutes of each study treatment.

**Figure 6. Change in Systolic Blood Pressure from Baseline  
(Study 102 Safety Population)**



Diastolic blood pressure measurements also did not show changes from baseline (not shown). Although there was minimal change in mean SBP over time for all four arms, a comparatively higher proportion of subjects with SBP drop greater than 10mmHg or 20mmHg were seen in the PM101 IV arm:

**Table 25. Proportion of subjects with  $\geq 10$ mm drop in Systolic Blood Pressure Across Timepoints (Study 102 Safety Population)**

ARM	T=0 to T=15 minutes, % (n/N)	T=0 to T=30 minutes, % (n/N)
PM101 I.V.	12.5% (14/112)	26.8% (30/112)
Amiodarone I.V. 15 sec	19.3% (11/57)	24.6% (14/57)
Amiodarone I.V. 10 min	15.8% (9/57)	19.3% (11/57)
Placebo	13.4% (15/112)	20.5% (23/112)

Source: Reviewer.

The relatively large proportion of subjects in the placebo arm with blood pressure drops  $\geq 10$ mmHg (above Table 25,) suggests that this subgroup analysis is not very informative.

**Table 26. Proportion of subjects with  $\geq 20$ mm drop in Systolic Blood Pressure Across Timepoints (Study 102, Safety Population)**

ARM	T=0 to T=15 minutes, % (n/N)	T=0 to T=30 minutes, % (n/N)
PM101 I.V.	2.7% (3/112)	4.5% (5/112)
Amiodarone I.V. 15 sec	1.8% (1/57)	3.5% (2/57)
Amiodarone I.V. 10 min	1.8% (1/57)	1.8% (1/57)
Placebo	0.9% (1/112)	0.9% (1/112)

Source: Reviewer.

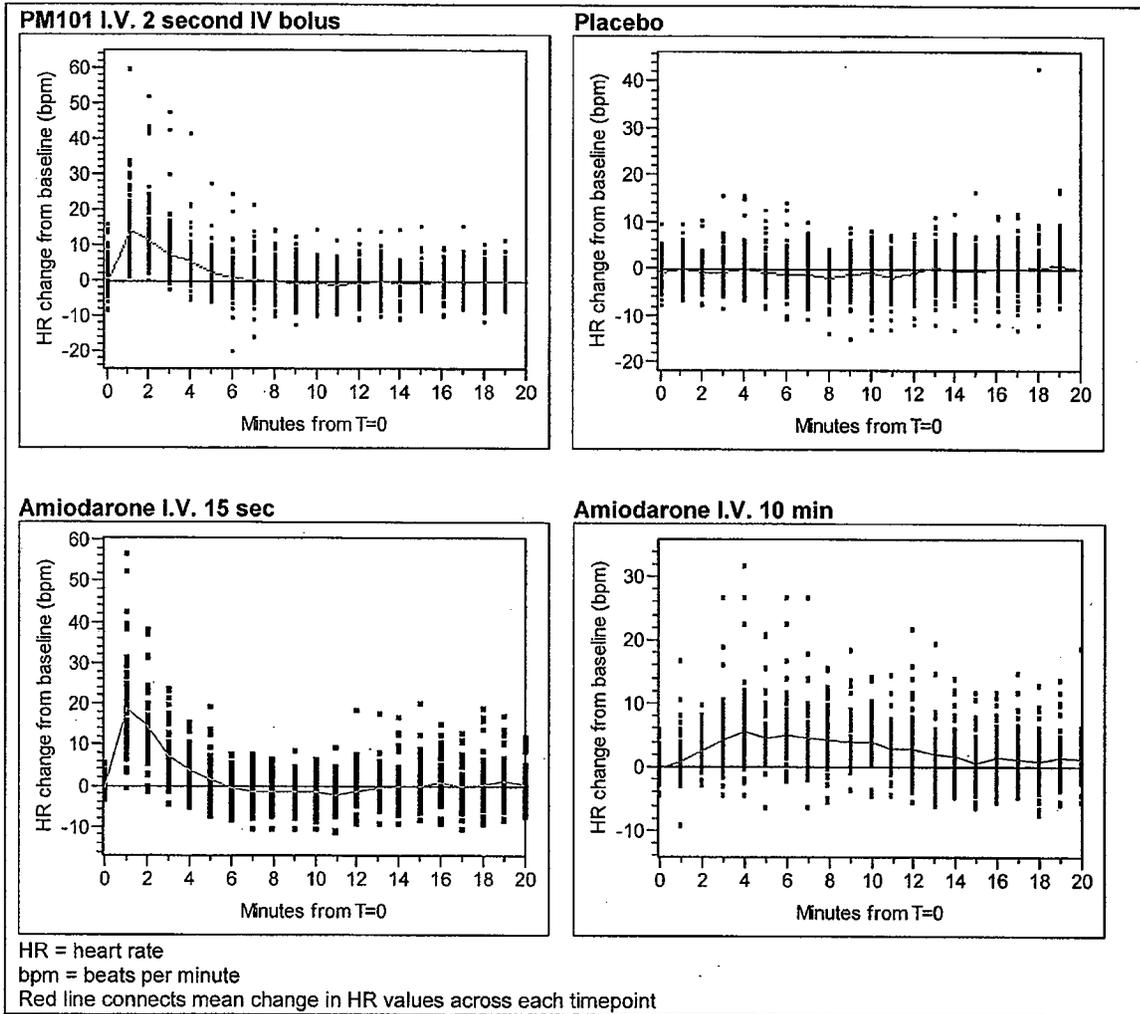
As shown above in Table 26, clinically concerning SBP changes  $\geq 20$ mmHg were uncommon but continued a trend toward a slightly higher rate in the PM101 IV arm.

The observed relationship between blood pressure and heart will be evaluated further below.

#### Heart Rate

In contrast, when graphed similarly to the blood pressure data, one can see an acute rise in mean heart rate from baseline in the PM101 IV 2-second bolus and Amiodarone IV 15-second rapid infusion arms:

**Figure 7. Change in Heart Rate From Baseline (Study 102, Safety Population), T=0 to T=20 minutes**

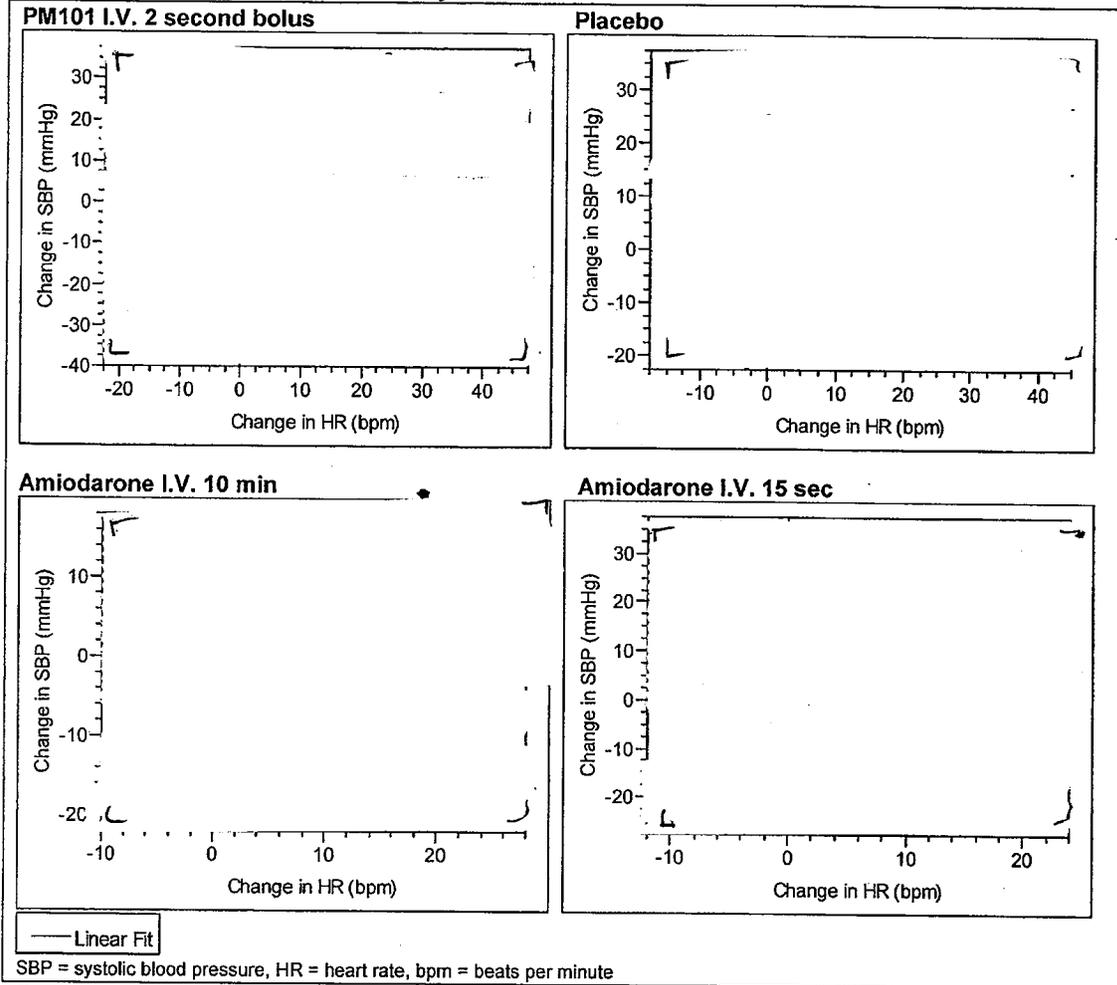


Source: Reviewer.

However, further analysis does not appear to support the hypothesis that the initial rise in heart rate seen in the PM101 IV arm (as well as the Amiodarone 15 second arm) was a compensatory increase secondary to a drop in blood pressure.

Scatterplots of each recorded change in HR and the concurrent change in SBP for each vital sign timepoint was generated for each arm. The scatterplot for the PM101 IV arm is shown in **Figure 8**.

**Figure 8: Scatterplots of Change in HR vs. concurrent change in SBP  
T=0 to T=30 minutes post bolus injection**



b(4)

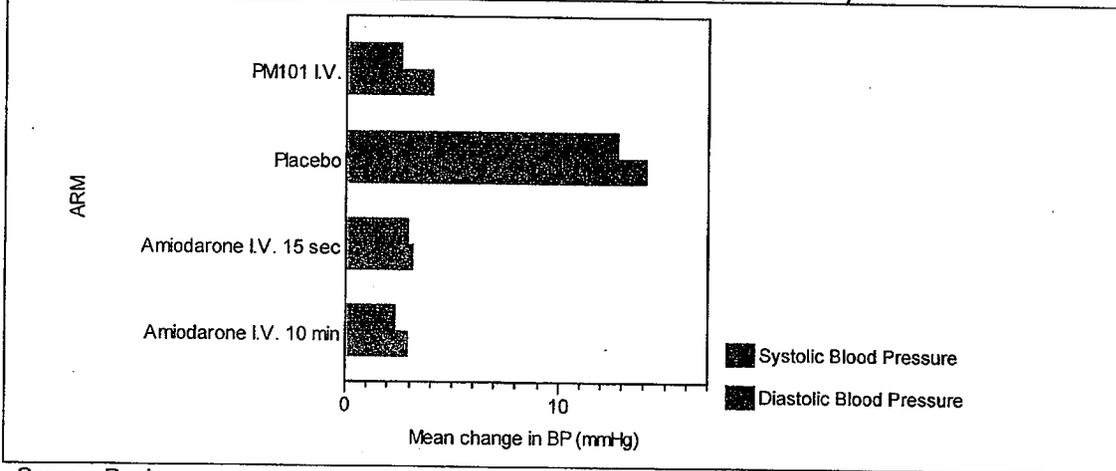
b(4)

Source: Reviewer

On average, there appears to be a positive correlation between changes in SBP and HR.

Furthermore, as shown below, the mean of all recordings of blood pressures that were associated with a  $\geq 10$  mmHg increase in HR were actually elevated. This does not support the supposition that increases in HR can be explained by drug-induced hypotension:

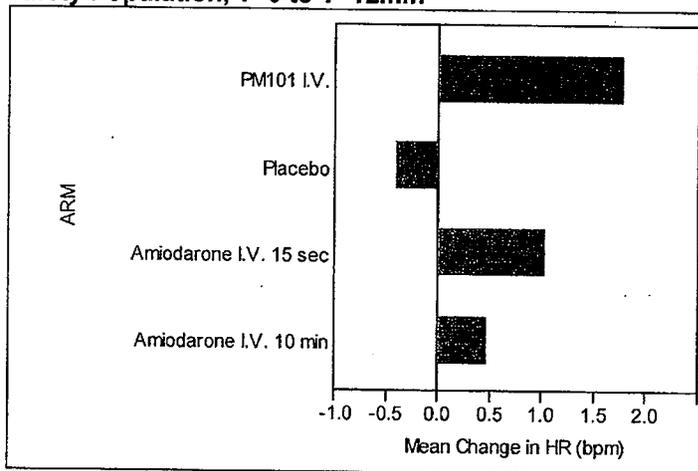
**Figure 9. Mean Change in Blood Pressure for Subjects with increase in HR  $\geq 10$ bpm Safety Population, T=0 to T=12min (across all time points, inclusive)**



Source: Reviewer

Below is illustrated the mean change in HR across all timepoints from T=0 to T=12 where subjects had a  $\geq 10$ mmHg drop in SBP. Again, mean changes in HR were insignificant ( $< 2$ bpm) in subjects who had  $\geq 10$ mmHg drop in SBP.

**Figure 10. Mean change in heart rate associated with  $\geq 10$ mmHg drop in recorded SBP, Safety Population, T=0 to T=12min**



Source: Reviewer.

*REVIEWER COMMENT: The data does not appear to support the conclusion that the*

**b(4)**

*To the contrary, the evidence suggests that both HR and SBP are directly (positively) correlated.*

b(4)

*Although there were no observable alterations in blood pressure, it remains possible that healthy subjects were able to compensate for any hemodynamic insults caused by the drug.*

#### 7.4.4 Electrocardiograms (ECGs)

The effects of amiodarone on cardiac electrophysiology are fairly well described. As noted in the current amiodarone label, the initial acute effects of amiodarone IV appear to be act on the AV node, causing an intranodal conduction delay and increased nodal refractoriness due to slow channel blockade (class IV activity) and noncompetitive adrenergic antagonism (class II activity).

Intravenous amiodarone administration prolongs intranodal conduction and refractoriness of the atrioventricular node but has little or no effect on sinus cycle length, refractoriness of the right atrium and right ventricle, repolarization (QTc), intraventricular conduction, and infranodal conduction.

In Study 101, a 12-Lead ECG was performed at screening, prior to dosing during each treatment period (Day 1) and at the conclusion of Period 2 (or early termination). During each period, subjects were continuously monitored via a telemetry unit through 6 hours following dosing. Clinically significant arrhythmias were recorded as an AE but the telemetry data were not collected for evaluation.

However, in Study 102 although ECG data was not collected after dosing, continuous monitoring via telemetry was performed from approximately 60 minutes pre-dose until 2 hours after stopping the maintenance infusion.

#### Study 102 Holter findings

The percentages of subjects in Study 102 with clinically significant Holter monitoring results are tabulated below.

**Figure 11. Study 102, Holter Monitoring, Safety Population**

Parameter/Category	Placebo (N=112)	PM101 I.V. (N=112)	Amiodarone I.V. 10 min (N=57)	Amiodarone I.V. 15 sec (N=57)
Subjects with Clinically Significant Treatment-Emergent Abnormal Holter Monitoring Results?				
Yes	2 ( 1.8%)	4 ( 3.6%)	1 ( 1.8%)	2 ( 3.6%)
No	109 ( 98.2%)	108 ( 96.4%)	56 ( 98.2%)	54 ( 96.4%)
Total	111	112	57	56

Source: Sponsor, Clinical Study Report 102, page 432, Table 14.3.5

Events for the above subjects are summarized in Table 27.

**Table 27. Study 102, Subjects with Treatment-Emergent Holter Monitoring Abnormalities (MITT Population)**

Group	Subject	Cardiologist Comments
Placebo	001-111	Intermittent accelerated idioventricular rhythm
Placebo	001-256	Sinus slowing with AV block (1 episode)
PM101	001-104	Mobitz I (Wenckebach) 2nd degree AV block (1 episode)
PM101	001-158	Mobitz I (Wenckebach) 2nd degree AV block (9 episodes)
PM101	001-233	Average HR < 40 for any one hour average HR of 40 for one hour
PM101	001-334	Mobitz I (Wenckebach) 2nd degree AV block (8 episodes)
Amiodarone I.V. 10 min	001-204	Mobitz I (Wenckebach) 2nd degree AV block (1 episode)
Amiodarone I.V. 15 sec	001-141	Mobitz I (Wenckebach) 2nd degree AV block (1 episode)
Amiodarone I.V. 15 sec	001-296	Mobitz I (Wenckebach) 2nd degree AV block (11 episodes)

Source: Sponsor, Clinical Study Report 102, page 94, Table 21.

Datasets (HL.xpt) were reviewed for the cardiologist's ECG interpretation and comments. The cases noted above were reviewed and confirmed.

*REVIEWER COMMENT: The occurrences of Mobitz I 2<sup>nd</sup> degree AV block are consistent with the known pharmacologic activity of amiodarone and would explain its occurrence in all three active treatment arms.*

#### **7.4.5 Special Safety Studies**

There were no additional studies designed to evaluate specific safety concern(s).

#### **7.4.6 Immunogenicity**

Compared to generics, there are no additional immunogenicity concerns with this amiodarone formulation.

### **7.5 Other Safety Explorations**

#### **7.5.1 Dose Dependency for Adverse Events**

The same 24-hour dose was used for each arm within each of these two trials; only the rate of infusion differed. Therefore this analysis was not performed.

#### **7.5.2 Time Dependency for Adverse Events**

Effects on vitals signs including blood pressure and heart rate were previously described.

Clinical Review  
Robert P. Fiorentino, MD, MPH  
NDA 022325  
Nexterone® Amiodarone HCl IV

---

The majority of adverse events were reported the same day of treatment administration. Adverse events reported beyond the first day of treatment were also related predominantly to infusion site reactions.

As discussed previously and as shown in **Table 22**, the higher rate of early-onset infusion site reactions in the PM101 IV bolus arm became generally equivalent to, if not more favorable than, the other arms at 24 hours.

There was no specific pattern of adverse events notable in the sparse AE reports beyond the first day of study administration.

### **7.5.3 Drug-Demographic Interactions**

#### *Analysis by Sex*

Sponsor did not perform subgroup analyses by sex; however this reviewer has performed the following analyses discussed below.

The most common treatment emergent adverse events were tabulated by treatment arm and sex. The most striking difference in the proportions of AEs reported between males and females appears to be seen in the PM101 IV arm, with less clear trends in the other arms. No unexpected safety signals between sexes are apparent from this data.

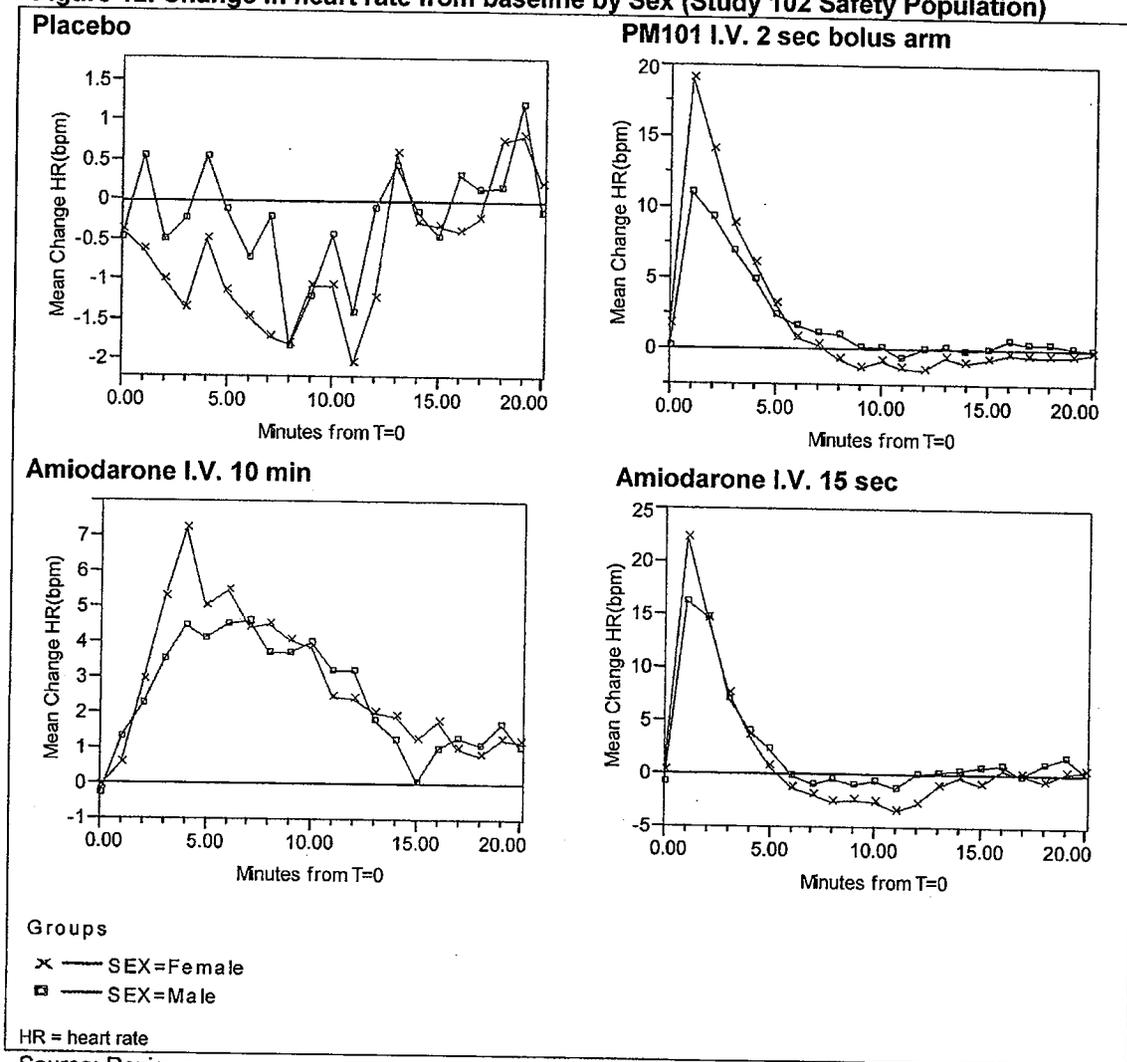
**Table 28. Treatment Emergent Adverse Events by Sex  
 (Study 102 Safety Population, Terms >2% in PM101 IV female study population)**

Lower Level AE Term	PM 101 IV 2 sec bolus (n=112)		Amiodarone IV 15 sec (n=57)		Amiodarone IV 10 min (n=57)		Placebo (n=112)	
	Female (n=49)	Male (n=63)	Female (n=26)	Male (n=31)	Female (n=25)	Male (n=32)	Female (n=49)	Male (n=63)
INFUSION SITE PAIN	40.8%	15.9%	34.6%	41.9%	48%	21.9%	16.3%	12.7%
SENSATION OF HEAT	38.8%	30.2%	34.6%	41.9%	4%	6.3%	4.1%	1.6%
INFUSION SITE PHLEBITIS	28.6%	17.5%	38.5%	38.7%	32%	25%	0%	0%
DIZZINESS	14.3%	1.6%	7.7%	0%	0%	0%	4.1%	0%
INFUSION SITE SWELLING	12.2%	0%	11.5%	9.7%	12%	3.1%	2%	0%
INFUSION SITE BURNING	10.2%	6.3%	0%	0%	4%	0%	0%	0%
INFUSION SITE REDNESS	8.2%	7.9%	15.4%	29%	16%	9.4%	4.1%	0%
HEADACHE	6.1%	4.8%	3.8%	3.2%	24%	3.1%	18.4%	6.3%
INFUSION SITE TENDERNESS	6.1%	0%	7.7%	0%	0%	0%	0%	1.6%
INTERMITTENT HEADACHE	6.1%	0%	0%	6.5%	0%	0%	0%	0%
BLOOD PRESSURE DECREASED	4.1%	0%	0%	0%	0%	0%	0%	0%
BURNING SENSATION	4.1%	0%	3.8%	0%	0%	0%	0%	0%
HOT FLUSHES	4.1%	1.6%	11.5%	9.7%	0%	0%	0%	0%
INFUSION SITE INDURATION	4.1%	6.3%	15.4%	6.5%	12%	3.1%	4.1%	3.2%
NAUSEA	4.1%	0%	15.4%	3.2%	16%	3.1%	8.2%	0%
SENSATION OF WARMTH	4.1%	0%	7.7%	0%	0%	0%	0%	0%

Source: Reviewer.

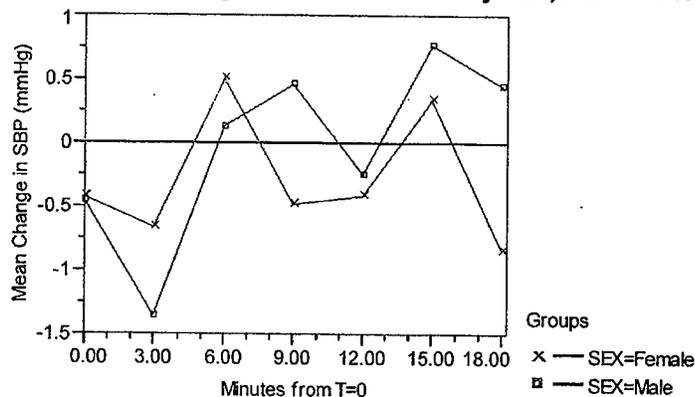
Because of the early increased heart rate seen in the PM101 IV arm discussed previously, separate analyses were performed according to sex. Figure 12 displays the change in heart rate from baseline by treatment arm and sex.

**Figure 12. Change in heart rate from baseline by Sex (Study 102 Safety Population)**



One can see in Figure 12 that females in the PM101 IV arm and Amiodarone IV 15 sec arm tended to have larger increases in heart rates in the first few minutes of study drug administration compared to males. However, there was no difference in blood pressure change from baseline according to sex. Shown in Figure 13 are the results for the PM101 IV arm (other arms show no change as well and are not reproduced here).

**Figure 13. Change in SBP over time by Sex, PM101 I.V. arm**



SBP = systolic blood pressure  
Source: Reviewer.

#### Analysis by Race/Ethnicity

Because there were few non-white study subjects, no analyses by race or ethnicity were performed.

#### **7.5.4 Drug-Disease Interactions**

All of the subjects were healthy adult volunteers, without active disease.

#### **7.5.5 Drug-Drug Interactions**

All of the subjects were healthy adult volunteers and no drug-drug interactions were studied or analyzed. However, in study 102, the most commonly used concomitant medications were contraceptives, followed by non-steroidal anti-inflammatory drugs for headache or injection site pain, and antibiotics for superficial infusion site phlebitis.

### **7.6 Additional Safety Explorations**

#### **7.6.1 Human Carcinogenicity**

No human carcinogenicity data is provided in this NDA. Amiodarone does not have positive genotoxicity or animal carcinogenicity findings nor is it a known immune modulator.

#### **7.6.2 Human Reproduction and Pregnancy Data**

There is no information on drug exposure in pregnant or lactating women provided in this NDA.

### **7.6.3 Pediatrics and Effect on Growth**

This NDA does not contain a discussion of a pediatric development plan, nor does it contain pediatric clinical data.

### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

Drug does not have significant, if any, potential for drug abuse. The applicant did not evaluate the potential for withdrawal or rebound phenomena.

### **7.7 Additional Submissions**

Sponsor has not indicated that they plan to submit additional submissions or updates.

## **8 Postmarketing Experience**

A recent analysis by Dr. Ana Szarfman of FDA's Adverse Event Reporting System (AERS) assessed 82% of 8713 amiodarone cases in AERS based on available route of administration data. A total of 6172 cases were recoded as oral amiodarone, and 930 as IV cases. A ranked tabulation of reported terms for the IV amiodarone group is displayed in **Table 29**. In general, IV amiodarone had more over-reporting of general, hepatic, cardiac, and investigational events. Of particular note is the high score of injection site AEs, as observed in this NDA.

**Table 29. AERS Analysis, Amiodarone IV**

Rank	SOC	Term	EBGM
1	Genrl	Injection site thrombosis	110.829
2	Genrl	Injection site extravasation	74.178
3	Genrl	Infusion site extravasation	46.969
4	Card	Torsade de pointes	40.143
5	Genrl	Extravasation	28.995
6	Hepat	Hepatitis toxic	23.507
7	Vasc	Phlebitis	23.352
8	Genrl	Injection site edema	23.244
9	Genrl	Injection site inflammation	22.293
10	Inv	Blood pressure immeasurable	22.098
11	Resp	Pulmonary toxicity	21.772
12	Hepat	Hepatitis acute	21.118
13	Inv	Electrocardiogram QT corrected interval prolonged	19.266
14	Genrl	Infusion site erythema	17.689
15	Hepat	Hepatotoxicity	17.617
16	Genrl	Injection site reaction	15.468
17	Card	Ventricular fibrillation	13.754
18	Immun	Reaction to preservatives	12.986
19	Endo	Hyperthyroidism	12.060
20	Gastr	Gastrointestinal hypomotility	11.985
21	Resp	Acute respiratory distress syndrome	11.806
22	Hepat	Hepatitis fulminant	11.714
23	Card	Ventricular tachycardia	11.128
24	Inv	Electrocardiogram QT prolonged	10.911
25	Genrl	Injection site erythema	6.943
26	Resp	Pneumonia lipoid	6.744
27	Genrl	Infusion site reaction	6.627
28	Card	Ventricular flutter	6.384
29	Hepat	Hepatitis	6.043
30	Genrl	Injection site induration	6.003
31	Resp	Bronchospasm	5.915
32	Infec	Abdominal infection	5.739
33	Hepat	Hepatic necrosis	5.739
34	Genrl	Injection site necrosis	5.439
35	Card	Cardiogenic shock	5.138

**EBGM = SOC = system organ class, Empirical bayes geometric mean**

Source: Reviewer.

## 9 Appendices

### 9.1 Literature Review/References

Sponsor has provided a fairly broad, yet selective list of reference articles to support the supposition that the proposed

A brief overview of key studies is provided below.

b(4)

There is some evidence that polysorbate 80 can cause cardiac depression and hypotension in animals and humans (Gough et al. 1982; Munoz et al. 1988). Gough showed that polysorbate 80 (10mg/kg) alone will lower blood pressure (BP) and cardiac output (CO) in the anesthetized dog. Munoz administered 5mg/kg amiodarone formulated either with or without polysorbate 80 to 20 subjects who were undergoing coronary angiography for evaluation of CAD. Treatment drugs were administered during catheterization directly into the RA over a 3 minute period. A fall in LV systolic pressure and aortic pressure was documented in both arms but were greater in the group with the polysorbate formulation. Also observed were a greater increase in HR in the group that received the polysorbate 80 formulation.

Munoz et al. (1988) evaluated the hemodynamic effects of amiodarone I.V. in formulations with and without polysorbate 80 in patients undergoing coronary angiography to determine their coronary status. Munoz et al. (1988) reported that amiodarone formulations with polysorbate 80 decreased LV systolic pressure by 16 mmHg more than the amiodarone formulation without polysorbate 80 ( $P < 0.01$ ). They also reported that reflex tachycardia was more pronounced in the amiodarone with polysorbate 80 group than without polysorbate 80.

Anastasiou-Nana et al. (1999) studied amiodarone I.V. (150mg) administered as a bolus injection over 15 seconds in patients with idiopathic dilated cardiomyopathy, NYHA functional class II, and mean left ventricular ejection fraction of 21%. This resulted in an increase in heart rate from  $82 \pm 17$  bpm to  $90 \pm 13$  bpm and a mean decrease in systolic blood pressure of 14mmHg two minutes after the drug administration. Author notes that "a single patient experienced flushing 1 minute after amiodarone injection, followed by dizziness and moderately severe hypotension."

The effect of rapid administration of Cordarone I.V. was also assessed by Cinelli et al. (1984). In this study Cordarone I.V. was administered at 5mg/kg over 30 seconds to twelve subjects hospitalized for alterations of heart rhythm, but without coronary heart disease or heart failure. The results indicated that heart rate increased with a peak at 90 seconds and diastolic blood pressure decreased with a peak of -11mmHg at 90 seconds. There was no significant change in systolic blood pressure. The authors noted that "five patients had a diffuse hot feeling lasting about 2 minutes and starting about 20-25 seconds after the beginning of the injection."

Bopp et al. (1985) evaluated the acute hemodynamic effects of rapid bolus of Cordarone I.V. (5mg/kg over 1 minute) on 16 male patients admitted for evaluation of coronary artery disease (CAD). Subjects were excluded if they had hypertension, overt heart failure and nonischemic cardiomyopathies, although 11 patients had documented history of MI. Author reports no

**Figure 14. Proposed Labeling with Recommended Deletion**

b(4)

Source: Sponsor, edits by reviewer

**9.3 Advisory Committee Meeting**

There was not an advisory committee meeting for this NDA nor is one planned.

**9.4 Detailed Overview of Clinical Protocols**

**STUDY 101**

**Objectives**

The primary objective of this study was to compare the relative bioavailability of the test (PM101 I.V., amiodarone hydrochloride) and reference (Amiodarone I.V., Reference Listed Drug [RLD], amiodarone hydrochloride—Cordarone® I.V. is no longer sold in the U.S.) products following intravenous injection.

**Overall Study Design and Plan**

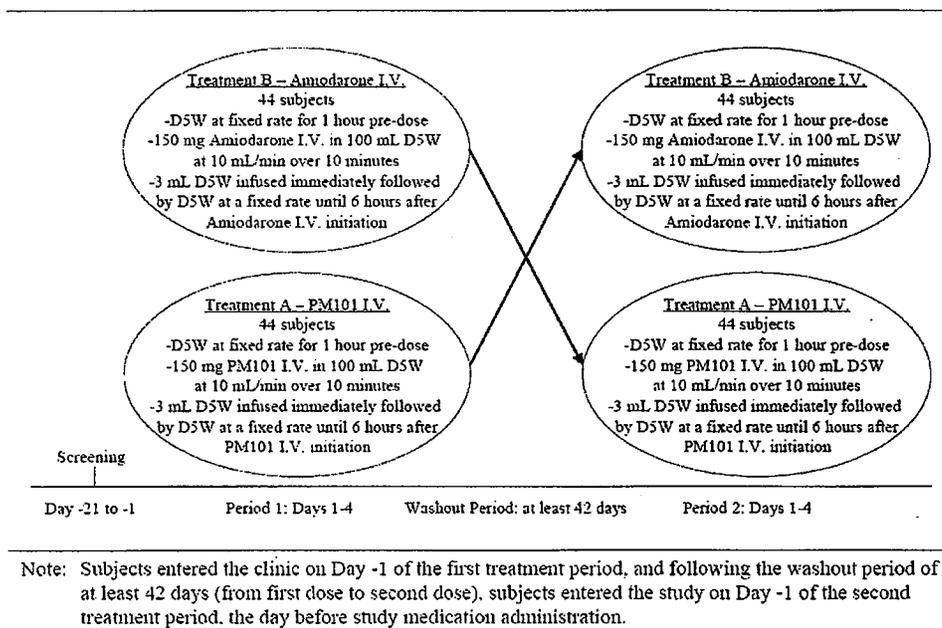
In this randomized, single-center, double-blind, 2-period crossover study to evaluate the relative bioavailability of PM101 I.V. (test) and Amiodarone I.V. (reference), 88 subjects were randomized to one of two treatment sequences—test drug followed by reference drug or reference drug followed by test drug. The two periods of each treatment sequence were separated by a washout period of at least 42 days (from the first dose to the second dose).

Study medication was administered after a 10-hour overnight fast as follows:

- Treatment A: PM101 I.V. (amiodarone hydrochloride)**
- 1 hr to 0 hr: Intravenous infusion (I.V.) of 5% dextrose in water (D5W) at a fixed rate to keep vein open
  - 0 hr to 10 min: 150 mg PM101 I.V. in 100 mL D5W at 10 mL/min
  - 11 min to 6 hrs: 3 mL D5W flush to clean line followed by D5W infused at a fixed rate to keep vein open
- Treatment B: Amiodarone I.V. (amiodarone hydrochloride)**
- 1 hr to 0 hr: Intravenous infusion of D5W at a fixed rate to keep vein open
  - 0 hr to 10 min: 150 mg Amiodarone I.V. in 100 mL D5W at 10 mL/min
  - 11 min to 6 hrs: 3 mL D5W flush to clean line followed by D5W infused at a fixed rate to keep vein open

Screening evaluations were performed within 21 days of study medication administration. For Period 1, subjects were admitted to the clinic the evening of Day -1, treated the morning of Day 1, and discharged 72 hours later on Day 4. Following the washout period of at least 42 days, subjects for Period 2 were admitted to the clinic the evening prior to treatment, administered treatment the next morning (alternate of drug infused in Period 1), and discharged 72 hours after treatment. Blood samples were collected at specified time points over the 72 hours following study medication administration in each period.

**Figure 15. Study 101, Study Design Schematic**



Source: Sponsor, Clinical Study Report, page 24, Figure 1.

**Study Population**

Potential subjects selected from healthy adult male and female volunteers in the general geographic area of the clinic were eligible to participate in the study if they met all of the following criteria.

### **Inclusion Criteria**

1. Be a healthy male or female 18 to 59 years of age, inclusive. Women of childbearing potential had to be using a medically acceptable form of birth control for the duration of the trial and had to have a negative serum pregnancy test at screening and upon check-in to the study facility.
2. Have a body mass index (BMI) within the range of 18-35 with BMI calculated as weight (kg)/height<sup>2</sup> (m<sup>2</sup>).
3. Be able to communicate effectively with the study personnel.
4. Have no significant disease or abnormal laboratory values as determined by medical history or physical examination or laboratory evaluations conducted at the screening visit or on admission to the clinic.
5. Have a normal 12-lead electrocardiogram (ECG) without any clinically significant abnormalities of rate, rhythm, or conduction, including normal QT segment time corrected for heart rate (QTc) (i.e., <430 msec for males and <450 msec for females).
6. Be nonsmokers defined as not having smoked in the past 6 months prior to dosing.
7. Be adequately informed of the nature and risks of the study and give written informed consent prior to receiving study medication.

### **Exclusion Criteria**

1. Known hypersensitivity or allergy to amiodarone, Captisol, or Cordarone I.V. or its excipients.
2. Known hypersensitivity or allergy to iodine or radio-opaque dyes.
3. Women who were pregnant or breast feeding.
4. A history or presence of asthma or other pulmonary disease, thyroid disease (hypo- or hyperthyroidism), hepatitis, or other liver disease.
5. Any disease or condition (medical or surgical) that, in the opinion of the investigator, might compromise hematologic, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or central nervous system function or any other conditions that might interfere with the absorption, distribution, metabolism, or excretion of the study drug or would place the subject at increased risk.
6. The presence of abnormal laboratory values that were considered clinically significant.
7. Positive screen for hepatitis B surface antigen (HbsAg), hepatitis C antibody (anti HCV), or human immunodeficiency virus (HIV-1 or HIV-2).
8. Received an investigational drug within 30 days prior to enrollment in the study.
9. Received any drug therapy within 2 weeks prior to administration of the first dose of any study-related treatment. This exclusion is extended to 4 weeks for any drugs known to induce or inhibit hepatic drug metabolism.
10. Consumption of alcohol within 48 hours prior to dose administration or during any in-patient period.
11. A positive urine drug screen, including cocaine, tetrahydrocannabinol (THC), ethanol, barbiturates, amphetamines, benzodiazepines, and opiates.
12. A history of alcohol abuse, drug abuse or addiction, including illicit drugs (use of soft drugs, such as marijuana, within 3 months prior to screening visit or use of hard drugs, such as cocaine, phencyclidine [PCP] and crack, within 1 year prior to the screening visit), physical dependence on any opioid, or significant mental illness.
13. A history of difficulty with donating blood.
14. Donation of plasma (500 mL) within 7 days prior to drug administration; donation or loss of whole blood (excluding blood drawn during the screening procedures of this study) as follows: 50 to 499 mL of whole blood within 30 days prior to study drug administration or more than 499 mL of whole blood within 56 days prior to study drug administration.

### **Doses in the Study**

The selected dose was 150 mg of PM101 I.V. or Amiodarone I.V. in 100 mL of D5W, the initial dose recommended for Amiodarone I.V.

#### **Selection and Timing of Dose for Each Subject**

All subjects reported to the clinic the evening of Day -1 of Period 1 and Period 2 for clinical laboratory tests, a urine drug screen, and a serum pregnancy test for female subjects. Eligible participants were randomized to treatment prior to the administration of study medication on Day 1 of Period 1. Subjects fasted overnight for 10 hours prior to study medication administration until 4 hours after study medication administration. A physician was on-site from approximately 1 hour prior to insertion of the I.V. port until approximately 6 hours after drug administration. At approximately 1 hour prior to dosing on Day 1 of Period 1 and 2, an I.V. port was inserted into the antecubital region of Arm 1, and infusion of D5W was initiated at a fixed rate to keep the vein open (a catheter was inserted in Arm 2 for blood sample collection within 30 minutes of the start of dosing). At Time 0, the D5W bag was replaced by an infusion bottle containing PM 101 I.V. or Amiodarone I.V. (150 mg of amiodarone hydrochloride in 100 mL D5W) and the dose was infused at a rate of 10 mL/min for 10 minutes. Immediately after the study drug infusion was completed, the line was flushed with 3 mL of D5W and the infusion of D5W was reinitiated at a fixed rate to keep the vein open until 6 hours after study drug initiation. Approximately 1 and 24 hours after the start of the infusion, the injection site was visually evaluated by the clinic staff, and approximately 1 hour after the start of infusion, subjects were asked if they had experienced any new health problem not already reported. Subjects received a standard diet except for xanthine-containing foods or beverages (e.g., coffee, tea, cola, chocolate) and grapefruit or grapefruit juice until discharged from the clinic after the completion of pharmacokinetic and safety assessments on Day 4 of both treatment periods. While in the clinic, subjects refrained from physical activity. Female subjects had a urine pregnancy test prior to discharge from the study unit following Period 2 or on early termination

#### **Blinding**

This was a double-blind, analytically blind study. The investigator, the study subjects, the analytical laboratory personnel, and other members of the staff involved with the study remained blinded to the treatment randomization schedule. The pharmacist at the site was unblinded and prepared the study treatments in accordance with the randomization schedule.

**Figure 16. Study 101, Pharmacokinetic and Safety Measurements and Flow Chart**

Assessment/Procedure	Screening	Treatment Periods 1 and 2				
	Visit 1	Visits 2 and 3				
	Day -21 to -1	Day -1	Day 1	Day 2	Day 3	Day 4
Medical history	X					
Informed consent	X					
Eligibility assessment	X	X				
Concomitant meds <sup>a</sup>	X	X				
Physical examination <sup>b</sup>	X					X
Body weight	X					
Hepatitis and HIV	X					
Serum pregnancy test	X	X				
Urine pregnancy test <sup>c</sup>						X
Urine drug screen	X	X				
Clinical lab tests <sup>b</sup>	X	X				X
Vital signs <sup>d</sup>	X		X	X	X	X
12-lead ECG <sup>b</sup>	X		X			X
ECG telemetry <sup>e</sup>			X			
Clinic admission		X				
Randomization <sup>f</sup>			X			
Study medication <sup>g</sup>			X			
PK blood samples <sup>h</sup>			X	X	X	X
AE assessment		X	X	X	X	X
Clinic discharge						X

<sup>a</sup> For Period 2, subjects were again assessed for any drug therapy within 2 weeks of study drug dose (within 4 weeks for drugs known to induce or inhibit hepatic drug metabolism).

<sup>b</sup> Day 4 physical examinations, 12-lead ECGs, and clinical laboratory tests were performed at the end of the study (Period 2) but not at the end of Period 1.

<sup>c</sup> A urine pregnancy test was performed at the end of the study (Period 2) but not at the end of Period 1.

<sup>d</sup> For Periods 1 and 2, blood pressure and pulse obtained in a semi-reclined position (after semi-reclined for 5 minutes) were checked before insertion of the I.V. port within approximately 10 minutes prior to the start of the study drug infusion at 0 hour and approximately 10, 30, and 60 minutes after the start of the study drug infusion. The 10-minute vital signs assessment was completed after the 10-minute PK blood sample was drawn. Routine vital signs were recorded once daily on Days 2-4.

<sup>e</sup> Continuous ECG telemetry monitoring was performed from the time the I.V. port was placed (approximately 1 hour pre-dose) through 6 hours post-dose.

<sup>f</sup> Randomization was performed on Day 1 of Period 1.

<sup>g</sup> PM101 I.V. or Amiodarone I.V. were infused intravenously at a rate of 10 mL/min for 10 minutes.

<sup>h</sup> PK blood samples were collected within 30 minutes prior to the start of the study drug infusion (0 hour) and 1, 5, 10, 20, and 30 minutes and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after the start of the study drug infusion. The 10-minute sample was obtained at the end of the study drug infusion.

Source: Sponsor, Clinical Study Report, page 32, Table 1.

#### Adverse Events

An adverse event (AE) was any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result, or worsening of a pre-existing condition that occurred during the course of the study or during a specified follow-up period. In addition to any AE reported spontaneously, subjects were monitored and asked non-leading questions while in the clinic. The investigator reviewed

all AEs. Any subject who was withdrawn from the study due to an AE was to be followed until the outcome of the event was determined. Each AE was evaluated for duration, intensity, and relationship to (or association with) the study treatment (or other causes). The intensity of an AE was rated as mild, moderate, or severe, and the relationship of an AE to the study drug was assessed as unrelated or possibly or probably related. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 9.0. Serious adverse events (SAEs) included any event that was fatal, life threatening, disabling, required or prolonged hospitalization, was a congenital anomaly/birth defect, or was considered an important medical event that jeopardized the subject and required medical or surgical intervention to prevent one of the previously listed outcomes. Any SAE was to be reported to the sponsor within 24 hours.

#### **Clinical Laboratory Tests**

A series of laboratory evaluations, including blood chemistry, hematology, and urinalysis, was obtained during screening, on check-in to the clinic for each treatment period (Day -1), and at the conclusion of Period 2 (or early termination). Tests for hepatitis and HIV infection were performed at screening, and a urine drug screen and a serum pregnancy test (all female subjects) were performed at screening and upon admission to the clinic on Day -1 for each treatment period. A urine pregnancy test was performed at the end of the study (Period 2) but not at the end of Period 1.

Any significant abnormalities were to be fully investigated and if serious or unexpected, promptly reported to the medical monitor.

#### **Vital Signs**

Routine vital signs, including pulse (heart rate), respiration, blood pressure and temperature were obtained at screening and once daily on Days 2–4 of each treatment period. In addition, blood pressure and heart rate were obtained before insertion of the I.V. port within approximately 10 minutes prior to the start of the study drug infusion (pre-dose), and approximately 10, 30, and 60 minutes after the start of the study drug infusion. At screening, blood pressure and pulse were obtained with the subject in a sitting position after sitting for 5 minutes. During the study, blood pressure and pulse were obtained with the subject in a semi-reclined position after being semi-reclined for 5 minutes.

#### **Electrocardiograms and Telemetry**

A 12-Lead ECG was performed at screening, prior to dosing during each treatment period (Day 1) and at the conclusion of Period 2 (or early termination). During each period, subjects were continuously monitored through a telemetry unit from the time the I.V. port was placed (approximately 1 hour pre-dose) through 6 hours following dosing. In the event that a clinically significant arrhythmia was observed, the event was recorded as an AE and appropriate treatment was initiated, but the telemetry data were not collected for evaluation.

#### **Physical Examinations**

A complete physical examination was performed at the screening visit and prior to discharge from the study unit following Period 2 or on early termination. Any findings or absence of findings relative to each subject's physical examination were carefully documented.

#### **Primary Pharmacokinetic Parameters**

The pharmacokinetic (PK) parameters shown below were estimated for all subjects with sufficient data to adequately assess the endpoint of interest.

**Figure 17. Study 101 Pharmacokinetic Parameters**

Parameter	Definition
C <sub>max</sub>	Maximum plasma concentration; the highest concentration observed during a dosage interval
T <sub>max</sub>	Time that C <sub>max</sub> was observed
C <sub>last</sub>	Last measured plasma concentration; last concentration above the lower limit of quantitation (LLOQ) within the specified sampling interval following a dose
AUCT	Area under the concentration versus time curve from time 0 to C <sub>last</sub> ; calculated using linear trapezoid rule
AUC	Area under the concentration versus time curve from time 0 to infinity; calculated as AUCT + C <sub>last</sub> /λ <sub>z</sub>
λ <sub>z</sub>	Terminal elimination rate constant; calculated using linear regression on the terminal portion of the ln-concentration versus time curve
T <sub>1/2</sub>	Terminal elimination half-life; calculated as 0.693/λ <sub>z</sub>

Source: Sponsor, Clinical Study Report, page 35, Table 2.

## STUDY 102

**Title:** A randomized, double-blind, double-dummy, placebo-controlled trial to determine the relative effect of PM101 I.V. versus placebo on hemodynamics in healthy adult volunteers

**Primary Objective:** The primary objective of the study was to compare the effect of PM101 administered as an immediate I.V. bolus push with placebo on systolic blood pressure (SBP).

**Study Design:** In this randomized, double-blind, double-dummy, placebo-controlled study to determine relative effect of PM101 versus placebo on BP in healthy adult volunteers, subjects were screened within 21 days of dosing and returned to the clinic on the evening of Day -2. Approximately 342 subjects (male or female) were to be randomized in a 2:2:1:1 ratio to one of the following I.V. treatment regimens.

- Treatments:
- A: PM101  
150 mg immediate I.V. bolus push (<2 seconds) and a  
1 mg/minute I.V. infusion for 6 hours and a  
0.5 mg/min I.V. infusion for 18 hours
  - B: Placebo I.V. (D5W served as the placebo)  
D5W immediate I.V. bolus push (<2 seconds) and a  
D5W I.V. infusion for 6 hours and a  
D5W I.V. infusion for 18 hours
  - C: Amiodarone I.V.  
150 mg/100 mL I.V. infusion over 10 min at 10 mL/min and a  
1 mg/minute I.V. infusion for 6 hours and a  
0.5mg/min I.V. infusion for 18 hours
  - D: Amiodarone I.V.  
150 mg I.V. infusion over 15 seconds and a  
1 mg/minute I.V. infusion for 6 hours and a  
0.5 mg/min I.V. infusion for 18 hours

Clinical Review  
Robert P. Fiorentino, MD, MPH  
NDA 022325  
Nexterone® Amiodarone HCl IV

---

On 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.

At approximately 2 hours prior to dosing (Day 1), an I.V. port was inserted into the antecubital region and infusion of D5W was initiated at a fixed rate in order to keep the vein open. A blood pressure cuff was placed on the non-dosing arm and BP measurements were made every 10 minutes starting at 60 minutes prior to study drug administration to obtain stabilized baseline measurements. At 21 minutes prior to study drug administration, a new bottle of D5W was placed, an immediate bolus push of 3mL D5W was administered, a 15 second infusion of 3 mL D5W was administered, and 100 mL of D5W was infused at 10 mL/min. The infusion rate was decreased to the previous fixed rate in order to keep the vein open at 11 minutes prior to study drug administration. Blood pressure measurements were conducted every 3 minutes until dosing (T-21 to T0) and HR measurements were conducted every 1 minute until dosing (T-21 to T0).

At T0, the D5W bottle was replaced by an infusion bottle containing Amiodarone I.V. 150 mg/100 mL (or matching placebo) and infused at a rate of 10 mL/min for 10 minutes. At T0 an immediate bolus push injection (<2 seconds) of PM101 150 mg/3 mL (or placebo-D5W) was administered through a side port. At T0 a 15 second injection of Amiodarone I.V. (150 mg/3 mL) (or matching placebo) was administered through a side port.

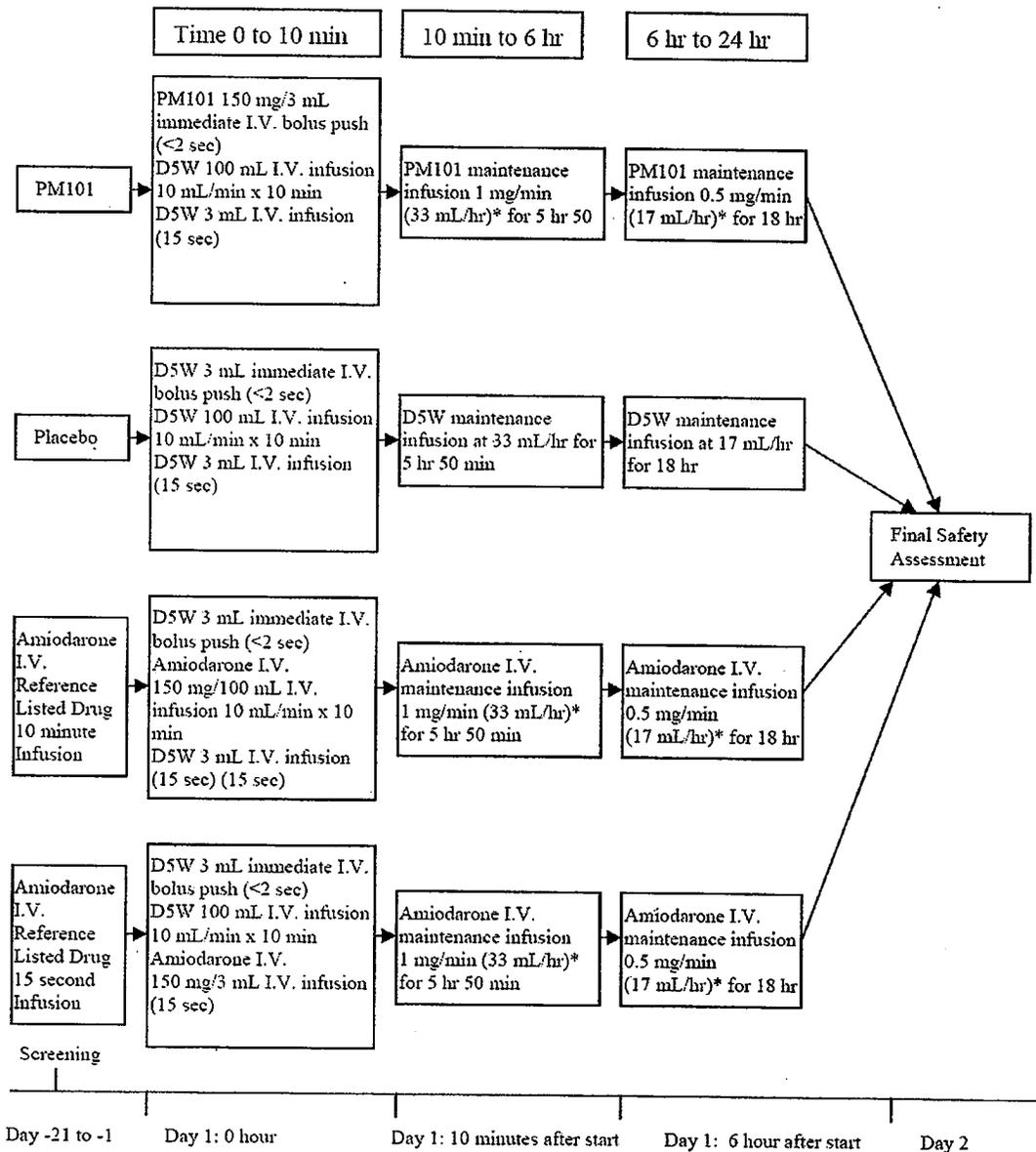
At T10 minutes, the D5W bottle was replaced with a D5W bottle of PM101 1.8 mg/mL, OR Amiodarone I.V. 1.8mg/ml OR placebo-D5W and infused at a rate of 1.0 mg/min for 5 hours and 50 minutes (Placebo rate was equivolume compared to the PM101 infusion).

At T6 hours, the flow rate of the D5W bottle containing PM101 1.8 mg/mL, OR Amiodarone I.V. 1.8mg/mL, OR placebo-D5W was changed to a rate of 0.5 mg/min for the next 18 hours. (Placebo rate was equivolume compared to the PM101 infusion).

BP was assessed every 3 minutes for the first 60 minutes (T0 to T60 min) following dosing, then every hour until 12 hours following dose initiation. A final BP measurement was conducted at 24 hours post dose. HR was assessed every 1 minute for the first 60 minutes (T0 to T60 min) after dosing and every then every hour until 12 hours after dosing. A final HR measurement was conducted at 24 hours post dose.

Subjects were discharged from the clinic on Day 2 following final safety assessments.

**Figure 18. Study 102 Flowchart**



Source: Sponsor, Clinical Study Report 102, page 29, Fig. 1

**Inclusion Criteria:**

Subjects accepted for this study must:

1. Be a healthy male or female 18 to 55 years of age, inclusive. Women of childbearing potential must be using a medically acceptable form of birth control for the duration of the trial and must have a negative serum pregnancy test at both screening and upon check-in to the study facility.

2. Have a body mass index (BMI) within the range of 18-35 kg/m<sup>2</sup>.
3. Be able to communicate effectively with the study personnel.
4. Have no significant disease or abnormal laboratory values as determined by medical history, physical examination or laboratory evaluations, conducted at the screening visit or on admission to the clinic.
5. Have a normal 12-lead electrocardiogram, without any clinically significant abnormalities of rate, rhythm or conduction (such as high grade atrioventricular block, bifascicular or trifascicular block), and a normal QTc interval (i.e., ≤450 msec for males and females).
6. Be a nonsmoker defined as not having smoked in the past 6 months prior to drug administration.
7. Be adequately informed of the nature and risks of the study and give written informed consent prior to receiving study medication.

**Exclusion Criteria:**

Subjects accepted for this study must not have:

1. Known hypersensitivity or allergy to Amiodarone, Captisol, Cordarone I.V. or its excipients.
2. Known hypersensitivity or allergy to iodine or radio-opaque dyes.
3. Women who are pregnant or breast-feeding.
4. A history or presence of asthma or other pulmonary disease, thyroid disease (hypo- or hyperthyroidism), hepatitis or other liver disease.
5. Any disease or condition (medical or surgical) which, in the opinion of the investigator, might compromise the hematologic, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or central nervous system; or other conditions that may interfere with the absorption, distribution, metabolism or excretion of study drug, or would place the subject at increased risk.
6. The presence of abnormal laboratory values which are considered clinically significant.
7. Positive screen for Hepatitis B (HbsAg, Hepatitis B Surface Antigen), Hepatitis C (anti HCV, Hepatitis C Antibody), or HIV (anti-HIV 1/2).
8. Received an investigational drug within a period of 30 days prior to enrollment in the study.
9. Received any drug therapy within 2 weeks prior to administration of the first dose of any study-related treatment. This exclusion is extended to 4 weeks for any drugs known to induce or inhibit hepatic drug metabolism. However, women of childbearing potential may receive hormonal contraceptives and the investigator may waive short-term use of a medication, which is not specifically prohibited, if the use occurred more than 5 half-lives prior to the first dose of any study-related treatment.
10. Consumption of alcohol within 48 hours prior to dose administration or during any in-patient period.
11. A positive urine drug screen including ethanol, cocaine, tetrahydrocannabinol (THC), barbiturates, amphetamines, benzodiazepines, and opiates.
12. Any history of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction.
13. Prior participation in a Prism Pharmaceuticals Amiodarone study.
14. Donation of plasma (500 mL) within 7 days prior to drug administration. Donation or loss of whole blood (excluding the volume of blood that will be drawn during the screening procedures of this study) prior to administration of the study medication as follows: 50 mL to 499 mL of whole blood within 30 days, or more than 499 mL of whole blood within 56 days prior to drug administration.
15. History of severe respiratory failure, circulatory collapse, severe arterial hypotension, heart failure, cardiomyopathy, or sinus node disease.

**Figure 19. Study 102 Assessments and Procedures**

STUDY PHASE	Screen	Treatment Period			
	1	2			
VISIT NUMBER	1	2			
DAY	-21	-2	-1	1	2
Medical History	X				
Informed Consent	X				
Assess Eligibility	X		X	X	
Physical Examination	X				X [A]
12-lead ECG	X	X			
Holter monitoring			X [B]	X [B]	X [B]
Clinical Lab Tests	X	X			X
Vital Signs	X				X
Body Weight	X				
Serum Pregnancy Test	X	X			
Urine Drug Screen	X	X			
Clinic Admission		X			
Randomization				[C]	
Medication Dose				[D]	[D]
BP Measurement				[E]	[E]
Heart Rate				[F]	[F]
Telemetry				[G]	[G]
Assessment of AEs				X	X
Clinic Discharge					X

[A] Abbreviated physical examination prior to clinic discharge

[B] Continuous 24-hour Holter monitoring from -25 to -1 hours (baseline), and -1 to 23 hours post dose (on treatment).

[C] After verification of eligibility

[D] According to the randomization schedule, combination of bolus/loading infusion + maintenance infusions

[E] BP Measurements at -60, -50, -40, -30, -21, -18, -15, -12, -9, -6, -3 and 0 minutes pre-dose; every 3 minutes for 60 minutes, then once hourly until 12 hours, and at 24 hours post-dose (from T = 0).

[F] Heart rate measurements at -60, -50, -40, -30, -21, -20, -19, -18, -17, -16, -15, -14, -13, -12, -11, -10, -9, -8, -7, -6, -5, -4, -3, -2, -1 and 0 minutes, pre-dose: every 1 minute for the first 60 minutes, then once hourly until 12 hours, and at 24 hours post-dose. (from T = 0).

[G] Continuous monitoring via telemetry from approximately 60 minutes pre-dose until 2 hours after stopping the maintenance infusion.

Source: Sponsor, Clinical Study Report 102, page 39, Table 1

### Testing

Laboratory evaluations, including blood chemistry, hematology, and urinalysis, were obtained during screening, upon admission to the clinic, and before discharge from the clinic. A urine drug screen and a serum pregnancy test for all female subjects were performed at screening and upon admission to the clinic on Day -2.

Routine vital signs for the assessment of subject eligibility, including pulse, respiration, blood pressure and temperature were obtained in conjunction with the physical examinations at screening and at the end of the study. Blood pressure and pulse were obtained with the subject in the sitting position, after sitting for 5 minutes. Orthostatic blood pressure measurements were obtained at screening to verify a normal cardiovascular response for subjects who report a history of orthostatic hypotension.

Physical examinations were performed at the screening visit, and an abbreviated physical examination was performed at the end of the study. Any findings or absence of findings relative to each subject's physical examination were documented.

#### **Primary Pharmacodynamic Variable**

The primary pharmacodynamic variable was SBP from baseline through 15 minutes post-dose.

#### **Secondary Pharmacodynamic Variables**

Secondary pharmacodynamic variables included blood pressure (BP) and HR at the following time points relative to the start of the I.V. bolus of study drug dose initiation:

- Pre-dose BP measurements at -60, -50, -40, -30, -21, -18, -15, -12, -9, -6, -3 and 0 minutes.
- Post-dose BP measurements every 3 minutes for the first 60 minutes following the initiation of administration, hourly through 12 hours, and at 24 hours (relative to study drug dose initiation).
- Pre-dose HR measurements at -60, -50, -40, -30, -21, -20, -19, -18, -17, -16, -15, -14, -13, -12, -11, -10, -9, -8, -7, -6, -5, -4, -3, -2, -1, and 0 minutes.
- Post-dose HR measurements every 1 minute for the first 60 minutes following the initiation of administration, hourly through 12 hours, and at 24 hours (relative to bolus or start of loading infusion).

#### **Analysis Populations**

Pharmacodynamic results were based on the Modified Intent-to-Treat Population (MITT), which included all randomized subjects who received any amount of study medication and had a baseline and at least one on-therapy assessment of SBP. The Per Protocol Population (PP), 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. Safety results, including the hemodynamic endpoints, were based on the Safety Population, which included all randomized subjects who received any amount of study medication.

#### **Statistical Analysis Plan**

The baseline blood pressure measurement for each subject was calculated as the average of the last 2 observations prior to the first dose of study medication administration. The baseline HR measurement for each subject was calculated as the average of the last 4 observations prior to the first dose of study medication administration. No imputation was performed for missing data. The scheduled study time point was used for the analyses. An analysis of variance (ANOVA) model with an effect for treatment was used for the efficacy analyses, unless otherwise noted. The data in the Amiodarone I.V. groups was summarized; however, no formal statistical tests were performed for comparisons between Amiodarone I.V. groups and other groups.

The primary pharmacodynamic endpoint was the change in SBP from baseline to the lowest value (peak reduction) after the start of study drug administration through 15 minutes postdose. The peak change from baseline SBP was the lowest post-dose value observed within the first 15 minutes (i.e., between T = 0 and 15 min). 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 for the PP Population. The ANOVA model included an effect for treatment. The mean difference (PM101-placebo) and the lower limit of its 90% CI were presented. Non-inferiority of PM101 compared to placebo for the primary endpoint was prospectively defined as a SBP decrease of  $\leq 5$  mmHg from baseline to the lowest value within 15 minutes after the start of study 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 in SBP (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 MITT Population to support the primary analysis.

### 9.5 Additional Tables & Figures Referenced in Review

**Table 30. Study 102, Subjects that discontinued due to adverse events**

Subject ID	Adverse Event Preferred Term	Start Date and Time Stop Date and Time	Time to Onset from Study Drug Administration	Relation to Study Drug per Investigator
<b>PM101 IV Treatment Group</b>				
001-018	Dyspnoea	06 July 2007; 09:35 06 July 2007; 09:38	3 minutes	Probable
001-068	Infusion site phlebitis	31 July 2007; 9:30 11 September 2007;	40 minutes	Probable
001-139	Infusion site phlebitis	17 August 2007; 12:25 02 September 2007; 08:00	4 hours 51 minutes	Probable
001-160	Infusion site pain	22 August 2007; 07:25 22 August 2007; 11:17	22 hours 31 minutes	Probable
<b>Amiodarone IV 10 minute</b>				
001-113	Infusion site phlebitis	11 August 2007; 02:30 14 August 2007; 20:00	17 hours 40 minutes	Probable
<b>Amiodarone IV 15 second</b>				
001-028	Infusion site phlebitis	17 July 2007;15:50 unknown	6 hours 56 minutes	Probable
001-154	Infusion site phlebitis	22 August 2007;05:00 07 September 2007;09:00	21 hours 26 minutes	Probable
001-157	Infusion site pain	21 August 2007;18:00 23 August 2007;08:00	9 hours 46 minutes	Probable
001-175	Infusion site phlebitis	24 August 2007;13:30 unknown	4 hours 36 minutes	Probable
001-218	Infusion site phlebitis	08 September 2007;02:30 12 September 2007	17 hours 40 minutes	Probable
001-247	Infusion site phlebitis	14 September 2007;22:17 unknown	14 hours 3 minutes	Probable

Source: Sponsor, Clinical Study Report 102, page 87, Table 19

Clinical Review  
 Robert P. Fiorentino, MD, MPH  
 NDA 022325  
 Nexterone® Amiodarone HCl IV

**Table 31. Study 102, Subjects not included in one of the defined analysis populations**

Subject ID	Treatment	Safety Population	ITT Population	PP Population
001-100	Amiodarone IV 10 min	Yes	Yes	No
001-159	Amiodarone IV 10 min	Yes	Yes	No
001-240	Amiodarone IV 10min	Yes	Yes	No
001-245	Amiodarone IV 10min	Yes	Yes	No
001-053	Amiodarone IV 15sec	No	No	No
001-200	Amiodarone IV 15sec	Yes	Yes	No
001-289	Amiodarone IV 15sec	Yes	Yes	No
001-005	Amiodarone IV15 sec	Yes	Yes	No
001-011	Placebo	No	No	No
001-103	Placebo	No	No	No
001-114	Placebo	Yes	Yes	No
001-302	PM101 IV	Yes	Yes	No
001-018	PM101 IV	Yes	Yes	No
001-042	PM101 IV	Yes	Yes	No
001-054	PM101 IV	No	No	No
001-101	PM101 IV	Yes	Yes	No
001-186	PM101 IV	Yes	Yes	No
001-199	PM101 IV	Yes	Yes	No
001-209	PM101 IV	Yes	Yes	No
001-240	PM101 IV	Yes	Yes	No

Source: Reviewer

**Table 32. Study 102, SAFETY POPULATION, ALL TREATMENT EMERGENT AE's**

SAFETY POPULATION, ALL TREATMENT EMERGENT AE's, All numbers are Percentages (%)				
Adverse Event	PM101 I.V.	Amiodarone I.V. 15 sec	Amiodarone I.V. 10 min	Placebo
FEELING HOT	37.5	40.4	5.3	3.6
INFUSION SITE PAIN	33.9	40.4	33.3	15.2
INFUSION SITE PHLEBITIS	22.3	38.6	28.1	.
HEADACHE	8	7	12.3	11.6
INFUSION SITE ERYTHEMA	8	22.8	12.3	1.8
DIZZINESS	7.1	3.5	.	1.8
FEELING COLD	5.4	5.3	.	0.9
INFUSION SITE INDURATION	5.4	10.5	7	3.6
INFUSION SITE SWELLING	5.4	10.5	7	0.9
HOT FLUSH	3.6	14	1.8	.
ABDOMINAL PAIN	1.8	3.5	.	1.8
BLOOD PRESSURE DECREASED	1.8	.	.	.
BURNING SENSATION	1.8	1.8	.	.
INFUSION SITE BRUISING	1.8	.	3.5	0.9
INFUSION SITE REACTION	1.8	3.5	5.3	.
INJECTION SITE PRURITUS	1.8	.	1.8	.
MUSCLE SPASMS	1.8	.	.	0.9
NAUSEA	1.8	8.8	8.8	3.6
PAIN IN EXTREMITY	1.8	1.8	3.5	0.9
BACK PAIN	0.9	.	.	.
BLOOD PRESSURE INCREASED	0.9	.	.	.

Clinical Review  
 Robert P. Fiorentino, MD, MPH  
 NDA 022325  
 Nexterone® Amiodarone HCl IV

<b>SAFETY POPULATION, ALL TREATMENT EMERGENT AE's, All numbers are Percentages (%)</b>				
<b>Adverse Event</b>	<b>PM101 I.V.</b>	<b>Amiodarone I.V. 15 sec</b>	<b>Amiodarone I.V. 10 min</b>	<b>Placebo</b>
CATHETER SITE PAIN	0.9	.	.	.
CHILLS	0.9	.	.	.
COLD SWEAT	0.9	1.8	.	.
DECREASED APPETITE	0.9	.	.	.
DYSPNOEA	0.9	3.5	1.8	0.9
FATIGUE	0.9	.	1.8	.
FEELING ABNORMAL	0.9	.	.	.
HEART RATE INCREASED	0.9	.	.	0.9
HYPERHIDROSIS	0.9	1.8	.	0.9
INFUSION SITE ANAESTHESIA	0.9	3.5	1.8	0.9
INFUSION SITE COLDNESS	0.9	1.8	.	2.7
INFUSION SITE OEDEMA	0.9	.	1.8	0.9
INFUSION SITE WARMTH	0.9	1.8	1.8	.
INJECTION SITE PAIN	0.9	.	.	.
LIMB DISCOMFORT	0.9	1.8	.	.
MUSCULAR WEAKNESS	0.9	1.8	.	.
MUSCULOSKELETAL CHEST PAIN	0.9	.	.	.
PALLOR	0.9	.	.	.
PALPITATIONS	0.9	.	.	.
POLAKIURIA	0.9	.	.	.
SENSATION OF HEAVINESS	0.9	3.5	.	.
SINUS TACHYCARDIA	0.9	1.8	.	.
SOMNOLENCE	0.9	.	1.8	0.9
THROAT IRRITATION	0.9	1.8	.	.
THROAT TIGHTNESS	0.9	.	.	.
URINE COLOUR ABNORMAL	0.9	.	.	.
ABDOMINAL PAIN UPPER	.	1.8	.	0.9
ALANINE AMINOTRANSFERASE INCREASED	.	.	.	0.9
ARTHRALGIA	.	.	.	1.8
ASTHENIA	.	5.3	1.8	.
CATHETER SITE ERYTHEMA	.	.	1.8	.
CHEST DISCOMFORT	.	.	1.8	.
CONTUSION	.	.	.	0.9
DISTURBANCE IN ATTENTION	.	3.5	.	.
DYSGEUSIA	.	3.5	.	.
ERYTHEMA	.	.	1.8	.
EUPHORIC MOOD	.	1.8	.	.
FEELING DRUNK	.	1.8	.	.
FLATULENCE	.	1.8	.	.
HAEMATOCHEZIA	.	.	.	0.9
HYPOAESTHESIA	.	1.8	.	.
HYPOAESTHESIA ORAL	.	1.8	.	.

Clinical Review  
 Robert P. Fiorentino, MD, MPH  
 NDA 022325  
 Nexterone® Amiodarone HCl IV

<b>SAFETY POPULATION, ALL TREATMENT EMERGENT AE's, All numbers are Percentages (%)</b>				
<b>Adverse Event</b>	<b>PM101 I.V.</b>	<b>Amiodarone I.V. 15 sec</b>	<b>Amiodarone I.V. 10 min</b>	<b>Placebo</b>
INFUSION SITE RASH	.	.	1.8	.
INJECTION SITE IRRITATION	.	1.8	.	.
MICTURITION DISORDER	.	1.8	.	.
NIGHTMARE	.	.	1.8	.
NON-CARDIAC CHEST PAIN	.	1.8	.	.
OCULAR HYPERAEMIA	.	.	1.8	.
OEDEMA PERIPHERAL	.	1.8	.	.
ORAL HERPES	.	.	.	0.9
PAROSMIA	.	.	.	0.9
PERIPHERAL COLDNESS	.	.	.	0.9
RASH	.	1.8	.	0.9
RHINORRHOEA	.	.	.	0.9
SENSORY DISTURBANCE	.	1.8	.	0.9
SKIN LACERATION	.	.	1.8	.
SKIN LESION	.	.	1.8	.
SPONTANEOUS PENILE ERECTION	.	.	.	0.9
STRESS	.	1.8	.	.
TREMOR	.	1.8	.	.
VENTRICULAR TACHYCARDIA	.	1.8	.	.
VESSEL PUNCTURE SITE HAEMATOMA	.	.	.	0.9
VISUAL DISTURBANCE	.	1.8	.	.
VOMITING	.	1.8	3.5	0.9

Source: Reviewer

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

/s/

-----  
Robert P Fiorentino  
11/24/2008 01:33:50 PM  
MEDICAL OFFICER