CLINICAL STUDY REPORT **VERI-305-AMIO (AVRO)**

A Phase III Prospective, Randomized, Double-Blind, Active-Controlled, Multi-Center, Superiority Study of Vernakalant Injection versus Amiodarone in Subjects with Recent Onset Atrial Fibrillation

Date of Report: 15 January 2010

Compound Name:	**Vernakalant injection**
Indication:	**Atrial fibrillation**
Study Initiation Date:	23 April 2008
Study Completion Date:	20 November 2009
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Contract Research Organizations:	Omnicare Clinical Research GmbH Mergenthaller Allee M55 65760 Eschborn, Germany Quintiles UK Ltd. Station House Bracknell Berkshire, England

This study was performed in compliance with Good Clinical Practice and the Declaration of Helsinki.

VERI-305-AMIO Clinical Study Report

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Quality Assurance Review:

This clinical study report has been reviewed against the appropriate source documents (study protocol, amendments, statistical analysis plan, statistical output including tables and listings) and provides a complete and accurate record of the study.

Joanne Brown
Quality Assurance, Cardiome Pharma Corp.

18 Jan 2010
Date

2 SYNOPSIS

Name of Sponsor/Company: Cardiome Pharma Corp.		
Name of Finished Product: Vernakalant injection		
Name of Active Ingredient: Vernakalant		

Study Title:

A Phase III Prospective, Randomized, Double-Blind, **A**ctive-Controlled, Multi-Center, Superiority Study of **V**ernakalant Injection versus Amiodarone in Subjects with **R**ecent **O**nset Atrial Fibrillation (AVRO)

Study Investigators and Centers:

Australia: Bradley (Adelaide), Brown (Perth), Roberts-Thomson (Hobart), Singh (Launceston); **Canada:** Costi (Montreal), Huynh (Montreal), Mayrand (Laval), Phaneuf (Terrebonne), Roy (Montreal), Sivilotti (Kingston), Stiell (Ottawa [primary site]), Stiell (Ottawa [satellite site]); **Czech Republic:** Cermak (Slany), Francek (Kromeriz), Grunfeldova (Caslav), Hondl (Decin II-Nove Mesto), Janota (Praha 2), Mikulova (Tabor), Oscipovsky (Kutna Hora), Polak (Pribram I.), Sabl (Semily), Sedlon (Praha 6), Vymazal (Praha 5), Zemek (Uherske Hradiste); **Denmark:** Frost (Silkeborg), Klarlund (Koge), Petersen (Hjorring), Skagen (Herlev), Torp-Pedersen (Hellerup); **Estonia:** Kaik (Haabneeme), Kolk (Tartu), Kork (Tallinn), Vahula (Parnu); **Finland:** Huikuri (Oulu); **France:** Aliot (Nancy), Babuty (Chambray-les-Tours), Leenhardt (Paris), Roul (Strasbourg); **Germany:** Axthelm (Pirna), Baer (Koln), Bollmann (Leipzig), Buerke (Halle), Butter (Bernau), Gronefeld (Hamburg), Haverkamp (Berlin), Hensen (Hannover), Hohnloser (Frankfurt), Lickfett (Bonn), Naegele (Reinbek), Prondzinsky (Merseburg), Schwencke (Hamburg), Sechtem (Stuttgart), Seidl (Ludwigshafen), Stangl (Berlin), Utech (Kassel), Wachter (Gottingen); **Latvia:** Erglis (Riga); **Lithuania:** Aidietis (Vilnius), Jarasuniene (Klaipeda), Sakalyte (Kaunas); **Netherlands:** Hertzberger (Nijmegen), Michels (Eindhoven), Moens (Maastricht), Nierop (Rotterdam), The (Hoogeveen), Viergever (Gouda), Willems (Arnhem); **Poland:** Chojnoswka-Jezierska / Broncel (Lodz), Derlaga (Tarnow), Hoffman (Bydgoszcz), Jonczy / Pulkownik (Torun), Kochmanski (Warszawa), Kubik / Kowal (Warszawa), Lewandowska-Stanek (Lublin), Makowiecki (Warszawa), Miekus (Gdynia), Pawlowicz (Torun), Ponikowski (Wroclaw), Trojnar (Lublin); **Serbia:** Borzanovic (Belgrade), Ilic (Niska Banja), Putnikovic (Zemun), Seferovic (Belgrade); **Slovakia:** Hasilla (Nitra), Kaliska (Banska Bystrica), Kycina (Liptovsky Mikulas), Macek (Trnava), Majdak (Bojnice), Margitfalvi (Bratislava), Spisak (Zilina), Urban (Ruzomberok); **Sweden:** Blomstrom (Uppsala), Fengsrud (Orebro), Juul-Moller (Malmo); **Ukraine:** Batushkin (Kiev), Faynyk (Lviv), Karpenko (Kiev), Kolomyyits (Odessa), Nalotov (Donetsk), Parkhomenko (Kiev), Potapenko (Lugansk), Tseluyko (Kharkiv).

Number and Location of Centers:

There were a total of 102 study centers in 16 countries: 4 in Australia, 8 in Canada, 12 in Czech Republic, 5 in Denmark, 4 in Estonia, 1 in Finland, 4 in France, 18 in Germany, 1 in Latvia, 3 in Lithuania, 7 in the Netherlands, 12 in Poland, 4 in Serbia, 8 in Slovakia, 3 in Sweden, and 8 in Ukraine. Of the 102 study centers activated for the study, 66 enrolled at least one subject.

Date First Subject Enrolled: 23 April 2008	**Development Phase:** 3

Date Last Subject Completed: 20 November 2009

Objectives:

The primary objective of the study was to demonstrate the superiority of vernakalant injection over amiodarone injection in the conversion of atrial fibrillation (AF) to sinus rhythm (SR) within 90 minutes of the start of drug administration.

The secondary objective was to compare the safety of vernakalant to amiodarone.

Design:

This was a phase 3, multicenter, randomized, double-blind, active-controlled, double-dummy study. Subjects were randomized to receive either vernakalant injection or amiodarone injection in a 1:1 ratio.

Number of Subjects (planned and analyzed):

Approximately 240 subjects were planned to be enrolled in the study, at approximately 70 study centers globally, with 120 subjects randomized to receive vernakalant injection and 120 subjects randomized to receive amiodarone injection.

A total of 254 subjects were enrolled in the study, at 2 centers in Australia, 7 in Canada, and 57 in Europe. There were 128 subjects randomized to vernakalant and 126 subjects randomized to amiodarone. A total of 232 of these subjects received study drug (116 in each treatment group) and made up the safety set (used for the safety analyses) and the full analysis set (the primary analysis set used for all efficacy analyses). There were 22 subjects (including 19 subjects who spontaneously converted to SR prior to receiving study drug) who were excluded from the primary analysis.

Diagnosis and Main Inclusion/Exclusion Criteria:

Subjects were males and females, between 18 and 85 years of age, with symptomatic AF (duration of 3 to 48 hours) who were eligible for cardioversion, hemodynamically stable, and on adequate anticoagulation therapy. Subjects with atrial flutter (AFL); unstable congestive heart failure (CHF), NYHA Class IV CHF, or CHF requiring inotropes; or previous exposure to vernakalant, were excluded from the study.

Test Product, Dose, and Mode of Administration:

Vernakalant injection

Subjects randomized to vernakalant received a 10-minute infusion of 3 mg/kg vernakalant followed by a 15-minute observation period. If the subject was still in AF, an additional 10-minute infusion of 2 mg/kg vernakalant was administered. To maintain blinding, a 60-minute infusion of placebo (5% dextrose in water [D5W]) was administered in a second infusion line, followed by a maintenance infusion of placebo for a minimum of an additional 60 minutes.

Amiodarone injection

Subjects randomized to amiodarone received a 60-minute infusion of 5 mg/kg amiodarone followed by a maintenance infusion of 50 mg amiodarone over an additional 60 minutes (equivalent to approximately 15 mg/kg over 24 hours). To maintain blinding, a 10-minute infusion of placebo (normal saline) was administered in a second infusion line, followed by a 15-minute observation period, and then an additional 10-minute infusion of placebo if the subject was still in AF.

Lot Numbers:

The lot number used in this study for vernakalant injection was 742015.

The lot numbers used in this study for amiodarone injection were CK001, DA001, 1542, 146841, 149008, and 153751.

The placebos used in this study (normal saline and D5W) were obtained by each site from a commercial source.

Duration of Study and Treatment:

Screening procedures were to take place within 12 hours prior to dosing. The infusion of study drug was started at T=0 (Day 1). The contents of the vernakalant/placebo infusion line were administered over 10 minutes. After a 15-minute observation period, a second 10-minute infusion was to be administered if the subject was still in AF. The contents of the amiodarone/placebo infusion line were to be administered over 60 minutes, followed by a maintenance infusion for an additional 60 minutes. Subjects were to remain in the clinic or in-patient facility for a minimum of 6 hours after the start of infusion. Electrical cardioversion or rate control medications were permitted two hours after the start of infusion if the subject was still in AF. Class I and Class III antiarrhythmics were not to be administered to the subject for at least 24 hours after the start of study drug infusion. Discharge was to occur at the discretion of the investigator, no sooner than 6 hours after the initiation of dosing. Subjects attended a follow-up visit at 7 (±2) days after treatment and received a follow-up telephone call at 30 (±3) days after treatment.

Efficacy Assessments and Variables:

The primary efficacy endpoint was the proportion of subjects with conversion of AF to SR within 90+3 minutes of first exposure to study medication and for a minimum duration of one minute.

The secondary efficacy endpoints included the time to conversion within 90+3 minutes after the start of infusion, the proportion of subjects exhibiting no AF symptoms at 90 minutes after the start of infusion, and the change in quality of life from screening to hour 2 using the EQ-5D Visual Analogue Scale (VAS).

Efficacy Assessments and Variables (cont.):

The following exploratory efficacy endpoints were also assessed:

1. Time to conversion of SR within the first 240 minutes after the start of infusion;
2. Subjects exhibiting no AF symptoms at Day 7;
3. Subjects exhibiting each AF symptom at minute 90 and Day 7;
4. Reduction in the number of symptoms at minute 90;
5. Reduction in the number of symptoms at Day 7;
6. Proportion of subjects who met the primary endpoint and maintained SR with no AF relapse at hour 4;
7. Proportion of subjects who met the primary endpoint and maintained SR with no AF relapse through Day 7;
8. Proportion of subjects who met the primary endpoint and maintained SR with no AF relapse through Day 30;
9. Assessment of each dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) of the descriptive system of the EQ-5D health-related quality of life tool.
10. Proportion of subjects ready for discharge at two hours.
11. For subjects who converted to SR within 90 minutes, a descriptive summary of the time to conversion was presented by treatment group; no comparison between groups was made.

Safety Assessments and Variables:

Safety was assessed at regular intervals during the study through the monitoring of adverse events (AEs) and serious adverse events (SAEs), vital signs (including blood pressure and heart rate), 12-lead electrocardiogram (ECG) intervals, clinical laboratory parameters, and physical examinations (only at screening and at discharge). In addition, continuous 12-lead Holter monitoring was performed from one hour predose to a minimum of 4 hours after the start of study drug infusion. The incidence of hypotension (based on AEs and vital signs), bradycardia (based on Holter, AEs, and vital signs), ventricular arrhythmia (based on Holter and AEs), and atrial flutter (based on Holter and AEs) was also assessed. All ventricular arrhythmias were adjudicated by the Ventricular Events Committee (VEC).

Statistical Methods:

The primary hypothesis was assessed by comparing the primary efficacy endpoint between treatment groups using a two-sided Cochran Mantel-Haenszel (CMH) test stratified by country, with a 0.05 significance level. The following statistics were presented: frequency and percentage of success and failures for each treatment group, the difference in the percentage of successes between treatment groups, the asymptotic 95% confidence interval (CI) of the difference in success between treatment groups, and the P-value for the difference between treatment groups. In addition, the relative risk in favor of conversion of the vernakalant group versus the amiodarone group along with 95% confidence limits was also estimated. Subjects for whom data were missing to derive the primary endpoint were counted as failures for the primary analysis.

For the secondary efficacy endpoint of the time to conversion to SR, the Kaplan-Meier method was used to summarize the distribution of conversion times and obtain estimates of the 25^{th} and 75^{th} percentiles and median time to conversion. The two treatment groups were compared using a two-sided log rank test with a 0.05 significance level. Subjects who did not convert to SR within 90+3 minutes had their time censored at 90 minutes. Additionally, subjects who withdrew prior to conversion to SR or who were electrically converted prior to 90 minutes were censored at the time at which they withdrew or were converted.

The secondary efficacy endpoint of the proportion of subjects with no AF symptoms at 90 minutes was summarized by treatment group. The frequency and percentage of subjects with no symptoms and at least one symptom were reported. A comparison between treatment groups was based on a two-sided CMH test, stratified by country, with a 0.05 significance level. Subjects who were missing data for all symptoms had a response of "symptom present" imputed. Additionally, the following statistics were presented: the difference in the percentage of successes between groups, the asymptotic 95% CI of the difference in success between treatment groups, and the relative risk in favor of the vernakalant group versus the amiodarone group along with 95% confidence limits.

The secondary efficacy endpoint of change in EQ-5D quality of life assessment VAS was modeled using a fixed effects general linear model with change as the dependent variable, baseline score and age as covariates, and treatment as a fixed effect. Subjects who were missing data had a change of 0 imputed. The adjusted mean changes and the difference in adjusted mean changes (along with 95% CI) were reported.

Disposition:

A total of 254 subjects were enrolled in the study, with 128 subjects in the vernakalant group and 126 subjects in the amiodarone group. The majority of randomized subjects (116 in each treatment group) received at least one dose of study medication. Twelve subjects in the vernakalant group did not receive study drug; 10 of these subjects spontaneously converted to SR prior to receiving vernakalant. Ten subjects in the amiodarone group did not receive study drug; 9 of these subjects spontaneously converted to SR prior to receiving amiodarone. Of the subjects who were treated, 6 vernakalant subjects and 1 amiodarone subject discontinued the study, mostly due to AEs. A total of 225 subjects completed the study through the Day 30 follow-up telephone call.

Demography and Baseline Characteristics:

Demographics were similar among the two treatment groups. The majority of subjects were white (95.7%), and approximately two-thirds were male (62.9%). The subjects had a mean age of 62.7±11.21 years (range of 32 to 85 years), and approximately 15% of subjects were $\geq$75 years of age.

Baseline characteristics and cardiovascular medical history were well balanced among the two treatment groups. The majority of subjects (164/232, 70.7%) had experienced at least one previous AF episode, with 34.5% of subjects having >3 previous episodes. The median duration of the current AF episode was 17.7 hours, and 40.5% of subjects had AF duration of >24 hours. There were 46 out of 232 subjects (19.8%) with a history of heart failure, with just over half of these subjects having NYHA Class II heart failure (25/46 subjects, 54.3%). There were no subjects with NYHA Class III heart failure enrolled in this study.

Efficacy Results:

Treatment with vernakalant resulted in a statistically significantly greater proportion of subjects converting from AF to SR within the first 90 minutes compared to amiodarone; a total of 60/116 (51.7%) vernakalant subjects met the primary endpoint compared to 6/116 (5.2%) amiodarone subjects (CMH P-value <0.0001).

Treatment with vernakalant also resulted in:

1. A statistically significantly faster conversion rate from AF to SR within the first 90 minutes compared to amiodarone; in the vernakalant group, 25% of subjects had converted to SR by minute 11 and 50% had converted by minute 50, as compared to the amiodarone group where only 5% of subjects had converted by minute 90 (log rank P-value <0.0001).
2. A statistically significantly greater proportion of subjects reporting no AF symptoms at 90 minutes compared to amiodarone; a total of 62/116 (53.4%) vernakalant subjects had no AF symptoms at 90 minutes compared to 38/116 (32.8%) amiodarone subjects (CMH P-value = 0.0012).
3. A statistically significantly greater improvement in a subject's perception of their state of health at hour 2 compared to amiodarone (as measured by the EQ-5D quality of life assessment VAS); in the vernakalant group, a mean adjusted change of 10.9 points was seen compared to a mean adjusted change of 5.6 points in the amiodarone group (P=0.0006).

Pharmacoeconomic Results:

The results of the pharmacoeconomic analyses are provided in a separate report.

Safety Results:

The incidence of treatment-emergent AEs was higher in the vernakalant group than in the amiodarone group. Treatment-emergent AEs that occurred in 3 or more subjects within a treatment group within 24 hours postdose included dysgeusia, cough, dizziness, nausea, atrial fibrillation, sneezing, and hypertension, most of which occurred at a higher incidence in the vernakalant group than the amiodarone group. The exception was dizziness, which occurred in 3 subjects in each group. Additional treatment-emergent AEs that occurred in more than one subject in the amiodarone group within 24 hours postdose included insomnia and prolonged activated partial thromboplastin time.

The majority of related treatment-emergent AEs within 24 hours postdose occurred in the vernakalant group, with dysgeusia being the most common. Other related treatment-emergent AEs that occurred in two or more subjects in the vernakalant group were sneezing, cough, bradycardia, nausea, paresthesia, pharyngolaryngeal pain, and throat irritation, most of which were transient and occurred within two hours postdose. In the amiodarone group, there were two related treatment-emergent AEs that occurred within 24 hours postdose: cardiac arrest (within 2 hours) and increased blood bilirubin (between 2 to 24 hours).

Safety Results (cont.):

The incidence of SAEs (11.2% vernakalant, 8.6% amiodarone) and related SAEs (2.6% vernakalant, 0.9% amiodarone) was low overall. Within 24 hours postdose, most of the SAEs that occurred in both treatment groups were cardiac disorders and none of the SAEs occurred in more than one subject. The SAEs occurring within 24 hours postdose that were considered by the investigator to be related to study drug included angina pectoris, hypersensitivity, and ventricular tachycardia (VT) in the vernakalant group, and cardiac arrest in the amiodarone group. These related SAEs were the only events in the study that led to discontinuation of study drug.

There was one death in the study, which occurred in the vernakalant group. The death occurred on Day 24 due to chronic obstructive pulmonary disease and pulmonary embolism, and was not considered to be related to study drug.

In regards to events of interest, hypotension, bradycardia, and ventricular arrhythmia were rare and occurred at a similar incidence rate between the two treatment groups. Within 24 hours postdose, there was one event of syncope reported as an SAE in the vernakalant group and one event of sinus bradycardia reported as an SAE in the amiodarone group. Additionally, there were two events of ventricular arrhythmia that were reported as an SAE within 24 hours postdose and which also led to discontinuation of study drug: ventricular tachycardia in the vernakalant group and cardiac arrest in the amiodarone group. There were no cases of torsades de pointes, ventricular fibrillation, or polymorphic or sustained VT in either treatment group.

There was a higher incidence of AFL in the vernakalant group (8.6%) compared to the amiodarone group (0.9%) within 4 hours postdose. There were no SAEs of atrial flutter and none of the subjects who developed AFL had 1:1 atrioventricular conduction during the AFL episodes.

Based on the ECG interval data, there was a decrease in heart rate over time in both treatment groups; at 60 minutes postdose the heart rate was reduced by 21.4 and 19.4 beats per minute (bpm) in the vernakalant and amiodarone groups, respectively. In the vernakalant group, the decrease in heart rate was primarily due to conversion to SR; in subjects remaining in AF there was a slight decrease in heart rate of approximately 4 bpm through 240 minutes postdose. Conversely, the decrease in heart rate in the amiodarone group appeared to be independent of conversion to SR.

The greatest mean change from baseline for systolic blood pressure (SBP) was approximately 6 mmHg in the vernakalant group and approximately -5 mmHg in the amiodarone group. There were two subjects in the amiodarone group who had a decrease in SBP to <90 mmHg; no subjects in the vernakalant group had a decrease in SBP to <90 mmHg.

Maximum mean increases (7.4 msec) in QRS were observed at 35 minutes postdose in the vernakalant group, and decreased over the remainder of the 4-hour period. Amiodarone showed consistent increases of approximately 1-3 msec over time. In the vernakalant group, maximum mean increases in QTcB (15.6 msec) and QTcF (23.7 msec) were observed at 10 minutes postdose, and decreased over the remainder of the 4-hour period. In the amiodarone group, QTcB remained relatively unchanged while QTcF progressively increased throughout the 4-hour observation period, with a maximum increase (21.7 msec) observed at 4 hours postdose.

There were no clinically significant trends over time and no significant differences between treatment groups for any of the laboratory parameters.

Conclusions:

- The data from this phase 3 study demonstrated that vernakalant injection had superior efficacy when compared directly to amiodarone injection for the rapid conversion of recent onset AF (3 to 48 hours duration) to sinus rhythm within 90 minutes. Additionally, vernakalant was associated with a higher rate of symptom relief and a greater improvement in a subject's perception of their state of health compared to amiodarone.
- Both vernakalant injection and amiodarone injection were safe and well tolerated in this study, although generally there was a higher incidence of AEs in the vernakalant group. There was one death in the study, which occurred in the vernakalant group on Day 24 and was assessed as being not related to study drug. There were no cases of torsades de pointes, ventricular fibrillation, or polymorphic or sustained VT in either treatment group.

Date of Clinical Study Report: 15 January 2010

3 TABLE OF CONTENTS

4 ABBREVIATIONS

ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
AE	Adverse event
AF	Atrial fibrillation
AFL	Atrial flutter
AHA	American Heart Association
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AMIO	Amiodarone injection
AV	Atrioventricular
BP	Blood pressure
bpm	Beats per minute
CEC	Clinical Events Committee
CHF	Congestive heart failure
CI	Confidence interval
CMH	Cochran Mantel-Haenszel
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CRO	Contract Research Organization
D5W	5% dextrose in water
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ECV	Electrical cardioversion
EDC	Electronic data capture
ESC	European Society of Cardiology
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
IHD	Ischemic heart disease
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive voice response system
LADD	Left atrial diastolic dimension
LS	Least squares
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NTF	Note-to-File
NYHA	New York Heart Association
PIPEDA	Personal Information Protection and Electronic Documents Act

ABBREVIATIONS (cont.)

QRS	ECG interval describing ventricular activation time
QT	ECG interval representing the total duration of ventricular electrical activity
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula
QTcF	QT interval corrected for heart rate using the Fridericia formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SHD	Structural heart disease
SOC	System organ class
SPC	Summary of Product Characteristics
SR	Sinus rhythm
TdP	Torsades de pointes
VAS	Visual Analogue Scale
VEC	Ventricular Events Committee
VERI	Vernakalant injection
VHD	Valvular heart disease
VT	Ventricular tachycardia

5 ETHICS

5.1 Ethics Committee or Institutional Review Board

The protocol and amendments, as well as the informed consent form (ICF), were reviewed and approved by an institutional review board (IRB) or ethics committee (EC) at each site. The IRB/EC was informed of any safety issues related to the study and the study medication, including reports of serious adverse events (SAEs) and all IND Safety Reports, as per applicable local regulations. A list of all IRBs/ECs used in this study is provided in Appendix 16.1.3.1.

5.2 Ethical Conduct of Study

The study was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with the ICH E6 guideline for Good Clinical Practice (GCP), as well as any governing local regulations.

5.3 Subject Information and Informed Consent

Written informed consent was obtained from subjects prior to enrollment in this study. Subjects in Europe provided consent in accordance with the EU Privacy Directive, as implemented by member states, and subjects in Canada provided consent in accordance with the Personal Information Protection and Electronic Documents Act (PIPEDA). Confidentiality of subject data was maintained in accordance with local laws. Elements of the informed consent are listed in the protocol in Appendix 16.1.1 and sample ICFs are provided in Appendix 16.1.3.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The sponsor of this study was Cardiome Pharma Corp, Vancouver, Canada. This study was conducted at 102 sites in 16 countries (Australia, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Latvia, Lithuania, the Netherlands, Poland, Serbia, Slovakia, Sweden, and Ukraine). Of the 102 sites activated for the study, 66 sites enrolled at least one subject. The principal investigator at each site was a licensed medical practitioner with experience in the management of subjects with atrial arrhythmia and the use of antiarrhythmic drugs. Investigator information is provided in Appendix 16.1.4 and the signature of the principal/coordinating investigator is provided in Appendix 16.1.5.

Cardiome managed the overall study and was also responsible for managing and monitoring clinical sites in Canada. Omnicare Clinical Research GmbH and Quintiles Ltd. were responsible for project and site management in other countries, including site and safety monitoring/reporting. A list of the contract research organizations (CROs) that were involved in the study is provided below.

Company	Location	Responsibility
Omnicare Clinical Research GmbH	Eschborn, Germany	Project and site management, including site and safety monitoring/reporting
Quintiles Ltd.	Bracknell, England / Dublin, Ireland	Project and site management, including site and safety monitoring/reporting
Cardiabase	Nancy, France	Central lab for evaluation of 12-lead electrocardiogram (ECG) and Holter data
BioClinica (formerly Phoenix Data Systems)	King of Prussia, PA, USA	Electronic data capture and data management
IVRESS, LLC	Hilton Head, SC, USA	Interactive voice response system (IVRS) for randomization
LabConnect, LLC	Johnson City, TN, USA	Central lab for clinical laboratory analyses
Synevo	Gdansk, Poland	Clinical laboratory analyses in Europe
Dorevitch	Heidelberg, Australia	Clinical laboratory analyses in Australia
Brecon Pharmaceuticals	Hay-on-Wye, England	Drug packaging and distribution

7 INTRODUCTION

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function [1], and is the most common arrhythmia encountered in the adult population [1,2]. It is estimated that 4.5 million individuals in the European Union and 2.2 million individuals in the United States have paroxysmal or persistent AF [1]. The prevalence of AF is estimated at 0.4-1.0% of the general population, increasing with age [1]. Atrial fibrillation can cause discomfort and is associated with a number of symptoms, such as palpitations, chest pain, dyspnea, fatigue, and light-headedness [1]. Atrial fibrillation can also lead to stroke, congestive heart failure, and an overall increase in morbidity and mortality, and is costly to health care systems due to hospitalizations [1,3,4].

There are two general therapeutic strategies used in treating subjects with AF. One strategy, termed “rate control” is to allow the AF to continue and to control the ventricular response rate by slowing the conduction through the atrioventricular (AV) node with digoxin, calcium channel blockers, or beta blockers. The other strategy, “rhythm control”, seeks to convert the AF and then maintain sinus rhythm (SR), thus attempting to avoid the morbidity associated with chronic AF. Existing antiarrhythmics are limited because of their proarrhythmic potential, poor tolerability, and other side effects limiting their chronic use. Most drugs currently used to treat or prevent atrial or ventricular arrhythmias have effects on the entire heart muscle, including both healthy and damaged tissue. These drugs, which globally block ion channels in the heart, have been associated with life-threatening ventricular arrhythmia, leading to increased rather than decreased mortality in broad patient populations. A need has been recognized for antiarrhythmic drugs that are more selective for the tissue responsible for the arrhythmia, leaving the rest of the heart to function normally. Such drugs are less likely to cause ventricular arrhythmias.

Additionally, it is desirable for antiarrhythmic agents to provide rapid conversion to SR. Many drugs have a delayed onset of action, and conversion may not occur for several days [1]. In acute AF, especially in patients with significant symptoms, conversion to SR is needed as soon as possible to improve symptoms and to prevent the potential detrimental effects of prolonged AF [5,6].

Amiodarone is categorized as a Class III antiarrhythmic agent and prolongs phase 3 of the cardiac action potential; however, it has many other effects, including actions that are similar to those of Class Ia, II, and IV antiarrhythmic agents. Amiodarone shows beta blocker and calcium channel blocking activity on the sinoatrial (SA) and AV nodes, increases the refractory period via sodium and potassium channel effects, and slows intra-cardiac conduction of the cardiac action potential via sodium channel effects. Additionally, amiodarone may take several hours or days for successful cardioversion and can require infusions of up to 24 hours.

Vernakalant is a novel antiarrhythmic that is being evaluated as a potential therapy for AF, and shows preferential effects for atrial tissue and limited actions on ventricular tissue. Vernakalant acts on the heart by concentration-dependent blockade of potassium channels (which predominantly affect atrial repolarization), combined with concentration-, voltage- and frequency-dependent blockade of sodium channels. These actions result in prolonged atrial refractoriness and rate-dependent slowing of atrial conduction, leading to the rapid conversion of AF to SR.

Vernakalant injection is an intravenous (IV) antiarrhythmic agent intended for the rapid conversion of AF to SR. Twelve clinical studies have been completed as part of the vernakalant injection program, in which 883 subjects have received vernakalant injection. In three pivotal phase 3 clinical trials, it was demonstrated that vernakalant injection rapidly and effectively converted recent onset AF (duration of <7 days) to SR and provided rapid relief of AF symptoms. Vernakalant injection was well tolerated in subjects with AF and/or atrial flutter (AFL).

This study was designed to investigate the efficacy and safety of vernakalant injection compared to amiodarone injection in subjects with AF. Amiodarone was selected as a comparator as it is one of the most commonly used antiarrhythmic agents for the conversion of AF in Europe and can be used in a broad AF population. An important consideration in understanding vernakalant's position relative to the currently available AF converting agents is to demonstrate vernakalant's relative speed and success rate in achieving SR and symptomatic relief.

8 STUDY OBJECTIVES

The primary objective of this study was to demonstrate the superiority of vernakalant injection over amiodarone injection in the conversion of AF to SR within 90 minutes after the start of drug administration.

The secondary objective was to assess the safety of vernakalant compared to amiodarone.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This was a phase 3, multicenter, randomized, double-blind, active-controlled, double-dummy study in subjects with symptomatic AF (of 3 to 48 hours duration) who were eligible for cardioversion. Approximately 240 subjects were planned to be enrolled in this study at approximately 70 clinical sites internationally.

Subjects went through screening procedures to determine eligibility. If eligible, and after obtaining informed consent, subjects were enrolled in the study. No more than 12 hours were to elapse between screening and the initiation of dosing. Subjects were randomized to receive vernakalant injection or amiodarone injection in a 1:1 ratio. To maintain blinding, subjects had two infusion lines: one for vernakalant injection or placebo and the other for amiodarone injection or placebo (see Section 9.4.1 for treatment administration details).

At two hours after the start of study drug infusion, if the subject was still in AF, electrical cardioversion may have been performed or rate control medications may have been administered. Class I and Class III antiarrhythmics were not to be administered to the subject for at least 24 hours after the start of study drug infusion. Subjects were to remain in the clinic for at least 6 hours after the start of infusion. Continuous telemetry monitoring was performed from baseline to discharge, and continuous 12-lead Holter monitoring was performed from one hour prior to dosing until a minimum of 4 hours after the start of infusion. Subjects were required to return to the clinic for a follow-up visit at 7 (±2) days after treatment. Subjects received a follow-up telephone call at 30 (±3) days after infusion.

Efficacy, pharmacoeconomic, and safety assessments were completed throughout the study. The schedule of study procedures is summarized in Table 1. A full description of study procedures for each assessment time point is provided in the protocol in Appendix 16.1.1.

Table 1. Schedule of Study Procedures

Study Procedure	Screening[a]	Baseline[a]	Minutes After Start of Infusions								Discharge[b]	Day 7 Visit[c]	Day 30 Call[c]
			0	5	20	30	40	90	120	240			
Informed consent	X												
Inclusion/exclusion criteria	X												
Medical history	X												
Pregnancy test (serum or urine)	X												
12-lead electrocardiogram (ECG)[d]	X	X[e]			X			X[f]		X	X	X	
Vital signs[g]	X	X		X	X	X	X	X		X	X	X	
AF symptom assessment	X							X				X	
Quality of life assessment	X								X[h]				
Limited physical examination	X										X		
Serum chemistry and hematology	X[i]										X	X	
Urine dipstick	X											X	
Randomization	X[j]												
Initiation of dosing			X										
Pharmacoeconomic assessments									X		X	X	
Echocardiogram												X	
Concomitant medications	Concomitant medications were to be recorded from screening to Day 7												X[k]
Telemetry		Continuous telemetry was to be performed from baseline to discharge											
12-lead ECG Holter		Continuous 12-lead Holter monitoring was to be performed from one hour predose to 4 hours after the start of study drug infusion											
Adverse events (AEs)[l]			AEs were to be recorded from the initiation of dosing to Day 7										X[k]

a Screening procedures were to occur within 12 hours of initiation of dosing; baseline procedures were to occur within one hour of initiation of dosing.

b Discharge was to occur at the discretion of the investigator, no sooner than 6 hours after the initiation of dosing.

c The Day 7 visit was to occur within ±2 days; the Day 30 telephone call was to occur within ±3 days.

d Two consecutive 12-lead ECGs (one minute apart) were also to be taken at the time of conversion.

e The 12-lead ECG performed at baseline was to confirm that the subject was in AF.

f For the minute 90 ECG, two consecutive ECGs were to be taken, one minute apart.

g At screening, vital signs were to include blood pressure (BP), heart rate (HR), respiration rate, temperature, and oxygen saturation; at subsequent time points, vital signs were to be limited to BP and HR.

h The quality of life assessment was to be performed prior to electrical cardioversion or the administration of rate control medications.

i Potassium and magnesium should have been within normal limits prior to administration of study treatment.

j Randomization was to occur once screening procedures had been completed and the subject was deemed eligible for the study.

k For serious adverse events (SAEs) only.

l The recurrence of AF was to be recorded as an AE if the subject was successfully converted to sinus rhythm (SR). If the subject did not convert to SR, their ongoing AF was not to be recorded as an AE.

9.2 Discussion of Study Design, Including Choice of Control Groups

The purpose of this study was to investigate the relative efficacy of vernakalant injection and amiodarone injection in the conversion of AF to SR. An important consideration in understanding vernakalant's position relative to the currently available AF converting agents is to demonstrate vernakalant's relative speed and success rate in achieving SR and symptomatic relief. The efficacy evaluation period of 90 minutes after the start of infusion was chosen because it mirrors that used in all preceding phase 3 trials with vernakalant, including the registration studies (ACT I and ACT III). Amiodarone was selected as a comparator as it is the most widely approved IV antiarrhythmic agent for the conversion of AF in Europe and can be used in a broad AF population.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

A subject was eligible for study participation if he/she met the following criteria:

1. Had symptomatic AF of 3 to 48 hours duration at baseline.
2. Was eligible for cardioversion.
3. Was 18 to 85 years of age.
4. Was able to comprehend and sign a written ICF (compliant with applicable regulatory requirements, such as the EU Privacy Directive as implemented by member states in national law, or the PIPEDA in Canada, as applicable).
5. Women must not have been pregnant or nursing, and if pre-menopausal, must have been using an effective form of birth control from the time of screening until 3 months after discharge. Methods of birth control considered to be effective included hormonal contraception (the pill), an intrauterine device (IUD), condoms in combination with a spermicidal cream, total abstinence, or sterilization. Men were advised not to conceive a child and were advised to use an effective form of birth control from admission until 3 months after discharge.
6. Had adequate anticoagulant therapy for cardioversion in accordance with standard of practice as recommended by ACC/AHA/ESC guidelines [1].
7. Was hemodynamically stable and had systolic blood pressure (SBP) above 100 mmHg and less than 160 mmHg, and diastolic BP less than 95 mmHg, at screening and baseline. Baseline BP was to be measured 3 times within 5 minutes, after resting supine for 5 minutes, and averaged to determine the baseline BP.
8. Had a body weight between 45 and 136 kg (99 and 300 lbs). For subjects weighing >113 kg (250 lbs), the vernakalant dose should have been based on a weight of 113 kg (250 lbs) and not higher.

9.3.2 Exclusion Criteria

A subject was excluded from study participation if he/she met any of the following criteria:

1. Had known or suspected prolonged QT or an uncorrected QT interval of >440 msec as measured at screening on a 12-lead ECG; familial long QT syndrome; or previous torsades de pointes (TdP), ventricular fibrillation, or sustained ventricular tachycardia (VT).
2. Had symptomatic bradycardia, sick sinus syndrome, or ventricular rate less than 50 beats per minute (bpm) as documented by 12-lead ECG at screening.
3. Had a QRS interval >140 msec.
4. Had any known concurrent temporary secondary causes of AF, such as alcohol intoxication, pulmonary embolism, hyperthyroidism, pneumonia, acute pericarditis, myocarditis, or hypoxemia (oxygen saturation less than 90% on room air).
5. Had atrial flutter.
6. Had significant valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis.
7. Had documented previous episodes of second or third degree AV block.
8. Had a myocardial infarction (MI), acute coronary syndrome, or cardiac surgery within 30 days prior to entry into the study.
9. Had an uncorrected electrolyte imbalance of serum potassium (K^+) <3.5 mmol/L or >5.5 mmol/L, or magnesium (Mg^{2+}) below the lower limit of normal (<0.65 mmol/L in subjects 65 years or younger and <0.80 mmol/L in subjects 66 years or older). Both K^+ and Mg^{2+} were to be corrected prior to dosing.
10. Had clinical evidence of digoxin toxicity in the opinion of the investigator.
11. Had failed electrical cardioversion during the current episode of AF.
12. Had received intravenous Class I or Class III antiarrhythmic drugs within 24 hours prior to dosing.
13. Had received any oral Class I or Class III antiarrhythmic drugs for the purpose of conversion of AF to SR within 24 hours prior to dosing.
14. Had received amiodarone injection within 30 days prior to dosing, or oral amiodarone within 90 days prior to dosing.
15. Had a pacemaker.
16. Had unstable congestive heart failure (CHF), NYHA Class IV CHF, or CHF requiring inotropes.
17. Had serious pulmonary, hepatic, metabolic, renal, gastrointestinal, central nervous system, or psychiatric disease; infection; febrile illness (oral temperature >38.5°C); end stage disease states; or any other disease that could have interfered with the conduct or validity of the study or compromised subject safety.

18. Had any evidence of an atrial thrombus.
19. Had troponin (I or T) levels above the upper limit of normal.
20. Had experienced a cerebrovascular accident within the past 3 months.
21. Had any other surgical or medical condition that, in the judgment of the clinical investigator, might warrant exclusion or be contraindicated for safety reasons.
22. Had thyroid dysfunction, hypersensitivity to iodine, or any other condition for which amiodarone injection is contraindicated.
23. Had previous exposure to vernakalant.
24. Had known or suspected hypersensitivity to vernakalant injection or any component of its formulation, or to amiodarone injection or any component of its formulation.
25. Was concurrently participating in another drug study or had received an investigational drug within 30 days prior to screening.
26. Was unable to communicate well with the investigator and to comply with the requirements of the entire study.

9.3.3 Removal of Subjects from Therapy or Assessment / Dose Stopping Criteria

Safety during dosing was assessed by the regular measurement of vital signs, continuous telemetry monitoring, and a 12-lead ECG at 20 minutes after the start of infusion. If any of the following criteria were observed at any time after the start of infusion, both study drug infusion lines were to be permanently stopped:

a) QTc >550 msec or QRS >180 msec;
b) Symptomatic bradycardia or heart rate (HR) <40 bpm;
c) Symptomatic hypotension or SBP <85 mmHg;
d) New bundle branch block;
e) Asymptomatic VT lasting 10 consecutive beats or longer, symptomatic VT of any duration, or any TdP or ventricular fibrillation;
f) One or more sinus pauses of 5 seconds or greater or a complete heart block;
g) Intolerable side effects as determined by the investigator;
h) Any changes in cardiac rhythm or AV conduction that, in the investigator's opinion, were a threat to subject safety.

Subjects for whom dosing was terminated continued to be followed according to the protocol.

Subjects were free to withdraw from the study at any time for any reason without penalty; however, they were still asked to complete safety assessments, per protocol.

9.4 Treatments

9.4.1 Treatments Administered

The unblinded pharmacist/designee prepared vernakalant injection or amiodarone injection and placebo as specified in the pharmacy manual. The dosing solutions were prepared in such a way as to ensure that blinding was maintained for personnel administering the infusions.

9.4.1.1 Vernakalant Injection

For subjects weighing more than 113 kg (250 lbs), the dose of vernakalant injection should have been based on a weight of 113 kg (250 lbs) and not higher. Once mixed for administration, the study drug was to be stored at controlled room temperature and used within 12 hours.

Subjects randomized to vernakalant injection received a 10-minute infusion of 3 mg/kg vernakalant in one infusion line, followed by a 15-minute observation period, followed by an additional 10-minute infusion of 2 mg/kg vernakalant if required (if the subject was still in AF). To maintain blinding, a 60-minute infusion of placebo (5% dextrose in water [D5W]) was administered in a second infusion line, followed by a maintenance infusion of placebo for a minimum of an additional 60 minutes.

9.4.1.2 Amiodarone Injection

Subjects randomized to amiodarone injection received a 60-minute infusion of 5 mg/kg amiodarone in one infusion line, followed by a maintenance infusion of 50 mg amiodarone over an additional 60 minutes (equivalent to approximately 15 mg/kg over 24 hrs). To maintain blinding, these subjects received a 10-minute infusion of placebo (normal saline) in a second infusion line, followed by a 15-minute observation period, followed by a 10-minute infusion of placebo if required (if the subject was still in AF).

9.4.1.3 Placebo

Normal saline was used as the placebo for vernakalant injection and D5W was used as the placebo for amiodarone injection. Thus, subjects randomized to receive vernakalant injection received D5W as a placebo, and subjects randomized to receive amiodarone injection received normal saline as a placebo.

9.4.2 Identity of Investigational Products

9.4.2.1 Vernakalant Injection

Vernakalant injection was supplied in a 10 mL glass vial (to deliver 10 mL) as an isotonic solution at 20 mg/mL in 40 mM citrate buffer at pH 5.5. All vials of vernakalant injection were labeled as required by the relevant regulatory agencies and were to be stored at controlled room temperature (15 to 30ºC) in a secure location.

Vernakalant injection was labeled with the following: protocol number, sponsor name, subject identification number, date and time dispensed, administration instructions, required statutory phrases, and storage conditions.

The lot number used in this study for vernakalant injection was 742015.

9.4.2.2 Amiodarone Injection

Amiodarone injection was supplied by the sponsor as commercially available Cordarone (Sanofi Aventis), except in Canada, where Amiodarone Hydrochloride Injection (Sandoz) was supplied. Both supplies of amiodarone were provided in 3 mL ampoules, 150 mg/ampoule.

Amiodarone was labeled with the following: protocol number, sponsor name, subject identification number, date and time dispensed, administration instructions, required statutory phrases, and storage conditions.

The lot numbers used in this study for amiodarone injection were CK001, DA001, 1542, 146841, 149008, and 153751.

9.4.2.3 Placebo

Normal saline and D5W were obtained by each site from a commercial source.

9.4.3 Method of Assigning Subjects to Treatment Groups

Each subject was randomized in a 1:1 ratio to receive either vernakalant injection or amiodarone injection by the central randomization center using an interactive voice response system (IVRS). In order to randomize a subject, the site was to call the randomization center via the IVRS. The IVRS confirmed that the eligibility criteria were met and assigned a unique randomization number. Once assigned, a randomization number was not reused. A listing of subjects by treatment group is provided in Appendix 16.1.7.

9.4.4 Selection of Doses in the Study

The selection of the vernakalant dose used in this study was based on the dosing regimen used in all phase 3 studies of vernakalant injection. A 10-minute infusion of 3 mg/kg vernakalant, followed by a 10-minute infusion of 2 mg/kg (if required), was found to be effective and well tolerated in subjects with AF.

The loading and maintenance dose of amiodarone used in this study was determined using literature reports and the UK Summary of Product Characteristics (SPC). The standard recommended dose in the SPC is an initial loading dose of 5 mg/kg by IV infusion over a period of 20 minutes to 2 hours, which may be followed by a repeat infusion of approximately 15 mg/kg over 24 hours. In keeping with this recommendation and in order to adequately compare amiodarone to vernakalant in a randomized, double-blind fashion, a loading dose of 5 mg/kg over 1 hour followed by a maintenance infusion of 50 mg for an additional 60 minutes (approximately equivalent to 15 mg/kg over 24 hrs) was chosen.

9.4.5 Selection and Timing of Dose for Each Subject

Subjects were to be adequately hydrated and hemodynamically optimized prior to receiving treatment, as both vernakalant and amiodarone may cause hypotension. The principal investigator or designee was to be at bedside for the first 45 minutes of drug administration,

and immediately available for the remainder of the infusion time. Particularly close attention was to be paid to vital signs and telemetry during the first 45 minutes after the start of infusion.

Subjects had two infusion lines for the administration of study drugs: one infusion line for vernakalant or placebo and the other infusion line for amiodarone or placebo. Both infusion lines were to be started at T=0. The contents of the vernakalant/placebo infusion line were administered over 10 minutes. After a 15-minute observation period, a second 10-minute infusion was to be administered if the subject was still in AF. The contents of the amiodarone/placebo infusion line were to be administered over 60 minutes, followed by a maintenance infusion for an additional 60 minutes. Subjects were to be in the supine position during drug administration and were to remain supine until completion of the maintenance infusion from the amiodarone/placebo infusion line.

For subjects converting to SR during the first 10-minute infusion of vernakalant/placebo (i.e., between minute 0 to minute 10), the first infusion was to be completed but the second 10-minute infusion of vernakalant/placebo was not to be administered. If the subject converted to SR after completion of the first 10-minute infusion, but before administration of the second 10-minute infusion of vernakalant/placebo (i.e., between minute 10 to minute 25), the second infusion of vernakalant/placebo was not to be administered. For subjects converting to SR during the second 10-minute infusion of vernakalant/placebo (i.e., between minute 25 and minute 35), the second infusion was to be completed. The 60-minute infusions of amiodarone/placebo were to be stopped immediately upon conversion to SR, regardless of when conversion occurred.

See Section 9.4.1 for treatment administration details.

9.4.6 Blinding

This was a double-blinded, double-dummy study in which all study staff were blinded, with the exception of the site pharmacist or designated third party unblinded dispenser. The unblinded pharmacist/designee prepared vernakalant injection or amiodarone injection and placebo as required.

Study drug assignment was to be revealed only for reasons relating to the subject's safety or when critical therapeutic decisions were contingent on knowing the assigned study drug. Except in the most pressing circumstances, a decision to break the blind was to be discussed with the Cardiome Medical Monitor or designee. Withdrawal of a subject from the study was not a sufficient reason to break the study blind.

If a blind was broken, an entry was to be made in the case report form (CRF), containing the date and time the blind was broken, the person who requested the blind to be broken, the person who broke the blind, and the Medical Monitor or designee contacted along with the reason for breaking the blind.

Randomization data were kept strictly confidential and accessible only to authorized persons, until the time of unblinding. Only when the study had been completed, the data file verified, and the protocol violations determined, were the drug codes broken and made available for data analysis.

9.4.7 Prior and Concomitant Medications and Therapies

All concomitant medications or therapies and the reasons for their use were to be recorded in the CRF. Medications that were considered necessary for the subject's welfare may have been given at the discretion of the investigator. Information about concomitant medications taken from 48 hours prior to screening until the Day 7 visit was to be recorded on the CRF. Information on concomitant medications used for any SAE was to be collected and captured on the CRF through to the 30-day follow-up telephone call.

Subjects were permitted to:

a) Receive rate control drugs such as beta-adrenergic blocking agents, calcium antagonists, or digoxin, as long as their HR was >50 bpm and the loading dose or bolus supplementation of these agents preceded study drug by at least two hours.

b) Receive rate control drugs or electrical cardioversion two hours after the start of study drug infusion. Electrical cardioversion may have been performed earlier if the investigator judged that it was necessary to restore SR more quickly due to electrical or hemodynamic instability.

Subjects were not permitted to:

a) Imbibe alcohol, caffeine, or smoke from screening until discharge.

b) Use herbal remedies, alternative medicines, or over-the-counter medications (especially cold medicines) from screening until discharge.

c) Receive any Class I or Class III antiarrhythmic medication from 24 hours prior to dosing until at least 24 hours after the start of infusion, unless the investigator judged that it was necessary to restore SR more quickly and electrical cardioversion was not a suitable alternative for the subject.

d) Receive any investigational drug for any therapeutic indication from 30 days prior to enrollment until 30 days following randomization.

9.4.8 Treatment Compliance

Compliance was assured by healthcare professionals responsible for administering the study drug. Study drug compliance was to be documented in the drug accountability record and the subject’s medical records at the site. After medication accountability had been performed by the study monitor, the vials were to be returned to Cardiome or its designee, or destroyed on site as instructed by Cardiome.

9.5 Efficacy, Pharmacoeconomic, and Safety Variables

9.5.1 Overview of Efficacy, Pharmacoeconomic, and Safety Assessments

A description of the efficacy, pharmacoeconomic, and safety assessments is provided below. See Table 1 in Section 9.1 for a schedule of study procedures.

9.5.1.1 Efficacy Assessments

The Clinical Events Committee's (CEC) interpretation of Holter and 12-lead ECGs was used in all efficacy analyses.

9.5.1.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects with conversion of AF to SR within 90+3 minutes of first exposure to study medication and for a minimum duration of one minute. This was derived based on the CEC's interpretation of both the 12-lead Holter ECGs and 12-lead ECGs. A subject was deemed to have met the endpoint of conversion to SR if the Holter or the 12-lead ECG documented conversion to SR, and the time of conversion to SR was within 90+3 minutes from the start of the first infusion. For the Holter monitor, a continuous recording of 60 seconds showing SR must have been present to document that the endpoint was achieved. For the 12-lead ECGs, two consecutive 12-lead ECGs recorded at least one minute apart and showing SR must have been present to document that the endpoint was achieved.

9.5.1.1.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints were investigated:

1. Time to conversion of SR within the first 90+3 minutes after the start of infusion. Subjects who did not convert within 90+3 minutes were censored at minute 90. Conversion was determined as outlined above (in Section 9.5.1.1.1) for the primary efficacy endpoint and the time was based on the earliest evidence of conversion.
2. Proportion of subjects exhibiting none of the following AF symptoms at 90 minutes: shortness of breath, palpitations, chest tightness/pain, dizziness, edema, fatigue, rapid heart beat, diaphoresis, orthopnea, paroxysmal nocturnal dyspnea, syncope, irregular pulse, nausea, vomiting, cough, and headache.
3. Change in EQ-5D quality of life assessment Visual Analogue Scale (VAS) from screening to hour 2.

9.5.1.1.3 Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints were also evaluated:

1. Time to conversion of SR within the first 240 minutes after the start of infusion. Subjects who did not convert within 240 minutes were censored at minute 240 (note, subjects who were electrically cardioverted were censored at the time of electrical conversion).
2. Subjects exhibiting no AF symptoms at Day 7.
3. Subjects exhibiting each AF symptom at minute 90 and Day 7.
4. Reduction in the number of symptoms at minute 90.
5. Reduction in the number of symptoms at Day 7.
6. Proportion of subjects who met the primary endpoint and maintained SR with no AF relapse at hour 4. A relapse was defined as AF occurring after conversion to SR had

been documented, lasting at least 30 seconds on Holter, or AF on two consecutive 12-lead ECGs taken at least 30 seconds apart.

7. Proportion of subjects who met the primary endpoint and maintained SR with no AF relapse through Day 7. A relapse was defined as above; however, if the Day 7 ECG showed AF, the subject was considered to have relapsed (the reason for this was that there was only a single 12-lead ECG collected at Day 7 and so documentation of AF for 30 seconds was not possible).
8. Proportion of subjects who met the primary endpoint and maintained SR with no AF relapse through Day 30. A relapse was defined based on adverse event (AE) data; any AE of AF or AFL occurring after a subject was successfully converted to SR within 90 minutes was counted as a relapse if the start date/time was prior to Day 30.
9. The descriptive system of the EQ-5D health-related quality of life tool consisted of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which had one of three responses. The responses recorded 3 levels of severity (no problems; some or moderate problems; extreme problems) within a particular EQ-5D dimension. Each dimension was assessed individually.
10. Proportion of subjects ready for discharge at two hours.
11. For subjects who converted to sinus rhythm within 90 minutes, a descriptive summary of the time to conversion was presented by treatment group; no comparison between groups was made.

9.5.1.2 Pharmacoeconomic Assessments

The pharmacoeconomic assessments and results are provided in a separate report.

9.5.1.3 Safety Assessments

Safety was assessed at regular intervals during the study through monitoring of the following parameters (see Table 1 for assessment time points):

1. Adverse events;
2. Serious adverse events;
3. Vital signs (including BP and HR);
4. ECG intervals;
5. Bradycardia (based on Holter);
6. Atrial flutter (based on Holter);
7. Ventricular arrhythmia (based on the Ventricular Events Committee's adjudication);
8. Laboratory parameters (serum chemistry, hematology, and urinalysis);
9. Physical exam (only at screening and at discharge).

The following chemistry and hematology parameters were assessed:

Serum chemistry: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), gamma glutamyl transferase (GGT), total and direct bilirubin, alkaline phosphatase, total protein, albumin, BUN, serum creatinine, uric acid, calcium, phosphorus, glucose, sodium, chloride, potassium, magnesium, bicarbonate, thyroid stimulating hormone (TSH), and cardiac enzymes (creatinine phosphokinase [CPK] with MB fraction and troponin [I or T]).

Hematology: Complete blood count (CBC) including hemoglobin, hematocrit, white blood cell (WBC) count with differential and platelets, and coagulation studies including international normalized ratio (INR) and partial thromboplastin time (PTT).

9.5.2 Appropriateness of Measurements

The safety and efficacy assessments are standard and frequently used in studies of this type.

9.5.3 Primary Efficacy Variable

The primary efficacy variable was pre-specified in the protocol and statistical analysis plan (SAP) and is outlined in Section 9.5.1.1.1.

9.5.4 Drug Concentration Measurements

No blood samples were taken to determine plasma drug levels in this study.

9.6 Data Quality Assurance

The investigator sites were monitored by study monitors from Cardiome and the CROs (Omnicare Clinical Research GmbH and Quintiles Ltd.) to ensure correct performance of the study procedures and to assure that the study was being conducted according to the relevant regulatory requirements. Cardiome attended site initiation visits and/or conducted co-monitoring visits with the assigned study monitors at selected investigator sites. Cardiome also performed on-site visits at BioClinica (electronic data capture [EDC] and data management vendor), Brecon (study drug packaging and distribution), CardiaBase (ECG core lab), and Dorevitch (central laboratory in Australia, partnered with LabConnect).

The sponsor provided the investigator with electronic case report forms (eCRFs) for collecting subject data. Study data was collected at the study site using EDC technology. A study monitor verified all eCRF entries against the source documentation (subject records).

Further details can be found in the Data Management Plan in Appendix 16.1.10.

Quality audits were performed for this study at one site each in Canada, Czech Republic, Estonia, Germany, and Poland, and at the following vendors:

- BioClinica (formerly Phoenix Data Systems), EDC and data management in USA
- CardiaBase, ECG core lab in France

- IVRESS, central randomization in USA
- LabConnect, central laboratory in USA
- Omnicare, project and site management CRO, office in Germany

The sites and vendors were selected based on criteria outlined in the Quality Plan, which can be found in Appendix 16.1.8.2; audit certificates can be found in Appendix 16.1.8.1.

9.7 Statistical Methods and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

The statistical and analytical methods used in this study are summarized below. The full SAP is provided in Appendix 16.1.9.

9.7.1.1 Hypothesis Tested

This study was designed to test if vernakalant injection was significantly more effective than amiodarone injection in the conversion of AF to SR in subjects with AF. The test for the superiority of vernakalant versus amiodarone was based on the following null hypothesis and alternative hypothesis:

$$H_o: P_{\text{Vernakalant IV}} = P_{\text{AmiodaroneIV,}}$$

$$H_a: P_{\text{Vernakalant IV}} \neq P_{\text{AmiodaroneIV,}}$$

where P was the estimated proportion of the population who converted to SR.

9.7.1.2 Multiplicity

The primary endpoint was tested using a two-sided 0.05 significance level. If the primary endpoint demonstrated a statistically significant positive finding based on the P-value, then each of the secondary endpoints were tested at a two-sided 0.05 significance level, according to the following pre-specified order:

1. Time to conversion of SR within the first 90+3 minutes after the start of infusion.
2. Proportion of subjects exhibiting none of the following AF symptoms at 90 minutes: shortness of breath, palpitations, chest tightness/pain, dizziness, edema, fatigue, rapid heart beat, diaphoresis, orthopnea, paroxysmal nocturnal dyspnea, syncope, irregular pulse, nausea, vomiting, cough, and headache.
3. Change in EQ-5D quality of life assessment VAS from screening to hour 2.

The P-value was the primary statistic used to determine if the endpoint was confirmative and to progress through the above order.

9.7.1.3 Analysis Sets

9.7.1.3.1 Safety Analysis Set

The safety analysis set consisted of all randomized subjects who received any amount of study medication, and was used for all safety analyses.

9.7.1.3.2 Full Analysis Set

The full analysis set is the same as the safety analysis set (consisting of all randomized subjects who received any amount of study medication), and was the primary analysis set used for all efficacy analyses.

It was anticipated that approximately 4% of subjects would spontaneously convert to SR prior to receiving study drug and that these subjects would not be included in the primary analysis. As the decision to exclude these subjects was not based on any knowledge of treatment assignment, use of this population adheres to the intention-to-treat (ITT) principle.

9.7.1.3.3 Per-Protocol Set

The per-protocol set consisted of all subjects in the full analysis set who were compliant with study medication, were not missing data for the primary endpoint, and did not have any major protocol violations (e.g., significant dosing error, administration of a prohibited concomitant medication, violation of any inclusion/exclusion criteria) that could have affected the primary endpoint. Protocol violations were identified prior to breaking the blind. This population was used to assess efficacy and provide support to the primary analyses with the full analysis set.

9.7.1.4 Statistical Methods

9.7.1.4.1 Efficacy Analyses

The primary and secondary efficacy summary tabulations and analyses were presented for both the full and per-protocol analysis sets. The exploratory efficacy summaries and analyses were presented for the full analysis set.

9.7.1.4.1.1 Primary Efficacy Analysis

The primary hypothesis was assessed by comparing the primary efficacy endpoint between treatment groups using a two-sided Cochran Mantel-Haenszel (CMH) test stratified by country, with a 0.05 significance level. The following statistics were presented: frequency and percentage of success and failures for each treatment group, the difference in the percentage of successes between treatment groups, the asymptotic 95% confidence interval (CI) of the difference in success between treatment groups, and the P-value for the difference between treatment groups. In addition, the relative risk in favor of conversion of the vernakalant group versus the amiodarone group along with 95% confidence limits was also estimated.

Subjects who were missing data to derive the primary endpoint were counted as failures for the primary analysis.

Results by country and center were also summarized.

9.7.1.4.1.2 Secondary Efficacy Analyses

The following procedures were used for the secondary efficacy endpoints:

1. For the secondary efficacy endpoint of the time to conversion to SR, the Kaplan-Meier method was used to summarize the distribution of conversion times and obtain estimates

of the 25th and 75th percentiles and median time to conversion. The two treatment groups were compared using a two-sided log rank test with a 0.05 significance level. Subjects who did not convert to SR within 90+3 minutes had their time censored at 90 minutes. Additionally, subjects who withdrew prior to conversion to SR or who were electrically converted prior to 90 minutes were censored at the time at which they withdrew or were converted.

2. The secondary efficacy endpoint of the proportion of subjects with no AF symptoms at 90 minutes was summarized by treatment group. The frequency and percentage of subjects with no symptoms and at least one symptom were reported. A comparison between treatment groups was based on a two-sided CMH test, stratified by country, with a 0.05 significance level. Subjects who were missing data for all symptoms had a response of "symptom present" imputed. Additionally, the following statistics were presented: the difference in the percentage of successes between groups, the asymptotic 95% CI of the difference in success between treatment groups, and the relative risk in favor of the vernakalant group versus the amiodarone group along with 95% confidence limits.
3. The secondary efficacy endpoint of change in EQ-5D quality of life assessment VAS was modeled using a fixed effects general linear model with change as the dependent variable, baseline score and age as covariates, and treatment as a fixed effect. Subjects who were missing data had a change of 0 imputed. The adjusted mean changes and the difference in adjusted mean changes (along with 95% CI) were reported.

9.7.1.4.1.3 Exploratory Efficacy Analyses

Details of the analyses performed for the exploratory efficacy endpoints are provided in the SAP in Appendix 16.1.9.

9.7.1.4.1.4 Subgroup Analyses

The treatment effect of vernakalant compared to amiodarone on the primary efficacy endpoint was investigated within and across the following subgroups:

- Gender
- Age: <65 vs ≥65 years and <75 vs ≥75 years
- AF duration: ≤24 vs >24 hours
- History of heart failure
- History of hypertension
- History of ischemic heart disease (IHD)
- History of valvular heart disease (VHD)
- History of myocardial infarction (MI)
- Left atrial diastolic dimension (LADD): ≤50 vs >50 mm
- Left ventricular ejection fraction (LVEF): normal (≥50%) vs abnormal (mild [36-49%], moderate [26-35%], or severe [≤25%])

Within subgroups, the same methodology applied to the primary endpoint was used, and the treatment difference and 95% CI were estimated. A visual comparison of the 95% CI between subgroups was used to assess the extent of any subgroup differences. No within or between group hypothesis tests were conducted.

9.7.1.4.2 Safety and Tolerability Analyses

All safety analyses were presented using the safety analysis set. Details on safety analyses not described below can be found in the SAP in Appendix 16.1.9.

9.7.1.4.2.1 Adverse Events

All AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 10.1). For tabulation purposes, only AEs with a start date and time during the first 10 days after the start of study drug were included, and each subject was categorized by the maximum severity and relationship to study drug reported for a given AE. Any missing severities were imputed as severe unless the subject experienced another occurrence of the same event for which the severity was recorded. In this case, the reported severity was summarized.

The following summaries were presented by treatment group using the MedDRA level hierarchy (system organ class [SOC], high level group term, high level term, and preferred term): all AEs, all AEs by severity, all related AEs, all related AEs by severity, all SAEs, all related SAEs, all AEs resulting in discontinuation of study drug, and all clinically significant AEs (defined as an SAE or AE resulting in discontinuation of study drug).

For relationship to study drug, events were coded as related if the investigator judged the event to be possibly, probably, or definitely related to study drug, and were coded as unrelated if the investigator judged the event to be not related or unlikely related to study drug.

To investigate the duration of AEs, a summary (n, median, minimum, and maximum) of the duration of all AEs and related AEs, by SOC and preferred term, was provided by treatment group. For this summary, all treatment-emergent AEs experienced by a subject were utilized.

To investigate the onset of AEs, a summary (n, median, minimum, and maximum) of the time from first dose to onset of related AEs, by SOC and preferred term, was provided by treatment group. For this summary, all treatment-emergent AEs experienced by a subject were utilized.

The above summaries were presented for the following time periods: 0-2 hours postdose, 2-24 hours postdose, 0-24 hours postdose, and all postdose events.

9.7.1.4.2.2 Adverse Events Post-Electrical Cardioversion

An additional summary of AEs was also presented for those subjects who had electrical cardioversion attempted. For this summary, only subjects who had electrical cardioversion attempted were included, with events occurring within two hours after the first attempt at electrical cardioversion summarized by treatment group; no estimates of treatment differences were presented. The following summaries were provided: all AEs by severity and all SAEs.

9.7.1.4.2.3 Events of Interest

Events of interest, as defined below, were summarized by treatment group. These summaries were presented for the following time periods: 0-2 hours postdose, 2-4 hours postdose, 0-4 hours postdose, and all postdose events.

Where possible, the excess risk was calculated along with the 95% CI using the Exact method.

An additional summary of the events of interest was also presented for those subjects who had electrical cardioversion attempted. For this summary, only subjects who had electrical cardioversion attempted were included, with events occurring within two hours after the first attempt at electrical cardioversion summarized by treatment group; no estimates of treatment differences were presented.

Bradycardia was reported from the following sources:

1. As an AE of bradycardia, heart rate decreased, sinus bradycardia, AV block complete, sinus arrest, sick sinus syndrome, or nodal rhythm;
2. By the cardiologist (blinded to treatment group) from the ECG core lab, based on their review of the Holter monitor;
3. Any post-baseline fall of the HR below 40 bpm based on vital signs.

Atrial flutter was reported from the following sources:

1. As an AE of atrial flutter;
2. By the cardiologist (blinded to treatment group) from the ECG core lab, based on their review of the Holter monitor.

Ventricular arrhythmia was reported by the Ventricular Events Committee (VEC), based on their review of:

1. Events identified on the Holter monitor by the cardiologist (blinded to treatment group) at the ECG core lab;
2. AEs submitted by the investigator.

Hypotension was reported from the following sources:

1. As an AE of dizziness postural, hypotension, hypovolemia, orthostatic hypotension, syncope, syncope vasovagal, blood pressure decreased, blood pressure systolic decreased, or blood pressure diastolic decreased;
2. Any post-baseline fall in SBP below 90 mmHg based on vital signs.

9.7.1.5 Interim Analysis

There were no interim analyses planned for this study.

9.7.2 Determination of Sample Size

Approximately 240 subjects were planned to be enrolled in this study, with 120 randomized to vernakalant injection and 120 randomized to amiodarone injection. The determination of sample size for this study was based on the number of subjects required to show a treatment effect with adequate power at the assumed conversion rates for amiodarone injection and vernakalant injection, as described below.

In a previously reported controlled clinical trial of amiodarone, flecainide, and propafenone in subjects with AF of ≤48 hours duration, approximately 20% of subjects treated with amiodarone (using an IV bolus of 5 mg/kg in 20 minutes followed by a continuous infusion of 50 mg/hour) converted to SR within 90 minutes [5].

In a previously reported clinical trial with vernakalant injection (ACT I), in the subgroup of subjects with an AF duration of 3 to 48 hours, 62% of subjects converted to SR within 90 minutes (95% CI = 52 to 72%) [7].

The required sample size to achieve 90% and 80% power, based on a two-sided chi-square test with a 5% significance level under varying conversion rate assumptions, is shown below.

Assumed Conversion Rate		Treatment Effect	Total Sample Size (90% Power)	Total Sample Size (80% Power)
Amiodarone	**Vernakalant**			
25%	50%	25%	148	110
30%	50%	20%	242	182
25%	45%	20%	230	171
30%	45%	15%	428	320

Based on the above estimates, a total sample size of approximately 230 subjects (115 per group) would provide approximately 90% power to detect a treatment effect of 20% (assuming an amiodarone conversion rate of 25%). Assuming approximately 4% of subjects would spontaneously convert to SR prior to receiving treatment and therefore not be evaluable, a total of 240 subjects was planned (120 subjects in each of the amiodarone and vernakalant groups).

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Amendments

There were 5 protocol amendments for this study. Amendments 1 and 4 were global amendments, whereas Amendment 2 applied only to France and Germany, Amendment 3 applied only to Denmark, and Amendment 5 applied only to France. A summary of the changes to the protocol made by these amendments is provided in Table 2. A full summary of changes for each amendment is provided in Appendix 16.1.1. Note that only the last revised global and country-specific protocols are provided in Appendix 16.1.1; earlier protocol amendments produced prior to the last global and country-specific revised protocols can be found in the essential documents file.

Table 2. Summary of Protocol Amendments

Amendment Number	Date of Amendment	Subjects Enrolled	Changes to Protocol
Amendment 1 (Global)	24 Mar 2008	0[a]	• The minimum period for which subjects were to be monitored in the hospital increased from 4 hours after the start of dosing to 6 hours after the start of dosing, to allow for 4 hours of monitoring after amiodarone dosing was completed. The informed consent form (ICF) was also updated to reflect this revision. • The period of time within which vernakalant injection was to be used once mixed for administration was changed from 24 hours to 12 hours to be consistent with the pharmacy manual.
Amendment 2 (France and Germany)	26 Mar 2008	0[b]	• Subjects were to have an echocardiogram performed within 30 days of study entry. An echocardiogram (transthoracic or transesophageal, as clinically appropriate) was to be performed at screening if no recent echocardiogram results were available, as this would provide an additional assessment of any cardiomyopathy that may have affected a subject's eligibility to participate in the study. The Day 7 echocardiogram assessment was removed. The ICF was also updated to reflect this revision.
Amendment 3 (Denmark)	10 Jun 2008	0[b]	• To comply with a request from the Danish Central Ethics Committee, subjects enrolled in the study were to be competent adults who were able to consent to participate in the study on their own behalf. Thus, the use of a "legally authorized representative" in obtaining consent was removed from the protocol.
Amendment 4 (Global)	06 Aug 2008	23[a]	• Canada was added as a country in which the study would be conducted. The ICF was also updated to reflect this revision.
Amendment 5 (France)	23 Apr 2009	5[b]	• To comply with a request from the French competent authority, exclusion criterion #6 was modified to further describe significant valvular stenosis.

a Includes the number of subjects enrolled as of the date of the amendment.
b Indicates the number of subjects enrolled in the applicable countries as of the date of the amendment.

In addition to the protocol amendments, there were two administrative changes to the protocol. The first administrative change (dated 11 May 2009) updated the contact names and details of the project team and clarified the medical monitor coverage. The second administrative change (dated 03 Jun 2009) updated the contact names and details of the project team, and updated the locations where the study was being conducted. Documentation of these administrative changes can be found in Appendix 16.1.1.7.

9.8.2 Other Changes in the Conduct of the Study or Planned Analyses

Per the Note-to-File (NTF) dated 09 Jul 2009 (Appendix 16.1.1.8), due to some previously open clinical trial sites closing and a slower recruitment rate than anticipated, the study was expanded

with additional countries and sites. As a result of the expansion, Quintiles Ltd. was added as a CRO (in addition to Omnicare) to manage the additional sites.

Per the NTF dated 22 Oct 2009 (Appendix 16.1.1.8), the use of a single harmonized reference range for laboratory data was not possible due to the use of multiple laboratories. The actual reference ranges for the different laboratories are documented in the NTF.

The protocol lists "BUN" (blood urea nitrogen) as a serum chemistry laboratory parameter; however, the actual parameter that was assessed was urea. The two terms are considered to be synonymous in this study.

There were no amendments to the SAP for this study; a copy of the final SAP is provided in Appendix 16.1.9. The following changes and additions to the final SAP were made after unblinding of the trial.

For the analysis of the secondary endpoint of change in EQ-5D quality of life assessment VAS, the model in Section 7.7.2 of the SAP was modified to include a treatment by baseline interaction term to improve the goodness of fit.

For the exploratory endpoint of the proportion of subjects who met the primary endpoint and maintained SR with no AF relapse to Day 7 (Section 7.7.3 of the SAP), an additional analysis was conducted that used a different definition of success. For this analysis, a subject who reported an adverse event of AF or AFL within the first 7 days was counted as a failure. By including this additional criterion, an additional 3 subjects in the vernakalant group and 0 subjects in the amiodarone group were counted as failures.

Two additional exploratory analyses were conducted to look for an association with conversion to SR within 90 minutes. The first analysis looked at an association between conversion to SR and absence of AF symptoms at 90 minutes and the second analysis looked at an association between conversion to SR and readiness for discharge at hour 2. Both analyses were done using a CMH test for association, irrespective of treatment group.

For the analysis of ECG interval data (Section 7.9.3.1 of the SAP), the mixed effect model was updated to include a treatment by time interaction term and a covariate to account for the time that had elapsed from conversion to SR. These modifications improved the goodness of fit. Due to the potential impact of conversion from AF to SR on ECG parameters, least square (LS) means are presented excluding the effect of conversion and time-post-conversion. Consequently, the estimates are for a subject on the given treatment who remains in AF, and the change-from-baseline estimates represent a pure drug effect on a subject in AF (and are not confounded by intrinsic changes associated with conversion).

The exploratory analysis of the PR interval to assess the impact of conversion on the PR interval (Section 7.9.3.1 of the SAP), was not conducted due to sparse data in the amiodarone group.

The above changes did not affect the overall safety or integrity of the study.

10 STUDY POPULATION

10.1 Disposition of Subjects

A summary of the subject disposition is presented in Table 3.

Table 3. Subject Disposition

	Number (%) of Subjects					
	Treatment Group					
	Vernakalant		Amiodarone		Total	
Randomized	128		126		254	
Treated (any amount)	116	(90.6)	116	(92.1)	232	(91.3)
Received dose one	116	(90.6)	116	(92.1)	232	(91.3)
Received dose two	68	(53.1)	114	(90.5)	182	(71.7)
Completed study (through Day 30 follow-up call)	110	(85.9)	115	(91.3)	225	(88.6)
Discontinued study (subjects not dosed)[a]	12	(9.4)	10	(7.9)	22	(8.7)
Spontaneous conversion to sinus rhythm	10	(7.8)	9	(7.1)	19	(7.5)
Other	2	(1.6)	1	(0.8)	3	(1.2)
Lack of investigational medicinal product	0		1	(0.8)	1	(0.4)
Not enough medication at site, subject was not treated	1	(0.8)	0		1	(0.4)
Subject developed an exclusion criterion (atrial flutter)	1	(0.8)	0		1	(0.4)
Discontinued study (subjects dosed)[b]	6	(5.2)	1	(0.9)	7	(3.0)
Adverse event[c]	4	(3.4)	1	(0.9)	5	(2.2)
Other	2	(1.7)	0		2	(0.9)
Lost to follow-up	1	(0.9)	0		1	(0.4)
Subject decided to stop study participation	1	(0.9)	0		1	(0.4)

[a] Denominators are based on the number of randomized subjects.

[b] Denominators are based on the number of treated subjects.

[c] One of the subjects in the vernakalant group did not complete the study because of death due to chronic obstructive pulmonary disease and pulmonary embolism.

Source: Appendix Table 14.1.1.1, 14.1.1.2.1, and 14.1.1.2.2

A total of 254 subjects were enrolled in the study, with 128 subjects in the vernakalant group and 126 subjects in the amiodarone group. The majority (91.3%) of randomized subjects received at least one dose of study medication (and made up the safety and full analysis sets), with the exception of 12 subjects in the vernakalant group and 10 subjects in the amiodarone group. Ten vernakalant and nine amiodarone subjects spontaneously converted to sinus rhythm prior to receiving study drug.

Of the subjects who were treated, 6 vernakalant subjects and 1 amiodarone subject discontinued the study, mostly due to AEs (see Section 12.3.3 for further details). A total of 225 subjects completed the study through the Day 30 follow-up telephone call.

An individual listing of subject disposition can be found in Appendix 16.2.1.

10.1.1 Unblinding

There were 3 subjects in this study who were unblinded, as discussed below. Narratives with further details on these events are provided in Appendix 16.4.

The blind was broken by the sponsor for the expeditable SAE of hypersensitivity (with symptoms of erythema, paresthesia, and sneezing) for subject 305-1608-004 (vernakalant group), as recommended for expedited reporting to regulatory authorities (as per ICH guidance E2A). The SAE of hypersensitivity began 7 minutes after the start of the first infusion of study drug, and was assessed by the investigator as being of mild severity and probably related to study drug. The symptoms resolved after 28 minutes; however, due to the subject's past medical history of multiple drug allergies and asthma, hospitalization was prolonged for two days to observe the subject after the event. Although all of the symptoms noted by the subject had been previously reported following vernakalant treatment, the investigator considered this event to be an allergic reaction, and as this specific term had not been previously identified as an "expected" event it was reported as an expedited SAE. Regulatory agencies, IRBs/ECs, and investigators in all participating countries were informed in a timely manner about this SAE, as per the local regulations.

The blind was also broken by the sponsor for the potentially expeditable SAE of cardiac arrest for subject 305-1614-005 (amiodarone group). The SAE of cardiac arrest began 37 minutes after the start of the first infusion of study drug, and resolved two minutes later. This SAE was assessed by the investigator as being severe, life-threatening, and probably related to study drug. Since the event was considered to be severe and amiodarone is commonly used to treat AF, the sponsor notified the investigator of this subject's treatment assignment to ensure appropriate medical action would be taken to avoid a future recurrence. This event was assessed as being not expeditable, and accordingly, no expedited reporting of this SAE occurred. For further details on this event, see Section 12.3.4.3.

In addition, the blind was broken by the investigator for subject 305-1703-001 (vernakalant group). An SAE of ventricular tachycardia started 10 minutes after the start of the first infusion of study drug, was assessed by the investigator as being of moderate severity and probably related to study drug, and resolved approximately 3 minutes later. The following day the subject had an AE of AF recurrence, and as the investigator wished to treat the subject with amiodarone, the blind was broken. For further details on this event, see Section 12.3.4.3.

10.2 Protocol Deviations

There were 3 subjects in each treatment group who had major protocol deviations that could have affected the primary endpoint, and as a result, these subjects were excluded from the per-protocol population. In the vernakalant group, subjects 305-1101-002 and 305-5002-001 were excluded due to dosing deviations for the second infusion and subject 305-2502-002 was excluded because the volume of the first infusion was unknown. In the amiodarone group, subjects 305-1104-004, 305-1505-018, and 305-2502-001 were excluded because of receiving an antiarrhythmic agent within 24 hours prior to dosing, a randomization error, and unknown dosing information, respectively (Appendix 16.2.2).

10.3 Data Sets Analyzed

The data sets analyzed for this study were the safety analysis set (also referred to as the full analysis set for the efficacy analysis) and the per-protocol analysis set. The safety analysis set and full analysis set consisted of all randomized subjects who received any amount of study

medication, and was used for all safety and efficacy analyses, respectively. The per-protocol analysis set consisted of all subjects in the full analysis set who were compliant with study medication, were not missing data for the primary endpoint, and did not have any major protocol violations that could have affected the primary endpoint. Exclusion from the per-protocol analysis set was determined prior to breaking the blind. The per-protocol set was used to assess efficacy and provide support to the primary analyses with the full analysis set. A summary of the number of subjects in each data set is provided in Table 4.

Table 4. Number of Subjects in Each Data Set Analyzed

	Number (%) of Subjects		
	Treatment Group		
	Vernakalant	Amiodarone	Total
Randomized	**128**	**126**	**254**
Safety Set	116 (90.6)	116 (92.1)	232 (91.3)
Full Analysis Set	116 (90.6)	116 (92.1)	232 (91.3)
Per-Protocol Set	113 (88.3)	113 (89.7)	226 (89.0)

Source: Appendix Table 14.1.1.1

There were 22 subjects who did not receive study drug and therefore were not included in the safety or full analysis sets (see Section 10.1 for further details). A further 6 subjects were excluded from the per-protocol set (due to major protocol violations that could have affected the primary endpoint), as discussed in Section 10.2.

10.4 Measurements of Treatment Compliance

Study drug was administered in hospital by study personnel. Treatment compliance of investigative sites was assessed during the trial by review of dosing records by an unblinded study monitor and also by blinded monitoring of study drug administration logs and other source data. For treatment administration/exposure details, see Section 12.1.

10.5 Demographic and Other Baseline Characteristics

10.5.1 Demographics

A summary of the subject demographics for the full analysis set is provided in Table 5.

Table 5. Summary of Demographics (Full Analysis Set)

Demographic Parameter	Treatment Group: Vernakalant (N=116)	Treatment Group: Amiodarone (N=116)	Total (N=232)
Gender, n (%)			
Male	75 (64.7)	71 (61.2)	146 (62.9)
Female	41 (35.3)	45 (38.8)	86 (37.1)
Race, n (%)			
White	111 (95.7)	111 (95.7)	222 (95.7)
Black	2 (1.7)	2 (1.7)	4 (1.7)
Other	3 (2.6)	3 (2.6)	6 (2.6)
Country, n (%)			
Poland	30 (25.9)	24 (20.7)	54 (23.3)
Germany	15 (12.9)	19 (16.4)	34 (14.7)
Canada	13 (11.2)	13 (11.2)	26 (11.2)
Estonia	10 (8.6)	13 (11.2)	23 (9.9)
Ukraine	8 (6.9)	12 (10.3)	20 (8.6)
Czech Republic	5 (4.3)	9 (7.8)	14 (6.0)
Slovakia	11 (9.5)	3 (2.6)	14 (6.0)
Lithuania	6 (5.2)	6 (5.2)	12 (5.2)
Netherlands	4 (3.4)	5 (4.3)	9 (3.9)
Denmark	6 (5.2)	1 (0.9)	7 (3.0)
France	4 (3.4)	3 (2.6)	7 (3.0)
Sweden	3 (2.6)	3 (2.6)	6 (2.6)
Australia	0	2 (1.7)	2 (0.9)
Serbia	1 (0.9)	1 (0.9)	2 (0.9)
Finland	0	1 (0.9)	1 (0.4)
Latvia	0	1 (0.9)	1 (0.4)
Age, years			
Mean (SD)	63.1 (10.81)	62.2 (11.63)	62.7 (11.21)
Median	64.0	62.5	63.0
Min, Max	34, 85	32, 84	32, 85
Age Category, n (%)			
<75 years	98 (84.5)	100 (86.2)	198 (85.3)
≥75 years	18 (15.5)	16 (13.8)	34 (14.7)
Weight, kg			
Mean (SD)	84.2 (14.95)	84.3 (15.87)	84.2 (15.39)
Median	82.3	83.0	83.0
Min, Max	48, 131	46, 128	46, 131

Source: Appendix Table 14.1.2.1

Demographics were similar among the two treatment groups. The majority of subjects were white (95.7%) and approximately two-thirds were male (62.9%), with a mean weight of 84.2±15.39 kg. The subjects had a mean age of 62.7±11.21 years (range of 32 to 85 years), and 14.7% of subjects were ≥75 years of age.

An individual listing of demographic data can be found in Appendix 16.2.4.1.

10.5.2 Baseline Characteristics and Medical History

A summary of baseline characteristics and cardiovascular medical history for the full analysis set is provided in Table 6.

Table 6. Summary of Baseline Characteristics and Cardiovascular Medical History (Full Analysis Set)

Baseline Characteristic	Treatment Group: Vernakalant (N=116)	Treatment Group: Amiodarone (N=116)	Total (N=232)
Medical History, n (%)			
Atrial fibrillation			
Number of previous episodes			
0	34 (29.3)	33 (28.4)	67 (28.9)
1	25 (21.6)	17 (14.7)	42 (18.1)
2	11 (9.5)	12 (10.3)	23 (9.9)
3	8 (6.9)	11 (9.5)	19 (8.2)
>3	38 (32.8)	42 (36.2)	80 (34.5)
Missing	0	1 (0.9)	1 (0.4)
Median duration of AF history, days	683.5	675.0	683.5
Median duration of current AF episode, hours	17.7	17.9	17.7
≤24 hours	73 (62.9)	65 (56.0)	138 (59.5)
>24 hours	43 (37.1)	51 (44.0)	94 (40.5)
Hypertension	86 (74.1)	80 (69.0)	166 (71.6)
Structural heart disease (SHD)[a]	36 (31.0)	45 (38.8)	81 (34.9)
Ischemic heart disease	22 (19.0)	30 (25.9)	52 (22.4)
Myocardial infarction	11 (9.5)	8 (6.9)	19 (8.2)
Valvular heart disease	4 (3.4)	12 (10.3)	16 (6.9)
Heart failure[b]	20 (17.2)	26 (22.4)	46 (19.8)
NYHA Class I[c]	9 (45.0)	12 (46.2)	21 (45.7)
NYHA Class II[c]	11 (55.0)	14 (53.8)	25 (54.3)
Left Atrial Diastolic Dimension (LADD), mm			
N	109	108	217
Mean (SD)	40.6 (6.77)	41.0 (6.04)	40.8 (6.40)
Median	40.0	41.0	41.0
Min, Max	23, 58	24, 56	23, 58
LADD >50 mm, n (%)[d]	5 (4.3)	7 (6.0)	12 (5.2)
Left Ventricular Ejection Fraction (LVEF)[e], %			
N	107	106	213
Mean (SD)	57.6 (7.34)	59.5 (6.97)	58.5 (7.21)
Median	60.0	60.0	60.0
Min, Max	40, 73	38, 79	38, 79
LVEF <50%, n (%)[d]	15 (12.9)	4 (3.4)	19 (8.2)

NYHA: New York Heart Association.

a Subjects with SHD may have had more than one condition listed under the SHD category.

b In the CRF, "CHF" was defined as chronic heart failure; however, in the study protocol "CHF" was defined as congestive heart failure. The two terms are considered to be synonymous for this study.

c Denominators are based on those who had a history of heart failure.

d Denominators are based on the number of treated subjects (N=116 per treatment group).

e Echocardiograms used to determine LVEF were taken at the Day 7 visit or within 30 days prior to the start of the study, except for subjects in France and Germany, for whom it was taken at the screening visit or within 30 days prior to screening.

Source: Appendix Table 14.1.2.2 and 14.1.2.4

Baseline characteristics and cardiovascular medical history were well balanced among the two treatment groups. The majority of subjects (164/232, 70.7%) had experienced at least one previous AF episode, with 34.5% of subjects having >3 previous episodes. Subjects were asked to report the date when they were first diagnosed with AF (i.e., AF history); the median duration of AF history was 683.5 days. The median duration of the current AF episode was 17.7 hours, and 40.5% of subjects had AF duration of >24 hours. Hypertension was common in this study population, with 71.6% of subjects having this condition. There were 46 out of 232 subjects (19.8%) with a history of heart failure, with just over half of these subjects having NYHA Class II heart failure (25/46 subjects, 54.3%). There were no subjects with NYHA Class III heart failure enrolled in this study.

A summary of other medical history can be found in Appendix Table 14.1.2.3 and an individual listing of other medical history can be found in Appendix 16.2.4.3.

10.5.3 Prior and Concomitant Medications

A summary of antiarrhythmic and rate control medications used within 7 days prior to the first dose of study drug is provided in Table 7 for the full analysis set.

Table 7. Summary of Antiarrhythmic and Rate Control Medications Used Within 7 Days Prior to the First Dose of Study Drug (Full Analysis Set)

	Number (%) of Subjects		
	Treatment Group		
Prior Medication	**Vernakalant (N=116)**	**Amiodarone (N=116)**	**Total (N=232)**
Any Rhythm Control	**10 (8.6)**	**16 (13.8)**	**26 (11.2)**
Class IA antiarrhythmics[a]	0	1 (0.9)	1 (0.4)
Class IC antiarrhythmics[b]	4 (3.4)	7 (6.0)	11 (4.7)
Class III antiarrhythmics[c]	6 (5.2)	8 (6.9)	14 (6.0)
Any Rate Control	**71 (61.2)**	**78 (67.2)**	**149 (64.2)**
Beta blockers[d]	63 (54.3)	76 (65.5)	139 (59.9)
Calcium channel blockers[e]	10 (8.6)	4 (3.4)	14 (6.0)
Digitalis glycosides[f]	6 (5.2)	10 (8.6)	16 (6.9)

a Includes procainamide.
b Includes propafenone and flecainide.
c Includes amiodarone and sotalol.
d Includes intravenous or oral non-selective and selective beta blockers (excluding sotalol) and alpha- and beta-blocking agents (e.g., carvedilol).
e Includes diltiazem and verapamil.
f Includes digoxin, digitoxin, and digitalis.
Source: Appendix Table 14.1.3.1

There were 8.6% of vernakalant subjects and 13.8% of amiodarone subjects receiving rhythm control medications within 7 days prior to the first dose of study drug. Rate control medications were being used by 64.2% of subjects prior to dosing, with beta blockers being the most common (59.9%); however, the use of beta blockers was numerically lower in the vernakalant group

(54.3%) compared to the amiodarone group (65.5%). An individual listing of antiarrhythmic and rate control medications can be found in Appendix 16.2.4.5.2.

A summary of the concomitant medications that were used prior to the first dose of study drug and continued after, and used by >10% of subjects in either treatment group in the full analysis set, is shown in Table 8.

Table 8. Summary of Concomitant Medications Used Prior to the First Dose of Study Drug and Continued After, and Used by >10% of Subjects in Either Treatment Group (Full Analysis Set)

	Number (%) of Subjects	
	Treatment Group	
Medication Class	**Vernakalant (N=116)**	**Amiodarone (N=116)**
Antithrombotic agents[a]	74 (63.8)	75 (64.7)
Beta blocking agents[b]	47 (40.5)	53 (45.7)
Angiotensin converting enzyme (ACE) inhibitors[c]	37 (31.9)	40 (34.5)
Lipid modifying agents[d]	35 (30.2)	37 (31.9)
Angiotensin II antagonists[e]	22 (19.0)	13 (11.2)
Selective calcium channel blockers with mainly vascular effects[f]	17 (14.7)	18 (15.5)
Low-ceiling diuretics, thiazides[g]	15 (12.9)	7 (6.0)
Drugs for peptic ulcer and gastroesophageal reflux disease (GERD)[h]	8 (6.9)	12 (10.3)

Note that any medications which were formulated as combination products were coded according to their individual components in the tables and listings.

a Includes acenocoumarol, acetylsalicyclic acid, clopidogrel, dalteparin, enoxaparin, fluindione, fondaparinux, heparin, nadroparin, phenprocoumon, ticlopidine, tinzaparin, and warfarin.

b Includes atenolol, betaxolol, bisoprolol, carvedilol, metoprolol, nebivolol, propranolol, and sotalol.

c Includes captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, and trandolapril.

d Includes atorvastatin, ezetimibe, fenofibrate, fluvastatin, pravastatin, rosuvastatin, and simvastatin.

e Includes candesartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan.

f Includes amlodipine, barnidipine, felodipine, isradipine, lacidipine, lercanidipine, and nifedipine.

g Includes hydrochlorothiazide.

h Includes esomeprazole, famotidine, lansoprazole, omeprazole, pantoprazole, and rabeprazole.

Source: Appendix Table 14.1.3.2

Medications used prior to the first dose of study drug and continued after were generally similar between treatment groups. The most commonly used medications among both groups were antithrombotic agents (149/232, 64.2%).

A summary of the concomitant medications that were started after the first dose of study drug and used by >10% of subjects in either treatment group in the full analysis set is shown in Table 9.

Table 9. Summary of Concomitant Medications Started After the First Dose of Study Drug and Used by >10% of Subjects in Either Treatment Group (Full Analysis Set)

	Number (%) of Subjects	
	Treatment Group	
Medication Class	**Vernakalant (N=116)**	**Amiodarone (N=116)**
Beta blocking agents[a]	61 (52.6)	52 (44.8)
Antithrombotic agents[b]	59 (50.9)	47 (40.5)
Anesthetics, general[c]	33 (28.4)	56 (48.3)
Antiarrhythmics, Class I and III[d]	43 (37.1)	37 (31.9)
Angiotensin converting enzyme (ACE) inhibitors[e]	27 (23.3)	15 (12.9)
Hypnotics and sedatives[f]	16 (13.8)	24 (20.7)
I.V. solutions[g]	16 (13.8)	13 (11.2)
Angiotensin II antagonists[h]	12 (10.3)	11 (9.5)
Lipid modifying agents[i]	13 (11.2)	9 (7.8)
Cardiac glycosides[j]	14 (12.1)	7 (6.0)
I.V. solution additives[k]	12 (10.3)	5 (4.3)

Note that any medications which were formulated as combination products were coded according to their individual components in the tables and listings.

a Includes betaxolol, bisoprolol, carvedilol, metipranolol, metoprolol, nebivolol, and sotalol.

b Includes acenocoumarol, acetylsalicyclic acid, clopidogrel, dalteparin, enoxaparin, fluindione, fondaparinux, heparin, heparin-fraction, nadroparin, phenprocoumon, and warfarin.

c Includes alfentanil, etomidate, fentanyl, propofol, sufentanil, and thiopental.

d Includes amiodarone, flecainide, moracizine, procainamide, and propafenone.

e Includes captopril, cilazapril, enalapril, lisinopril, perindopril, quinapril, ramipril, and trandolapril.

f Includes bromisoval, diphenhydramine, estazolam, midazolam, nitrazepam, phenobarbital, promethazine, valocordin, and zopiclone.

g Includes calcium chloride dihydrate, glucose, magnesium sulfate, mannitol, potassium, potassium chloride, ringerlactate, and sterofundin.

h Includes candesartan, irbesartan, losartan, telmisartan, and valsartan.

i Includes atorvastatin and simvastatin.

j Includes digitoxin and digoxin.

k Includes sodium chloride.

Source: Appendix Table 14.1.3.4

Medications started after the first dose of study drug were generally similar between treatment groups for the majority of medication classes. The use of general anesthetics was lower in the vernakalant group compared to the amiodarone group, which was likely due to the higher rate of electrical cardioversion in the amiodarone group (see Section 12.4.2). The most commonly used concomitant medications among both groups were beta blocking agents (113/232, 48.7%) and antithrombotic agents (106/232, 45.7%).

11 EFFICACY EVALUATION

11.1 Primary Efficacy Variable

The primary efficacy endpoint was the proportion of subjects who converted to SR within 90 (+3) minutes of first exposure to study medication and for a minimum duration of one minute. Treatment-induced conversion from AF to SR was determined by the CEC's confirmation of a continuous recording from the Holter (of a minimum of 60 seconds) showing SR and/or two consecutive 12-lead ECGs (recorded at least one minute apart) showing SR. A summary of the results for the primary efficacy endpoint for the full analysis set is shown in Table 10.

Table 10. Treatment-Induced Conversion from Atrial Fibrillation to Sinus Rhythm Within 90 Minutes (Full Analysis Set)

	Number (%) of Subjects Treatment Group				% Difference of Success			Relative Risk	
	Vernakalant (N=116)		Amiodarone (N=116)		(95% CI)[a]		P-value[b]	(95% CI)[c]	
All Sites									
Conversion	60	(51.7)	6	(5.2)	46.6	(36.6, 56.5)	<0.0001	10.0	(4.5, 22.2)
No conversion	56	(48.3)	110	(94.8)					
By Country									
Poland	17/30	(56.7)	1/24	(4.2)					
Canada	11/13	(84.6)	2/13	(15.4)					
Estonia	7/10	(70.0)	0/13						
Germany	6/15	(40.0)	0/19						
Netherlands	4/4	(100.0)	1/5	(20.0)					
Slovakia	5/11	(45.5)	0/3						
Czech Republic	1/5	(20.0)	1/9	(11.1)					
Denmark	2/6	(33.3)	0/1						
France	2/4	(50.0)	0/3						
Lithuania	2/6	(33.3)	0/6						
Sweden	2/3	(66.7)	0/3						
Australia	0/0		1/2	(50.0)					
Ukraine	1/8	(12.5)	0/12						
Finland	0/0		0/1						
Latvia	0/0		0/1						
Serbia	0/1		0/1						

[a] % success in vernakalant group – % success in amiodarone group. Missing values were considered as not converting.

[b] P-value is from a CMH test stratified by country.

[c] Relative risk in favor of conversion for vernakalant.

Source: Appendix Table 14.1.2.1 and 14.2.1.1

Treatment with vernakalant resulted in a statistically significantly greater proportion of subjects converting from AF to SR within the first 90 minutes compared to amiodarone. A total of 60 of 116 (51.7%) vernakalant subjects met the primary endpoint, compared to 6 of 116 (5.2%) amiodarone subjects (CMH P-value <0.0001), demonstrating that subjects treated with vernakalant were 10 times more likely to convert to SR within 90 minutes as compared to subjects treated with amiodarone (95% CI, 4.5 to 22.2). There was no evidence of heterogeneity across countries (Breslow-Day P-value = 0.6950).

Results for the per-protocol population were consistent with the primary analysis (Appendix Table 14.2.1.2), with a total of 59 of 113 (52.2%) vernakalant subjects meeting the primary endpoint compared to 6 of 113 (5.3%) amiodarone subjects (P<0.0001).

11.2 Secondary Efficacy Variables

11.2.1 Time to First Treatment-Induced Conversion from Atrial Fibrillation to Sinus Rhythm Within 90 Minutes

The time to the first treatment-induced conversion from AF to SR within the first 90 minutes after the start of infusion is shown in Figure 1 for the full analysis set.

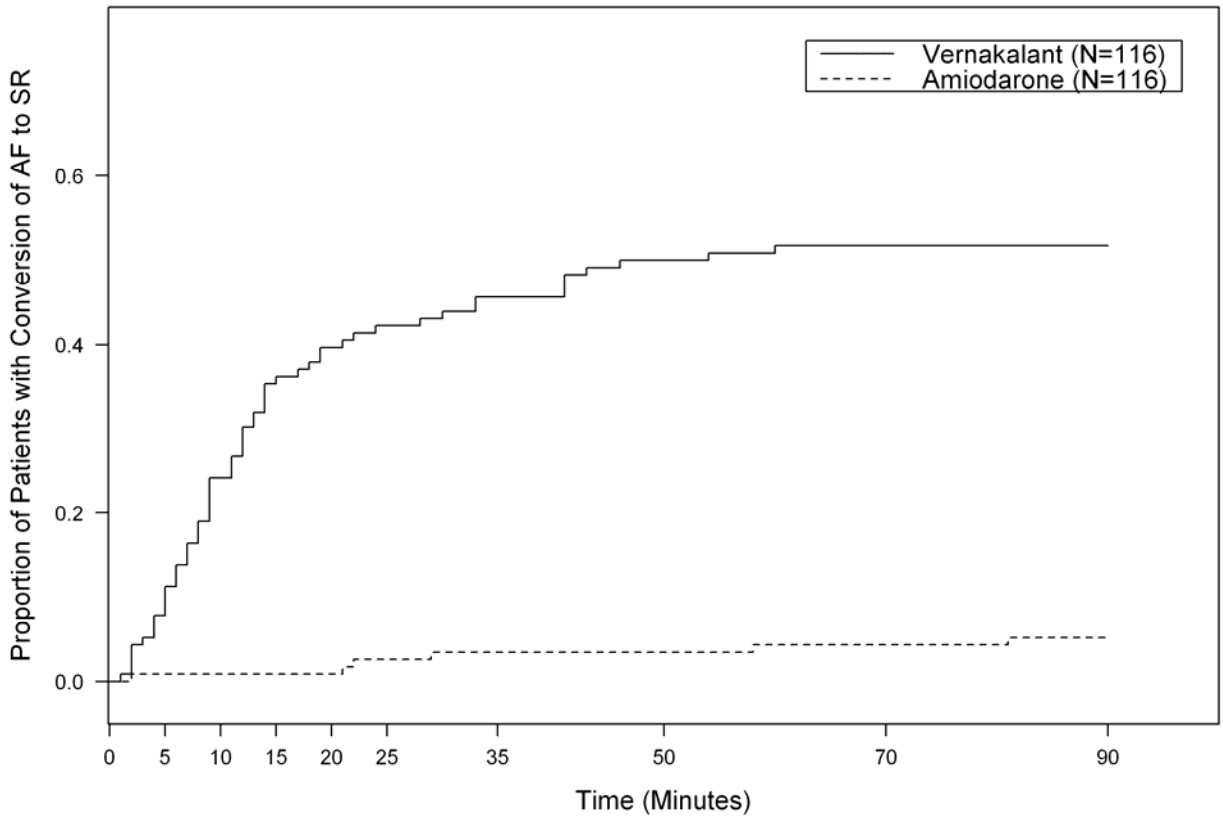


Figure 1. Time to First Treatment-Induced Conversion from Atrial Fibrillation to Sinus Rhythm Within the First 90 Minutes (Full Analysis Set)

Treatment with vernakalant resulted in a statistically significantly faster conversion rate from AF to SR within the first 90 minutes compared to amiodarone (log rank P-value <0.0001). In the vernakalant group, 25% of subjects had converted to SR by minute 11, and 50% had converted by minute 50, as compared to the amiodarone group where only 5% of subjects had converted by minute 90. In the group of 60 subjects who responded to vernakalant, the median time to conversion was 11.0 minutes. In the group of 6 subjects who responded to amiodarone, the median time to conversion was 25.5 minutes (Appendix Table 14.2.11).

Results for the per-protocol population were consistent with the full analysis set (Appendix Table 14.2.2.2).

11.2.2 Proportion of Subjects Without Atrial Fibrillation Symptoms at 90 Minutes

All subjects enrolled in this study reported at least 1 of the 16 possible AF symptoms at screening (see Table 13). A summary of the proportion of subjects without any AF symptoms at 90 minutes is presented for the full analysis set in Table 11.

Table 11. Proportion of Subjects Without Atrial Fibrillation Symptoms at 90 Minutes (Full Analysis Set)

	Number (%) of Subjects Treatment Group							
	Vernakalant (N=116)		Amiodarone (N=116)		% Difference of Success (95% CI)[a]	P-value[b]	Relative Risk (95% CI)[c]	
All Sites								
No symptoms	62	(53.4)	38	(32.8)	20.7 (8.2, 33.2)	0.0012	1.63	(1.20, 2.23)
Symptoms	54	(46.6)	78	(67.2)				
By Country[d]								
Poland	17/30	(56.7)	7/24	(29.2)				
Germany	9/15	(60.0)	11/19	(57.9)				
Canada	9/13	(69.2)	5/13	(38.5)				
Estonia	8/10	(80.0)	4/13	(30.8)				
Czech Republic	3/5	(60.0)	3/9	(33.3)				
Slovakia	5/11	(45.5)	1/3	(33.3)				
France	3/4	(75.0)	1/3	(33.3)				
Netherlands	3/4	(75.0)	0/5					
Ukraine	1/8	(12.5)	2/12	(16.7)				
Denmark	2/6	(33.3)	0/1					
Lithuania	0/6		2/6	(33.3)				
Sweden	1/3	(33.3)	1/3	(33.3)				
Australia	0/0		1/2	(50.0)				
Serbia	1/1	(100.0)	0/1					
Finland	0/0		0/1					
Latvia	0/0		0/1					

a % success in vernakalant group – % success in amiodarone group. Missing values were considered as having symptoms.

b P-value is from a CMH test stratified by country.

c Relative risk in favor of conversion for vernakalant.

d Numbers listed are for those who did not have any AF symptoms at 90 minutes.

Source: Appendix Table 14.1.2.1 and 14.2.3.1

Treatment with vernakalant resulted in a statistically significantly greater proportion of subjects reporting no AF symptoms at 90 minutes compared to amiodarone. A total of 62 of 116 (53.4%) vernakalant subjects had no AF symptoms at 90 minutes, compared to 38 of 116 (32.8%) amiodarone subjects (CMH P-value = 0.0012), demonstrating that subjects treated with vernakalant were 1.63 times more likely to be free of their AF symptoms at 90 minutes as compared to subjects treated with amiodarone (95% CI, 1.20 to 2.23). There was no evidence of heterogeneity across countries (Breslow-Day P-value = 0.2521).

Results for the per-protocol population were consistent with the primary analysis (Appendix Table 14.2.3.2), with a total of 61 of 113 (54.0%) vernakalant subjects reporting no AF symptoms as compared to 38 of 113 (33.6%) amiodarone subjects (CMH P-value = 0.0019).

11.2.3 EQ-5D Quality of Life Visual Analogue Scale Assessment at Hour 2

A summary of the EQ-5D quality of life assessment (VAS) for subjects in the full analysis set is provided in Table 12.

Table 12. EQ-5D Quality of Life Visual Analogue Scale (VAS) Assessment (Full Analysis Set)

Time Point	Treatment Group: Vernakalant (N=116)	Treatment Group: Amiodarone (N=116)	Treatment Difference (VERI – AMIO)
Baseline[a]	**N=115**	**N=114**	
Mean (SD)	63.5 (17.76)	68.4 (15.86)	
Median	65.0	70.0	
Min, Max	17, 100	20, 100	
Hour 2	**N=113**	**N=112**	
Mean (SD)	76.0 (15.06)	72.9 (14.92)	
Median	80.0	75.0	
Min, Max	30, 100	40, 100	
Change[b]			
Least squares mean (SE)	10.9 (1.09)	5.6 (1.09)	5.4
95% CI	8.78, 13.06	3.42, 7.73	2.31, 8.39
P-value			0.0006

AMIO: amiodarone injection; VERI: vernakalant injection.
The EQ-5D VAS is scored from 0 (poor state of health) to 100 (best state of health).

a The schedule of study procedures (Table 1) shows that the quality of life assessment was to be performed at screening; however, the tables and listings use the time point of baseline. The two terms are considered to be synonymous in this case, as the definition of baseline for analysis purposes was the last observation prior to study drug.

b Based on a fixed effects model with change (hour 2 – baseline) as the dependent variable, baseline and age as covariates, treatment as a fixed effect, and a baseline by treatment interaction. Missing data was imputed as a change of 0. Least square (LS) means were based on a baseline score of 66 using the average age of the study population.

Source: Appendix Table 14.2.4.1

Treatment with vernakalant resulted in a statistically significantly greater improvement in a subject's perception of their state of health at hour 2 compared to amiodarone. In the vernakalant group, a mean adjusted change of 10.9 points was seen compared to a mean adjusted change of 5.6 points in the amiodarone group (P=0.0006).

Results for the per-protocol population were consistent with the full analysis set (Appendix Table 14.2.4.2).

In addition, the data showed that subjects in the vernakalant group with a worse self-perceived state of health at baseline demonstrated a greater improvement, compared to amiodarone, than subjects with a better state of health at baseline (Figure 2).

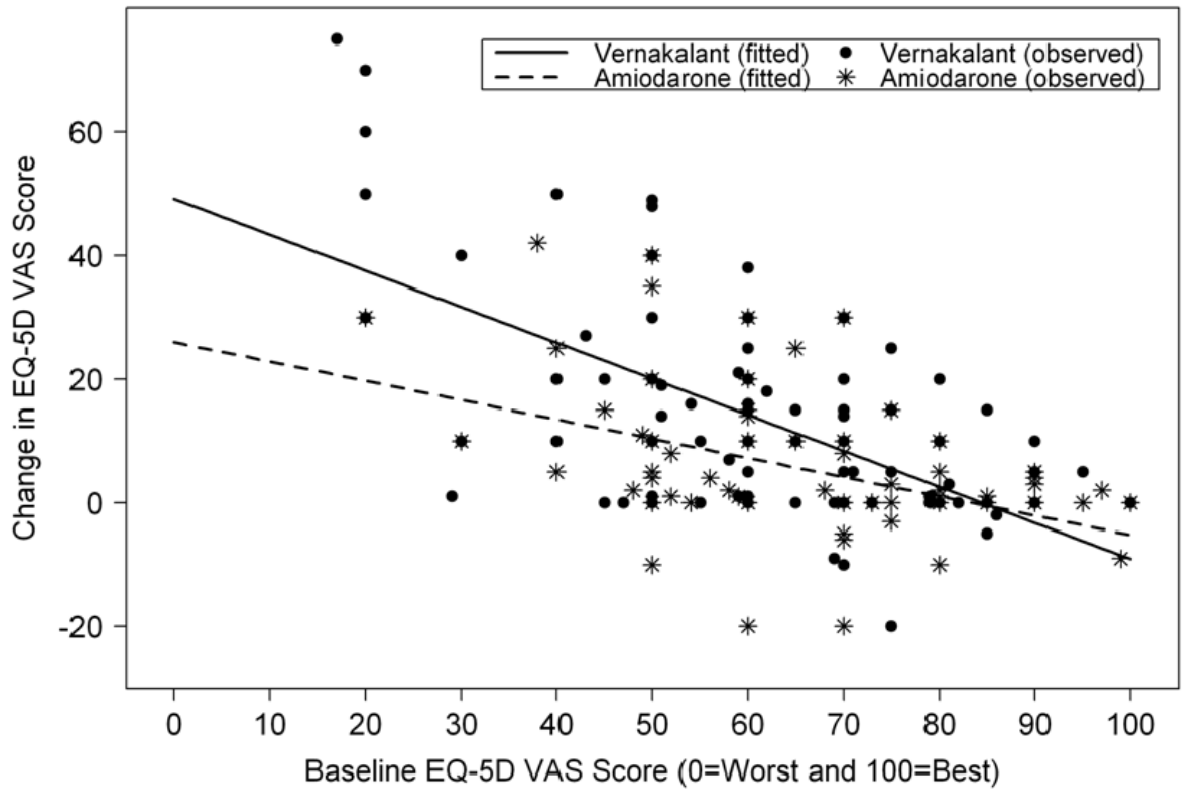


Figure 2. Scatter Plot of Change from Baseline (Hour 2 – Baseline) in EQ-5D VAS Versus Baseline Score. Superimposed regression line is from a general linear model with treatment as a fixed effect, age and baseline as covariates, and a treatment by baseline interaction term.

11.3 Exploratory Efficacy Variables

For all exploratory analyses, unless otherwise noted, all P-values were adjusted based on the Sidak adjustment (with k=40) to prevent a false positive conclusion. Unadjusted P-values can be found in the referenced appendix tables.

11.3.1 Time to First Treatment-Induced Conversion from Atrial Fibrillation to Sinus Rhythm Within 240 Minutes

The time to the first treatment-induced conversion from AF to SR within the first 240 minutes after the start of infusion is shown in Figure 3 for the full analysis set. Subjects who did not convert within 240 minutes were censored at minute 240, and subjects who were electrically cardioverted were censored at the time of electrical conversion. Electrical cardioversion was permitted two hours after the start of infusion if the subject was still in AF.

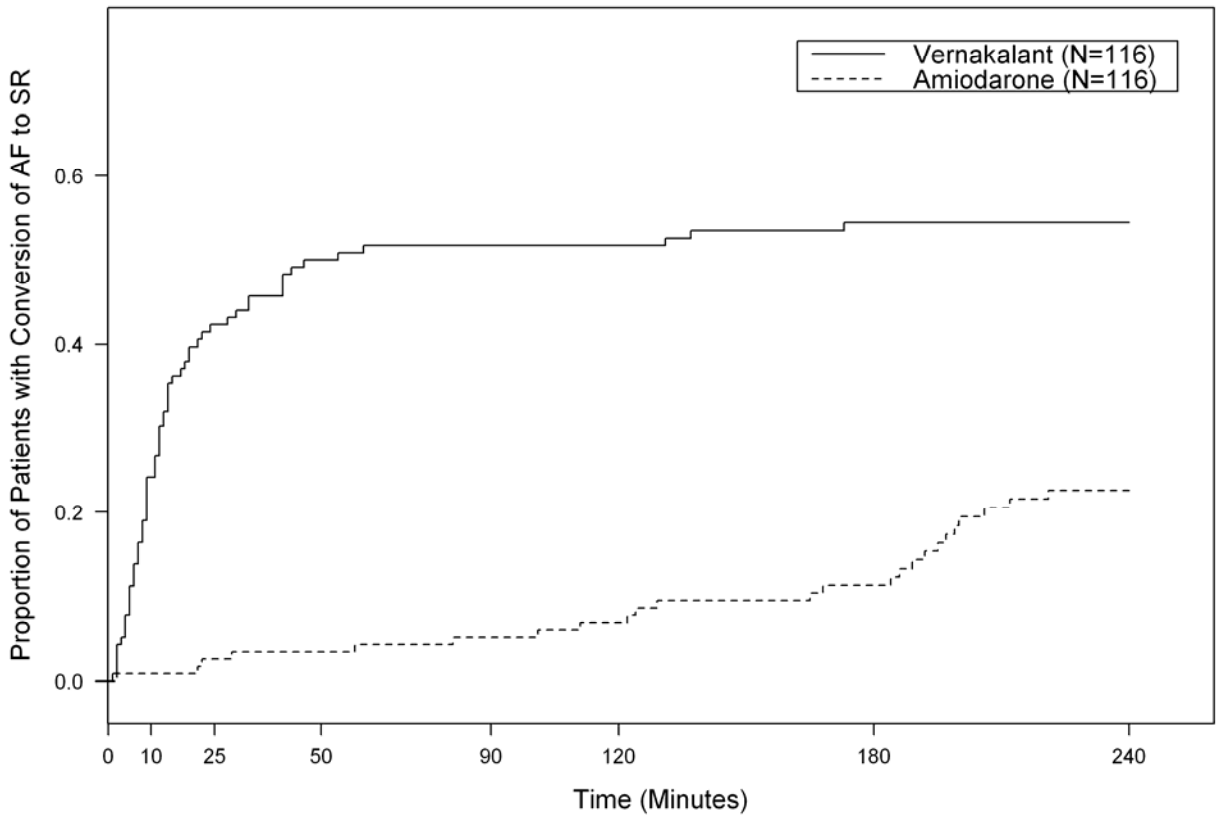


Figure 3. Time to First Treatment-Induced Conversion from Atrial Fibrillation to Sinus Rhythm Within the First 240 Minutes (Full Analysis Set)

A significantly greater proportion of subjects in the vernakalant group converted to SR within the first 4 hours postdose compared to the amiodarone group (adjusted log rank P-value <0.0001, Appendix Table 14.2.5). In the vernakalant group, 25% of subjects converted to SR by minute 11 and 50% converted by minute 50, as compared to the amiodarone group in which <25% of subjects had converted to SR by 4 hours postdose. By 4 hours postdose, 54.4% of vernakalant subjects and 22.6% of amiodarone subjects had converted to SR.

11.3.2 Analysis of Atrial Fibrillation Symptoms

At Day 7, 75.9% (88/116) of vernakalant subjects and 85.3% (99/116) of amiodarone subjects had no AF symptoms (P=0.9674) (Appendix Table 14.2.6.1).

A summary of AF symptoms for subjects in the full analysis set is presented by time point and treatment group in Table 13.

Table 13. Summary of Atrial Fibrillation Symptoms by Scheduled Time Point (Full Analysis Set) (page 1 of 2)

Time Point AF Symptom	Number (%) of Subjects Treatment Group Vernakalant (N=116)	Amiodarone (N=116)	P-value[a]	Adjusted P-value[b]
Screening[c]	**N=116**	**N=116**		
At least one symptom	116 (100.0)	116 (100.0)		
Palpitations	65 (56.0)	89 (76.7)		
Irregular pulse	55 (47.4)	54 (46.6)		
Rapid heart beat	49 (42.2)	44 (37.9)		
Fatigue	43 (37.1)	38 (32.8)		
Shortness of breath	27 (23.3)	31 (26.7)		
Dizziness	18 (15.5)	18 (15.5)		
Chest tightness/pains	17 (14.7)	17 (14.7)		
Diaphoresis	5 (4.3)	10 (8.6)		
Nausea	8 (6.9)	6 (5.2)		
Headaches	5 (4.3)	6 (5.2)		
Paroxysmal nocturnal dyspnea	4 (3.4)	1 (0.9)		
Orthopnea	1 (0.9)	3 (2.6)		
Cough	2 (1.7)	1 (0.9)		
Edema	0	1 (0.9)		
Syncope	1 (0.9)	0		
Vomiting	1 (0.9)	0		
Minute 90[c]	**N=113**	**N=114**		
At least one symptom	51 (44.0)	76 (65.5)		
Irregular pulse	23 (19.8)	39 (33.6)	0.0251	0.6388
Palpitations	21 (18.1)	41 (35.3)	0.0045	0.1639
Fatigue	13 (11.2)	23 (19.8)	0.1012	0.9860
Rapid heart beat	8 (6.9)	17 (14.7)	0.0884	0.9753
Shortness of breath	3 (2.6)	14 (12.1)	0.0097	0.3234
Headaches	4 (3.4)	6 (5.2)	0.7483	1.0000
Dizziness	3 (2.6)	6 (5.2)	0.4990	1.0000
Chest tightness/pains	3 (2.6)	4 (3.4)	1.0000	1.0000
Diaphoresis	2 (1.7)	5 (4.3)	0.4458	1.0000
Cough	4 (3.4)	1 (0.9)	0.2125	0.9999
Nausea	3 (2.6)	0	0.1217	0.9944
Orthopnea	0	1 (0.9)	1.0000	1.0000
Edema	0	0		
Paroxysmal nocturnal dyspnea	0	0		
Syncope	0	0		
Vomiting	0	0		
Day 7[c]	**N=114**	**N=115**		
At least one symptom	26 (22.4)	16 (13.8)		
Fatigue	12 (10.3)	6 (5.2)	0.1491	0.9984
Irregular pulse	9 (7.8)	4 (3.4)	0.1661	0.9993
Palpitations	5 (4.3)	6 (5.2)	1.0000	1.0000
Shortness of breath	6 (5.2)	5 (4.3)	0.7683	1.0000
Rapid heart beat	4 (3.4)	2 (1.7)	0.4459	1.0000
Dizziness	3 (2.6)	2 (1.7)	0.6834	1.0000
Headaches	4 (3.4)	0	0.0598	0.9151
Cough	2 (1.7)	1 (0.9)	0.6217	1.0000

Table 13. Summary of Atrial Fibrillation Symptoms by Scheduled Time Point (Full Analysis Set) (page 2 of 2)

Time Point AF Symptom	Number (%) of Subjects Treatment Group Vernakalant (N=116)	Amiodarone (N=116)	P-value[a]	Adjusted P-value[b]
Day 7 (cont.)[c]	**N=114**	**N=115**		
Chest tightness/pains	1 (0.9)	1 (0.9)	1.0000	1.0000
Diaphoresis	2 (1.7)	0	0.2467	1.0000
Nausea	1 (0.9)	1 (0.9)	1.0000	1.0000
Edema	0	1 (0.9)	1.0000	1.0000
Orthopnea	0	1 (0.9)	1.0000	1.0000
Paroxysmal nocturnal dyspnea	0	1 (0.9)	1.0000	1.0000
Vomiting	0	1 (0.9)	1.0000	1.0000
Syncope	0	0		

The numbers shown are for those who had the symptom.

a P-value is from a Fisher's exact test and does not include missing data; the P-value is only displayed when yes and no categories both exist.

b Adjusted P-value is based on the Sidak adjustment (k=40).

c The N's listed for each time point do not include subjects with missing data; however, the denominators for all symptoms at each time point are based on the number of treated subjects (N=116 per treatment group).

Source: Appendix Table 14.2.6.2

The most frequently reported AF symptoms at entry were palpitations, irregular pulse, rapid heart beat, fatigue, shortness of breath, dizziness, and chest tightness/pain. The proportion of subjects reporting these symptoms at 90 minutes and at 7 days was reduced in both treatment groups.

An additional analysis, not pre-specified in the protocol or SAP, was conducted to look for an association between conversion to SR within 90 minutes and the proportion of subjects without AF symptoms at 90 minutes. Table 14 shows the results of this analysis, suggesting that irrespective of treatment group, subjects were more likely to be free of symptoms at 90 minutes if they converted to SR.

Table 14. Association Between Conversion to Sinus Rhythm Within 90 Minutes and Atrial Fibrillation Symptom Relief at 90 Minutes

Treatment Group	Conversion to SR	AF Symptom Relief at 90 Minutes Yes	No	Odds Ratio	P-Value[a]
Vernakalant (N=113)	Yes	50	7	26.19	<0.0001
	No	12	44		
Amiodarone (N=114)	Yes	5	0	25.12[b]	
	No	33	76		

Missing data was excluded from this analysis.

a P-value is unadjusted and based on a one degree of freedom CMH test of association.

b Odds ratio was estimated by adding 0.5 to each cell.

A summary of the number of AF symptoms, and reduction in the number of AF symptoms, at minute 90 and at Day 7 for subjects in the full analysis set is provided in Table 15.

Table 15. Summary of the Number of Atrial Fibrillation Symptoms at Minute 90 and at Day 7 (Full Analysis Set)

	Treatment Group		
Time Point	**Vernakalant (N=116)**	**Amiodarone (N=116)**	**Treatment Difference (VERI – AMIO)**
Baseline (data collected at screening)			
Mean (SD)	2.6 (1.36)	2.8 (1.64)	
Median	2.0	2.0	
Min, Max	1, 7	1, 8	
Minute 90	**N=113**	**N=114**	
Mean (SD)	0.8 (1.15)	1.4 (1.58)	
Median	0	1.0	
Min, Max	0, 6	0, 8	
Change[a]			
Least squares mean (SE)	-1.8 (0.11)	-1.3 (0.11)	-0.52
95% CI	-2.05, -1.60	-1.53, -1.08	-0.83, -0.20
P-value			0.0015
Day 7	**N=114**	**N=115**	
Mean (SD)	0.4 (0.95)	0.3 (1.00)	
Median	0	0	
Min, Max	0, 4	0, 9	
Change[a]			
Least squares mean (SE)	-2.2 (0.09)	-2.4 (0.09)	0.18
95% CI	-2.38, -2.02	-2.56, -2.19	-0.08, 0.44
P-value			0.1807

AMIO: amiodarone injection; VERI: vernakalant injection.

[a] Change = minute 90 – baseline or Day 7 – baseline; as the AF symptoms were assessed at screening, the screening value was treated as baseline in this case. Statistics were based on a fixed effects model with change as the dependent variable, baseline and age as covariates, and treatment as a fixed effect. Missing data was imputed as a change of 0. Score was calculated as the sum of the AF symptoms checked; missing checks were treated as having a symptom.

Source: Appendix Table 14.2.6.3 and 14.2.6.4

At study entry both treatment groups were well balanced with respect to the number of AF symptoms per subject, with a maximum of 7 symptoms seen in the vernakalant group and 8 symptoms seen in the amiodarone group (a median of two symptoms per subject in each group). At minute 90, a greater reduction in the number of AF symptoms was seen in the vernakalant group as compared to the amiodarone group (LS mean difference [vernakalant – amiodarone] = -0.52 [95% CI, -0.83 to -0.20]). At Day 7, the reduction in symptoms was comparable between the two groups.

11.3.3 Analysis of Maintenance of Sinus Rhythm

A summary of the proportion of subjects who met the primary endpoint with no evidence of AF relapse is provided in Table 16 for the full analysis set. The relapse of AF to hour 4 was defined as AF >30 seconds on Holter or AF on two 12-lead ECGs at least 30 seconds apart.

The absence of AF relapse to Day 7 was calculated two ways: 1) based on continuous monitoring to hour 4 (as described previously) and the absence of AF on the Day 7 ECG; 2) based on continuous monitoring to hour 4 (as described previously), the absence of AF on the Day 7 ECG, and no AEs of AF/AFL up to Day 7. The absence of AF relapse to Day 30 was based on the absence of AEs of AF/AFL up to Day 30.

Table 16. Summary of the Proportion of Subjects Who Converted Within 90 Minutes and Maintained Sinus Rhythm with No Atrial Fibrillation Relapse up to Hour 4, and Subjects who Converted Within 90 Minutes and were in Sinus Rhythm at Day 7 and at Day 30 (Full Analysis Set - Subjects Who Met the Primary Endpoint)

Time Point	Number (%) of Subjects Treatment Group: Vernakalant (N=60)		Amiodarone (N=6)		% Difference of Success (95% CI)		P-value[a]	Relative Risk (95% CI)[b]	
Hour 4[c]									
Success	59	(98.3)	6	(100.0)	-1.7	(-4.9, 1.6)		0.98	(0.95, 1.02)
Failure	1	(1.7)	0						
Day 7[d]									
Success	58	(96.7)	5	(83.3)	13.3	(-16.8, 43.5)	0.0643	1.16	(0.81, 1.66)
Failure	2	(3.3)	1	(16.7)					
Day 7[e]									
Success	55	(91.7)	5	(83.3)	8.3	(-22.3, 39.0)	0.1902	1.10	(0.76, 1.59)
Failure	5	(8.3)	1	(16.7)					
Day 30[f]									
Success	53	(88.3)	4	(66.7)	21.7	(-16.9, 60.3)	0.0622	1.33	(0.75, 2.35)
Failure	7	(11.7)	2	(33.3)					

a P-value is from a CMH test stratified by country.

b Relative risk in favor of vernakalant for maintenance.

c Based on continuous Holter monitoring and ECGs up to hour 4. Success was defined as a subject who converted to SR within 90 minutes and did not have a relapse of AF though to hour 4. Failure was defined as a subject who converted to SR within 90 minutes and had a relapse of AF through to hour 4.

d Based on continuous Holter monitoring and ECGs up to hour 4 and then a Day 7 ECG. Success was defined as a subject who converted to SR within 90 minutes and did not have a relapse of AF though to hour 4 and did not have AF/AFL on the Day 7 ECG. Failure was defined as a subject who converted to SR within 90 minutes and either had a relapse of AF through to hour 4 or had AF/AFL on the Day 7 ECG.

e Based on continuous Holter monitoring and ECGs up to hour 4 and then a Day 7 ECG or AEs. Success was defined as a subject who converted to SR within 90 minutes and did not have a relapse of AF though to hour 4, did not have AF/AFL on the Day 7 ECG, and did not have an AE of AF/AFL up to Day 7. Failure was defined as a subject who converted to SR within 90 minutes and either had a relapse of AF through to hour 4, had AF/AFL on the Day 7 ECG, or had an AE of AF/AFL up to 7 days.

f Based on AEs. Success was defined as a subject who converted to SR within 90 minutes and did not have an AE of AF/AFL through to Day 30. Failure was defined as a subject who converted to SR within 90 minutes and had an AE of AF/AFL through to Day 30.

Source: Appendix Table 14.2.7.1, 14.2.7.2, 14.2.7.3, and 14.2.7.4

11.3.4 Analysis of EuroQoL Group Foundation EQ-5D Questionnaire

A summary of the EQ-5D quality of life assessment descriptive system is presented in Table 17 for the full analysis set.

Table 17. Summary of the EQ-5D Quality of Life Assessment Descriptive System (Full Analysis Set)

		Number (%) of Subjects	
		Treatment Group	
Time Point Parameter		**Vernakalant (N=116)**	**Amiodarone (N=116)**
Screening			
Mobility	No problem	77 (66.4)	87 (75.0)
	Some problem	33 (28.4)	26 (22.4)
	Confined to bed	5 (4.3)	3 (2.6)
Self care	No problem	102 (87.9)	111 (95.7)
	Some problem	12 (10.3)	3 (2.6)
	Unable to wash or dress	1 (0.9)	2 (1.7)
Usual activities	No problem	82 (70.7)	89 (76.7)
	Some problem	27 (23.3)	24 (20.7)
	Unable to perform usual activity	6 (5.2)	3 (2.6)
Pain/discomfort	No pain or discomfort	72 (62.1)	72 (62.1)
	Moderate pain or discomfort	42 (36.2)	44 (37.9)
	Extreme pain or discomfort	1 (0.9)	0
Anxiety/depression	Not anxious/depressed	79 (68.1)	80 (69.0)
	Moderately anxious/depressed	35 (30.2)	33 (28.4)
	Extremely anxious/depressed	1 (0.9)	3 (2.6)
Hour 2			
Mobility	No problem	85 (73.3)	94 (81.0)
	Some problem	23 (19.8)	15 (12.9)
	Confined to bed	5 (4.3)	5 (4.3)
Self care	No problem	103 (88.8)	107 (92.2)
	Some problem	9 (7.8)	6 (5.2)
	Unable to wash or dress	1 (0.9)	1 (0.9)
Usual activities	No problem	92 (79.3)	91 (78.4)
	Some problem	17 (14.7)	19 (16.4)
	Unable to perform usual activity	4 (3.4)	4 (3.4)
Pain/discomfort	No pain or discomfort	89 (76.7)	79 (68.1)
	Moderate pain or discomfort	24 (20.7)	35 (30.2)
Anxiety/depression	Not anxious/depressed	88 (75.9)	86 (74.1)
	Moderately anxious/depressed	24 (20.7)	26 (22.4)
	Extremely anxious/depressed	1 (0.9)	2 (1.7)

The percentages are based on the number of subjects in the full analysis set (N=116 per treatment group). Subjects with missing data are not shown.
Source: Appendix Table 14.2.8.1

Further details can be found as part of the pharmacoeconomic analyses which will be provided in a separate report.

11.3.5 Analysis of Discharge

Per protocol, subjects were to remain in hospital for a minimum of 6 hours following study drug infusion; however, at two hours investigators were questioned on whether or not the subject was ready for discharge. There were 37.1% (43/116) of vernakalant subjects and 9.5% (11/116) of amiodarone subjects ready for discharge at two hours according to the investigator (unadjusted P-value <0.0001) (Appendix Table 14.2.10).

An additional analysis, not pre-specified in the protocol or SAP, was conducted to look for an association between conversion to SR within 90 minutes and physician-assessed readiness for discharge at hour 2. Table 18 shows the results of this analysis, suggesting that irrespective of treatment group, subjects were more likely to be ready for discharge at hour 2 if they converted to SR.

Table 18. Association Between Conversion to Sinus Rhythm Within 90 Minutes and Physician-Assessed Readiness for Discharge at Hour 2

		Ready for Discharge at Hour 2			
Treatment Group	**Conversion to SR**	**Yes**	**No**	**Odds Ratio**	**P-Value[a]**
Vernakalant (N=116)	Yes	41	19	58.3	<0.0001
	No	2	54		
Amiodarone (N=116)	Yes	3	3	12.8	
	No	8	102		

[a] P-value is unadjusted and based on a one degree of freedom CMH test of association.

11.3.6 Subgroup Analysis of Primary Efficacy Endpoint

A summary of the subgroup analyses of treatment-induced conversion from AF to SR within 90 minutes is shown for the full analysis set in Figure 4. Further details can be found in Appendix Table 14.2.9.1 to 14.2.9.11.

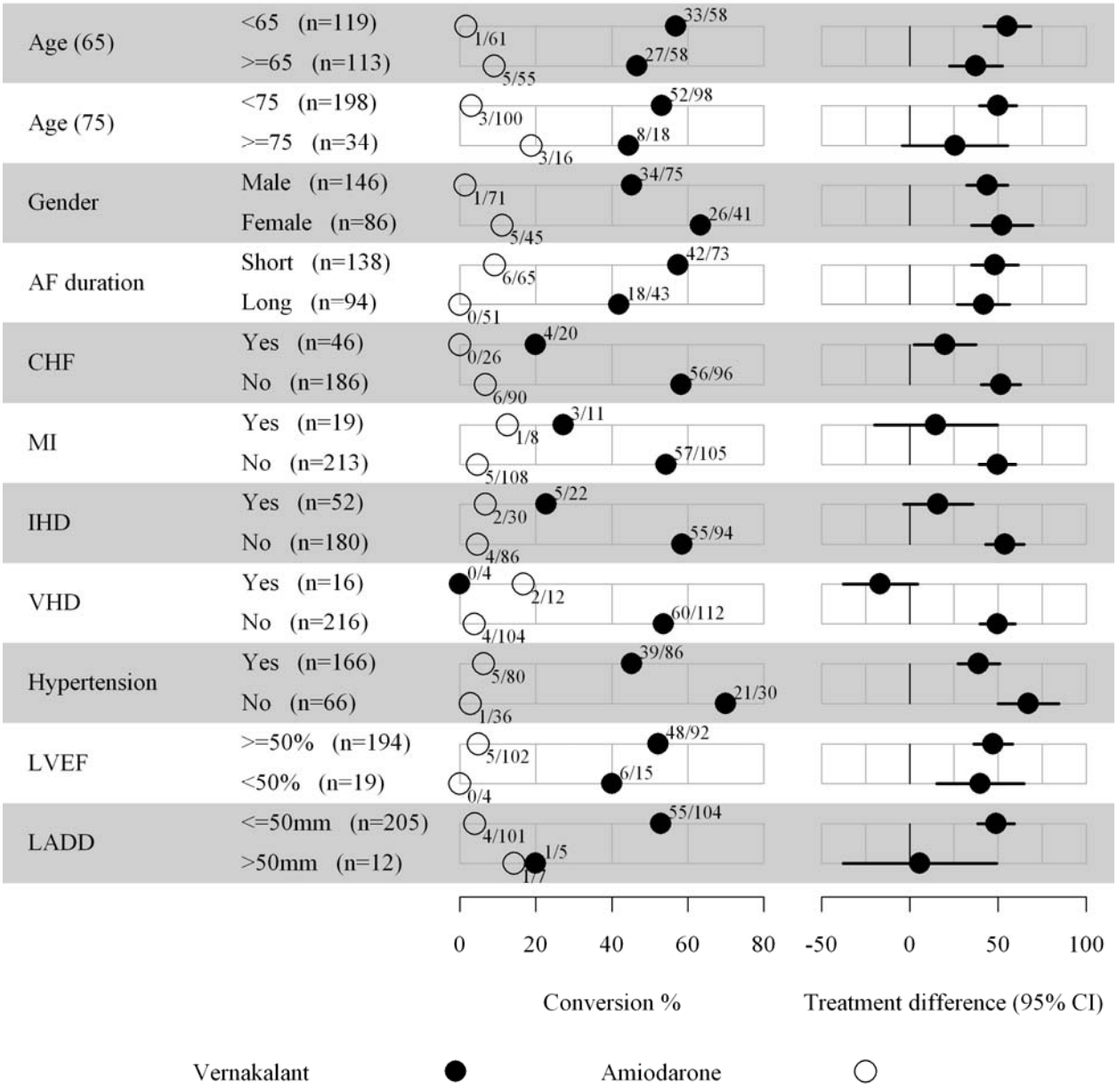


Figure 4. Summary of Treatment-Induced Conversion from Atrial Fibrillation to Sinus Rhythm Within 90 Minutes by Subgroups (Full Analysis Set)

The subgroup analysis was limited by small sample sizes in various subgroups, including MI, VHD, LVEF <50%, and LADD >50 mm, as well as imbalances between treatment groups within certain subgroups (e.g., VHD 1:3 vernakalant:amiodarone). Within these limitations, vernakalant consistently converted a greater proportion of subjects from AF to SR within the first 90 minutes compared to amiodarone for most of the subgroups, with the exception of VHD.

11.4 Efficacy Conclusions

- Vernakalant met all primary and secondary efficacy endpoints in this study.
- Treatment with vernakalant resulted in a statistically significantly faster conversion rate from AF to SR within the first 90 minutes compared to amiodarone (log-rank P-value <0.0001). By minute 90, a total of 51.7% of vernakalant subjects had converted to SR, compared to 5.2% of amiodarone subjects.
- Vernakalant treatment resulted in a statistically significantly greater proportion of subjects reporting no AF symptoms at 90 minutes (53.4% vernakalant versus 32.8% amiodarone, CMH P-value = 0.0012).
- There was a statistically significant improvement in vernakalant-treated subjects' perception of their state of health at hour 2 compared to amiodarone-treated subjects (P=0.0006).
- In the group of subjects who responded to vernakalant within 90 minutes (N=60), the median time to conversion was 11.0 minutes; in the group of subjects who responded to amiodarone within 90 minutes (N=6), the median time to conversion was 25.5 minutes.
- In subjects receiving vernakalant who converted to SR within 90 minutes (N=60), sinus rhythm was maintained through 4 hours for 98.3% of subjects, and at Day 7, 91.7% of vernakalant subjects remained in SR without evidence of relapse.
- At two hours, there were significantly more vernakalant subjects (37.1%) than amiodarone subjects (9.5%) ready for discharge (unadjusted P-value <0.0001).

12 SAFETY EVALUATION

12.1 Extent of Exposure

A summary of the exposure to study drug for subjects in the full analysis set who received any portion of study drug is shown in Table 19.

Table 19. Summary of Exposure to Study Drug (Full Analysis Set)

	Treatment Group	
Infusion Duration	**Vernakalant (N=116)**	**Amiodarone (N=116)**
Dose #1 duration, minutes		
N	116	115[a]
Mean (SD)	10.0 (0.70)	59.1 (5.01)
Median	10.0	60.0
Min, Max	5, 15	23, 64
Dose #2 duration, minutes		
N	65	109
Mean (SD)	10.4 (3.22)	59.6 (4.07)
Median	10.0	60.0
Min, Max	2, 32	20, 70

a One subject (305-2502-001) is not included in the amiodarone group as the dosing information is unknown.
Source: Appendix Table 14.1.4

In the vernakalant group, the first 10-minute infusion was administered in its entirety to the majority of subjects, with a mean duration of 10.0 minutes. There were 65 of 116 subjects (56.0%) who received the second infusion of vernakalant. In the amiodarone group, the first 60-minute infusion was administered in its entirety to the majority of subjects, with a mean duration of 59.1 minutes. There were 109 of 115 subjects (94.8%) who received the second 60-minute infusion, as a result of the low conversion rate.

Individual listings of study drug administration, including the dates and times of dosing, can be found in Appendix 16.2.5.

12.2 Adverse Events

12.2.1 Safety Overview

An overview of the number of subjects experiencing treatment-emergent AEs, SAEs, discontinuations due to AEs, clinically significant events, and deaths is provided in Table 20.

Table 20. Safety Overview (Safety Set)

	Number (%) of Subjects	
	Treatment Group	
	Vernakalant (N=116)	Amiodarone (N=116)
Any AE	59 (50.9)	45 (38.8)
Any related AE	27 (23.3)	3 (2.6)
Any SAE	13 (11.2)	10 (8.6)
Any related SAE	3 (2.6)	1 (0.9)
Discontinuation of study drug due to an AE	3 (2.6)	1 (0.9)
Discontinuation of study drug due to a related AE	3 (2.6)	1 (0.9)
Clinically significant events[a]	13 (11.2)	10 (8.6)
Death	1 (0.9)	0

[a] Defined as an SAE or an AE resulting in discontinuation of study drug.
Source: Appendix Table 14.3.1.1, 14.3.3.1, 14.3.5.1, 14.3.6.1, 14.3.7.1, and 14.3.8.1, and Appendix 16.2.7.2 and 16.2.7.3

A greater number of treatment-emergent AEs were reported in the vernakalant group than in the amiodarone group. The incidence of related events was also higher in the vernakalant group compared to the amiodarone group. The incidence of SAEs and related SAEs, discontinuations due to AEs and due to related AEs, and clinically significant events was low overall and similar between the two treatment groups. There was one death in this study, which occurred in the vernakalant group and was not considered to be related to study drug.

12.2.2 Summary of Adverse Events

In the sections that follow, the analysis of AEs is shown for 3 time periods: 0-2 hours postdose, 2-24 hours postdose, and 0-24 hours postdose. The 0-2 hour postdose time period was selected as this was the infusion period for amiodarone and also the period of vernakalant's maximum effects. Vernakalant plasma levels peak at the end of infusion [8], and concentrations decrease by >40% within 5 minutes after the end of infusion and are negligible by 24 hours postdose [9]. Further, the study design limited electrical cardioversion within two hours after the start of study drug infusion, unless the investigator concluded it was necessary to restore sinus rhythm quickly. Thus, the time frames for AE analysis were chosen in an effort to distinguish AEs associated with vernakalant injection from those associated with follow up treatments.

A summary of the incidence of treatment-emergent AEs by time period is provided for the safety set in Table 21. A summary of all postdose AEs can be found in Appendix Table 14.3.1.1 and an individual listing of all AEs can be found in Appendix 16.2.7.1.

Table 21. Summary of Treatment-Emergent Adverse Events by Time Period (Safety Set) (page 1 of 3)

	Number (%) of Subjects											
	0-2 Hours Postdose				2-24 Hours Postdose				0-24 Hours Postdose			
System Organ Class Preferred Term	VERI (N=116)		AMIO (N=116)		VERI (N=116)		AMIO (N=116)		VERI (N=116)		AMIO (N=116)	
Any Adverse Event	**32**	**(27.6)**	**10**	**(8.6)**	**21**	**(18.1)**	**15**	**(12.9)**	**43**	**(37.1)**	**24**	**(20.7)**
Cardiac Disorders	**6**	**(5.2)**	**2**	**(1.7)**	**9**	**(7.8)**	**3**	**(2.6)**	**14**	**(12.1)**	**5**	**(4.3)**
Angina pectoris	1	(0.9)	0		0		0		1	(0.9)	0	
Aortic valve stenosis	0		0		0		1	(0.9)	0		1	(0.9)
Atrial fibrillation	0		0		4	(3.4)	0		4	(3.4)	0	
Atrial flutter	2	(1.7)	0		0		0		2	(1.7)	0	
Atrial tachycardia	0		0		1	(0.9)	0		1	(0.9)	0	
Atrial thrombosis	0		0		1	(0.9)	0		1	(0.9)	0	
Bradycardia	1	(0.9)	1	(0.9)	1	(0.9)	0		2	(1.7)	1	(0.9)
Cardiac arrest	0		1	(0.9)	0		0		0		1	(0.9)
Coronary artery disease	0		0		0		1	(0.9)	0		1	(0.9)
Mitral valve incompetence	0		0		1	(0.9)	0		1	(0.9)	0	
Sinus arrhythmia	1	(0.9)	0		0		0		1	(0.9)	0	
Sinus bradycardia	0		0		0		1	(0.9)	0		1	(0.9)
Supraventricular tachycardia	0		0		1	(0.9)	0		1	(0.9)	0	
Ventricular tachycardia	1	(0.9)	0		1	(0.9)	0		2	(1.7)	0	
Endocrine Disorders	**1**	**(0.9)**	**1**	**(0.9)**	**1**	**(0.9)**	**0**		**2**	**(1.7)**	**1**	**(0.9)**
Hyperthyroidism	1	(0.9)	1	(0.9)	1	(0.9)	0		2	(1.7)	1	(0.9)
Gastrointestinal Disorders	**5**	**(4.3)**	**0**		**1**	**(0.9)**	**4**	**(3.4)**	**6**	**(5.2)**	**4**	**(3.4)**
Abdominal discomfort	1	(0.9)	0		0		0		1	(0.9)	0	
Diarrhoea	1	(0.9)	0		0		1	(0.9)	1	(0.9)	1	(0.9)
Flatulence	1	(0.9)	0		0		0		1	(0.9)	0	
Gastritis erosive	0		0		1	(0.9)	0		1	(0.9)	0	
Nausea	3	(2.6)	0		0		2	(1.7)	3	(2.6)	2	(1.7)
Vomiting	1	(0.9)	0		0		1	(0.9)	1	(0.9)	1	(0.9)
General Disorders and Administration Site Conditions	**2**	**(1.7)**	**0**		**2**	**(1.7)**	**2**	**(1.7)**	**4**	**(3.4)**	**2**	**(1.7)**
Asthenia	0		0		1	(0.9)	0		1	(0.9)	0	
Catheter site erythema	1	(0.9)	0		0		0		1	(0.9)	0	
Chest pain	0		0		1	(0.9)	0		1	(0.9)	0	

Table 21. Summary of Treatment-Emergent Adverse Events by Time Period (Safety Set) (page 2 of 3)

System Organ Class Preferred Term	Number (%) of Subjects									
	0-2 Hours Postdose		2-24 Hours Postdose		0-24 Hours Postdose	
	VERI (N=116)	AMIO (N=116)	VERI (N=116)	AMIO (N=116)	VERI (N=116)	AMIO (N=116)
General Disorders and Administration Site Conditions (cont.)						
Face oedema	0	0	1 (0.9)	0	1 (0.9)	0
Fatigue	1 (0.9)	0	0	1 (0.9)	1 (0.9)	1 (0.9)
Feeling abnormal	0	0	0	1 (0.9)	0	1 (0.9)
Immune System Disorders	**1 (0.9)**	**0**	**0**	**0**	**1 (0.9)**	**0**
Hypersensitivity	1 (0.9)	0	0	0	1 (0.9)	0
Infections and Infestations	**1 (0.9)**	**0**	**0**	**0**	**1 (0.9)**	**0**
Urinary tract infection	1 (0.9)	0	0	0	1 (0.9)	0
Investigations	**3 (2.6)**	**5 (4.3)**	**5 (4.3)**	**3 (2.6)**	**7 (6.0)**	**7 (6.0)**
Activated partial thromboplastin time prolonged	0	1 (0.9)	0	1 (0.9)	0	2 (1.7)
Blood bilirubin increased	0	0	0	1 (0.9)	0	1 (0.9)
Blood glucose abnormal	0	1 (0.9)	0	0	0	1 (0.9)
Blood pressure decreased	0	0	0	1 (0.9)	0	1 (0.9)
Blood pressure diastolic increased	1 (0.9)	0	0	0	1 (0.9)	0
Blood pressure systolic decreased	0	1 (0.9)	0	0	0	1 (0.9)
Blood potassium increased	0	0	1 (0.9)	0	1 (0.9)	0
Blood thyroid stimulating hormone abnormal	0	1 (0.9)	0	0	0	1 (0.9)
Blood thyroid stimulating hormone decreased	0	0	1 (0.9)	0	1 (0.9)	0
Electrocardiogram QT prolonged	0	0	1 (0.9)	0	1 (0.9)	0
Heart rate decreased	0	1 (0.9)	1 (0.9)	0	1 (0.9)	1 (0.9)
Red blood cell count increased	1 (0.9)	0	0	0	1 (0.9)	0
Troponin increased	0	0	1 (0.9)	0	1 (0.9)	0
Urine output decreased	1 (0.9)	0	0	0	1 (0.9)	0
White blood cell count increased	1 (0.9)	0	0	0	1 (0.9)	0
Metabolism and Nutrition Disorders	**1 (0.9)**	**0**	**0**	**0**	**1 (0.9)**	**0**
Hypokalaemia	1 (0.9)	0	0	0	1 (0.9)	0
Nervous System Disorders	**13 (11.2)**	**1 (0.9)**	**4 (3.4)**	**3 (2.6)**	**16 (13.8)**	**4 (3.4)**
Dizziness	1 (0.9)	0	2 (1.7)	3 (2.6)	3 (2.6)	3 (2.6)
Dysgeusia	8 (6.9)	0	0	0	8 (6.9)	0

Table 21. Summary of Treatment-Emergent Adverse Events by Time Period (Safety Set) (page 3 of 3)

System Organ Class Preferred Term	Number (%) of Subjects					
	0-2 Hours Postdose		2-24 Hours Postdose		0-24 Hours Postdose	
	VERI (N=116)	AMIO (N=116)	VERI (N=116)	AMIO (N=116)	VERI (N=116)	AMIO (N=116)
Nervous System Disorders (cont.)						
Dysphasia	0	0	1 (0.9)	0	1 (0.9)	0
Headache	2 (1.7)	1 (0.9)	0	0	2 (1.7)	1 (0.9)
Paraesthesia	2 (1.7)	0	0	0	2 (1.7)	0
Restless legs syndrome	1 (0.9)	0	0	0	1 (0.9)	0
Syncope	0	0	1 (0.9)	0	1 (0.9)	0
Psychiatric Disorders	**0**	**1 (0.9)**	**1 (0.9)**	**1 (0.9)**	**1 (0.9)**	**2 (1.7)**
Insomnia	0	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)	2 (1.7)
Renal and Urinary Disorders	**1 (0.9)**	**0**	**0**	**0**	**1 (0.9)**	**0**
Chromaturia	1 (0.9)	0	0	0	1 (0.9)	0
Respiratory, Thoracic, and Mediastinal Disorders	**10 (8.6)**	**0**	**0**	**4 (3.4)**	**10 (8.6)**	**4 (3.4)**
Choking sensation	1 (0.9)	0	0	0	1 (0.9)	0
Cough	4 (3.4)	0	0	2 (1.7)	4 (3.4)	2 (1.7)
Dyspnoea	1 (0.9)	0	0	0	1 (0.9)	0
Emphysema	0	0	0	1 (0.9)	0	1 (0.9)
Nasal congestion	1 (0.9)	0	0	0	1 (0.9)	0
Pharyngolaryngeal pain	2 (1.7)	0	0	0	2 (1.7)	0
Pleural effusion	0	0	0	1 (0.9)	0	1 (0.9)
Sneezing	4 (3.4)	0	0	0	4 (3.4)	0
Throat irritation	2 (1.7)	0	0	0	2 (1.7)	0
Skin and Subcutaneous Tissue Disorders	**2 (1.7)**	**1 (0.9)**	**0**	**0**	**2 (1.7)**	**1 (0.9)**
Dermatitis contact	0	1 (0.9)	0	0	0	1 (0.9)
Hyperhidrosis	1 (0.9)	0	0	0	1 (0.9)	0
Rash pruritic	1 (0.9)	0	0	0	1 (0.9)	0
Urticaria	0	1 (0.9)	0	0	0	1 (0.9)
Vascular Disorders	**3 (2.6)**	**0**	**0**	**0**	**3 (2.6)**	**0**
Hypertension	3 (2.6)	0	0	0	3 (2.6)	0

AMIO: amiodarone injection; VERI: vernakalant injection.
Within a system organ class, subjects may have experienced more than one adverse event.
Source: Appendix Table 14.3.1.2, 14.3.1.3, and 14.3.1.4

The incidence of treatment-emergent AEs was higher for the vernakalant group compared to the amiodarone group within each time period. Treatment-emergent AEs that occurred in 3 or more subjects within a treatment group within 24 hours postdose included dysgeusia, cough, dizziness, nausea, atrial fibrillation, sneezing, and hypertension. Most of these events occurred at a higher incidence in the vernakalant group compared to the amiodarone group. The exception was dizziness, which occurred in 3 subjects in each group. Additional treatment-emergent AEs that occurred in more than one subject in the amiodarone group within 24 hours postdose included insomnia and prolonged activated partial thromboplastin time. In the vernakalant group, most of the common AEs occurred within 2 hours postdose (with the exception of AF and dizziness); in the amiodarone group, most of the common AEs occurred between 2 to 24 hours postdose.

The majority of all postdose AEs were of mild or moderate severity. A total of 4 subjects (3.4%) in the vernakalant group and 3 subjects (2.6%) in the amiodarone group had AEs that were considered to be severe in intensity. These included one event each of increased INR, stomach discomfort, and pulmonary embolism for 3 subjects in the vernakalant group, in addition to one subject who had severe events of chronic obstructive pulmonary disease (COPD) and pulmonary embolism. In the amiodarone group there was one severe event each of atrial fibrillation, cardiac arrest, and pneumothorax (Appendix Table 14.3.2.1). Only the AE of cardiac arrest in the amiodarone group occurred within 24 hours postdose; all other severe AEs occurred after 24 hours postdose (Appendix Table 14.3.2.4).

12.2.3 Related Adverse Events

A summary of treatment-emergent AEs that were considered by the investigator to be possibly, probably, or definitely related to study drug is provided by time period (through 24 hours postdose) for the safety set in Table 22. A summary of all postdose related AEs can be found in Appendix Table 14.3.3.1.

Table 22. Summary of Related Treatment-Emergent Adverse Events by Time Period (Safety Set) (page 1 of 2)

	Number (%) of Subjects					
	0-2 Hours Postdose		2-24 Hours Postdose		0-24 Hours Postdose	
System Organ Class Preferred Term	**VERI (N=116)**	**AMIO (N=116)**	**VERI (N=116)**	**AMIO (N=116)**	**VERI (N=116)**	**AMIO (N=116)**
Any Related Adverse Event	**22 (19.0)**	**1 (0.9)**	**4 (3.4)**	**1 (0.9)**	**24 (20.7)**	**2 (1.7)**
Cardiac Disorders	**5 (4.3)**	**1 (0.9)**	**2 (1.7)**	**0**	**7 (6.0)**	**1 (0.9)**
Angina pectoris	1 (0.9)	0	0	0	1 (0.9)	0
Atrial flutter	1 (0.9)	0	0	0	1 (0.9)	0
Bradycardia	1 (0.9)	0	1 (0.9)	0	2 (1.7)	0
Cardiac arrest	0	1 (0.9)	0	0	0	1 (0.9)
Sinus arrhythmia	1 (0.9)	0	0	0	1 (0.9)	0
Supraventricular tachycardia	0	0	1 (0.9)	0	1 (0.9)	0
Ventricular tachycardia	1 (0.9)	0	0	0	1 (0.9)	0
Gastrointestinal Disorders	**3 (2.6)**	**0**	**0**	**0**	**3 (2.6)**	**0**
Diarrhoea	1 (0.9)	0	0	0	1 (0.9)	0
Nausea	2 (1.7)	0	0	0	2 (1.7)	0
Vomiting	1 (0.9)	0	0	0	1 (0.9)	0
Immune System Disorders	**1 (0.9)**	**0**	**0**	**0**	**1 (0.9)**	**0**
Hypersensitivity	1 (0.9)	0	0	0	1 (0.9)	0
Investigations	**1 (0.9)**	**0**	**2 (1.7)**	**1 (0.9)**	**2 (1.7)**	**1 (0.9)**
Blood bilirubin increased	0	0	0	1 (0.9)	0	1 (0.9)
Blood pressure diastolic increased	1 (0.9)	0	0	0	1 (0.9)	0
Electrocardiogram QT prolonged	0	0	1 (0.9)	0	1 (0.9)	0
Heart rate decreased	0	0	1 (0.9)	0	1 (0.9)	0
Nervous System Disorders	**10 (8.6)**	**0**	**0**	**0**	**10 (8.6)**	**0**
Dysgeusia	8 (6.9)	0	0	0	8 (6.9)	0
Paraesthesia	2 (1.7)	0	0	0	2 (1.7)	0
Restless legs syndrome	1 (0.9)	0	0	0	1 (0.9)	0
Renal and Urinary Disorders	**1 (0.9)**	**0**	**0**	**0**	**1 (0.9)**	**0**
Chromaturia	1 (0.9)	0	0	0	1 (0.9)	0

Table 22. Summary of Related Treatment-Emergent Adverse Events by Time Period (Safety Set) (page 2 of 2)

System Organ Class Preferred Term	Number (%) of Subjects					
	0-2 Hours Postdose		2-24 Hours Postdose		0-24 Hours Postdose	
	VERI (N=116)	AMIO (N=116)	VERI (N=116)	AMIO (N=116)	VERI (N=116)	AMIO (N=116)
Respiratory, Thoracic, and Mediastinal Disorders	**10 (8.6)**	**0**	**0**	**0**	**10 (8.6)**	**0**
Choking sensation	1 (0.9)	0	0	0	1 (0.9)	0
Cough	3 (2.6)	0	0	0	3 (2.6)	0
Dyspnoea	1 (0.9)	0	0	0	1 (0.9)	0
Nasal congestion	1 (0.9)	0	0	0	1 (0.9)	0
Pharyngolaryngeal pain	2 (1.7)	0	0	0	2 (1.7)	0
Sneezing	4 (3.4)	0	0	0	4 (3.4)	0
Throat irritation	2 (1.7)	0	0	0	2 (1.7)	0
Skin and Subcutaneous Tissue Disorders	**2 (1.7)**	**0**	**0**	**0**	**2 (1.7)**	**0**
Hyperhidrosis	1 (0.9)	0	0	0	1 (0.9)	0
Rash pruritic	1 (0.9)	0	0	0	1 (0.9)	0

AMIO: amiodarone injection; VERI: vernakalant injection.
Within a system organ class, subjects may have experienced more than one adverse event.
Source: Appendix Table 14.3.3.2, 14.3.3.3, and 14.3.3.4

The majority of treatment-emergent AEs that were considered to be related to study drug within 24 hours postdose occurred in the vernakalant group, with dysgeusia being the most common. Other related treatment-emergent AEs that occurred within 24 hours postdose in two or more subjects in the vernakalant group were sneezing, cough, bradycardia, nausea, paresthesia, pharyngolaryngeal pain, and throat irritation. With the exception of one event of bradycardia, all of these events occurred within the first two hours postdose. There were two subjects in the amiodarone group who had treatment-emergent AEs that were considered to be related to study drug within 24 hours postdose: cardiac arrest occurring within two hours postdose and increased blood bilirubin occurring within 2 to 24 hours postdose. All of the related treatment-emergent AEs were of mild or moderate severity, with the exception of the event of cardiac arrest in the amiodarone group (Appendix Table 14.3.4.1).

There were 5 subjects in the study who had related treatment-emergent AEs occurring between 24 hours postdose and 7 days. In the vernakalant group, one subject had related AEs of increased ALT and increased AST, and two subjects had related AEs of abnormal blood bilirubin and hyperbilirubinemia. In the amiodarone group, two subjects had related AEs of increased AST (Appendix 16.2.7.1).

A summary of the time of onset and duration of related treatment-emergent AEs (those with a relationship of definitely, probably, or possibly related to study drug) occurring in >2 subjects within 24 hours postdose is presented in Table 23.

Table 23. Time of Onset and Duration of Related Treatment-Emergent Adverse Events Occurring in >2 Subjects Within 24 Hours Postdose (Safety Set)

Subject Number[a]	Adverse Event (Preferred Term)	Time of Onset (min)	Duration (min)
305-9003-001	Dysgeusia	4	5
305-2513-004	Dysgeusia	4	8
305-1003-001	Dysgeusia	5	4
305-9002-005	Dysgeusia	6	12
305-1504-004	Dysgeusia	7	10
305-1703-003	Dysgeusia	40	199
305-7019-002	Dysgeusia	46	60
305-1608-003	Dysgeusia	65	30
305-5007-001	Sneezing	6	1
305-1101-001	Sneezing	7	5
305-1108-002	Sneezing	22	75
305-7019-002	Sneezing	46	60
305-1502-001	Cough	2	36
305-9003-001	Cough	4	5
305-2901-003	Cough	34	10

[a] Note that all subjects listed were in the vernakalant group.
Source: Appendix 16.2.7.1

The majority of the related treatment-emergent AEs occurring in >2 subjects within 24 hours postdose began during or shortly after the infusion of study drug and were generally transient.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Deaths

There was one death in this study, occurring in the vernakalant group.

Subject 305-4005-001 was a 68-year-old white male with a long history of chronic obstructive pulmonary disease (COPD) and a history of turberculosis, in addition to coronary heart disease, ischemic heart disease, hypertension, and AF since 1991, acute myocardial infarction in 1991, NYHA Class II heart failure (duration of >12 months), and a recent diagnosis of hyponatremia. The subject received both infusions of vernakalant and was electrically cardioverted to sinus rhythm on Day 1. An SAE of COPD began on Day 17, for which the subject was hospitalized. The subject's respiratory condition worsened and artificial lung ventilation was initiated. On Day 24 an SAE of pulmonary embolism began, which resulted in the subject's death approximately 2.5 hours later. The investigator assessed both SAEs to be severe and not related to study drug.

A narrative with further details on this death is provided in Appendix 16.4.

12.3.2 Serious Adverse Events Other Than Death

A summary of the incidence of treatment-emergent SAEs by time period (through 24 hours postdose) is provided for the safety set in Table 24. A summary of all postdose SAEs can be found in Appendix Table 14.3.5.1 and an individual listing of all SAEs can be found in Appendix 16.2.7.2.

Table 24. Summary of Treatment-Emergent Serious Adverse Events by Time Period (Safety Set)

	Number (%) of Subjects					
	0-2 Hours Postdose		2-24 Hours Postdose		0-24 Hours Postdose	
System Organ Class Preferred Term	VERI (N=116)	AMIO (N=116)	VERI (N=116)	AMIO (N=116)	VERI (N=116)	AMIO (N=116)
Any Serious Adverse Event	**3 (2.6)**	**1 (0.9)**	**2 (1.7)**	**1 (0.9)**	**5 (4.3)**	**2 (1.7)**
Any Related Serious Adverse Event	**3 (2.6)**	**1 (0.9)**	**0**	**0**	**3 (2.6)**	**1 (0.9)**
Cardiac Disorders	**2 (1.7)**	**1 (0.9)**	**1 (0.9)**	**1 (0.9)**	**3 (2.6)**	**2 (1.7)**
Angina pectoris[a]	1 (0.9)	0	0	0	1 (0.9)	0
Atrial thrombosis	0	0	1 (0.9)	0	1 (0.9)	0
Cardiac arrest[a]	0	1 (0.9)	0	0	0	1 (0.9)
Sinus bradycardia	0	0	0	1 (0.9)	0	1 (0.9)
Ventricular tachycardia[a]	1 (0.9)	0	0	0	1 (0.9)	0
Immune System Disorders	**1 (0.9)**	**0**	**0**	**0**	**1 (0.9)**	**0**
Hypersensitivity[a]	1 (0.9)	0	0	0	1 (0.9)	0
Nervous System Disorders	**0**	**0**	**1 (0.9)**	**0**	**1 (0.9)**	**0**
Syncope	0	0	1 (0.9)	0	1 (0.9)	0

AMIO: amiodarone injection; VERI: vernakalant injection.
Within a system organ class, subjects may have experienced more than one adverse event.
[a] These SAEs were considered by the investigator to be related to study drug.
Source: Appendix Table 14.3.5.2, 14.3.5.3, 14.3.5.4, 14.3.6.2, 14.3.6.3, and 14.3.6.4

The incidence of SAEs and related SAEs within 24 hours postdose was low overall. In both treatment groups, most of the SAEs that occurred were cardiac disorders. There were no SAEs that occurred in more than one subject within 24 hours postdose. The SAEs occurring within 24 hours postdose that were considered by the investigator to be related to study drug included angina pectoris, hypersensitivity, and ventricular tachycardia in the vernakalant group, and cardiac arrest in the amiodarone group (Appendix Table 14.3.6.4). All of these related SAEs led to permanent discontinuation of study drug (see Section 12.3.3 for further details). The SAEs of cardiac arrest, sinus bradycardia, syncope, and ventricular tachycardia (as listed in Table 24) are discussed further in Section 12.3.4 as events of interest.

The incidence of SAEs occurring between 24 hours postdose and 30 days was similar between both treatment groups. In the vernakalant group, there were four SAEs of atrial fibrillation and one event each of ischemic stroke, pulmonary embolism, and stomach discomfort. Additionally, one subject had two SAEs of COPD and pulmonary embolism (see Section 12.3.1) and one subject had two SAEs of atrial fibrillation and increased INR. In the amiodarone group, there were six SAEs of atrial fibrillation, and one event each of cardiac failure and pneumothorax. None of the SAEs occurring between 24 hours postdose and 30 days were considered to be related to study drug (Appendix 16.2.7.2).

Narratives with further details on these SAEs are provided in Appendix 16.4.2.

12.3.3 Adverse Events Resulting in Discontinuation

A summary of all treatment-emergent AEs that led to discontinuation of study drug is provided for the safety set in Table 25. A listing of all subjects with AEs that led to discontinuation of study drug can be found in Appendix 16.2.7.3.

Table 25. Summary of All Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug (Safety Set)

	Number (%) of Subjects	
	Treatment Group	
System Organ Class Preferred Term	**Vernakalant (N=116)**	**Amiodarone (N=116)**
Any Adverse Event	**3 (2.6)**	**1 (0.9)**
Any Related Adverse Event	**3 (2.6)**	**1 (0.9)**
Cardiac Disorders	**2 (1.7)**	**1 (0.9)**
Angina pectoris	1 (0.9)	0
Cardiac arrest	0	1 (0.9)
Ventricular tachycardia	1 (0.9)	0
Immune System Disorders	**1 (0.9)**	**0**
Hypersensitivity	1 (0.9)	0

Within a system organ class, subjects may have experienced more than one adverse event.
Source: Appendix Table 14.3.7.1 and Appendix 16.2.7.3

The incidence of discontinuations due to AEs was low overall. All treatment-emergent AEs that led to discontinuation of study drug were considered to be serious and related to study drug. In both treatment groups, these AEs began within 40 minutes after the start of the first infusion

of study drug and resolved within 5 minutes, with the exception of the SAE of hypersensitivity, for which the symptoms resolved after 28 minutes (see Section 10.1.1 for further details).

Narratives with further details on the treatment-emergent AEs that led to discontinuation of study drug are provided in Appendix 16.4.

12.3.4 Adverse Events of Special Interest

Based on the safety profile of other antiarrhythmic agents and following review of the safety data for vernakalant, certain AEs of interest have been identified, including hypotension, bradycardia, ventricular arrhythmia, and atrial flutter. Special analyses of the incidence of these events were generated from multiple data sources (e.g., Holter, AEs, vital signs) as an additional means of investigating these events in this study, and the results of these analyses are discussed below. The analyses were conducted for 3 time periods relative to dosing: 0-2 hours postdose, 2-4 hours postdose, and 0-4 hours postdose. The 0-4 hour postdose time period reflects the period of Holter monitoring in this study.

12.3.4.1 Hypotension

Subjects in this study were to be adequately hydrated and hemodynamically optimized prior to receiving treatment, as both vernakalant and amiodarone may cause hypotension. Hypotension events occurring within 0-2, 2-4, and 0-4 hours postdose, with the percent risk difference (vernakalant minus amiodarone), are presented for the safety set in Table 26.

Table 26. Incidence of Hypotension Events from Multiple Data Sources (Safety Set)

Postdose Time Period Event	Number (%) of Subjects Vernakalant (N=116)	Amiodarone (N=116)	Percent Risk Difference	(95% CI)
0-2 Hours Postdose				
Any hypotension event (all sources)	**0**	**1 (0.9)**	**-0.9**	**(-14.1, 12.4)**
Hypotension from AE database[a]	0	1 (0.9)	-0.9	(-14.1, 12.4)
Hypotension from vital signs[b]	0	1 (0.9)	-0.9	(-14.1, 12.4)
2-4 Hours Postdose				
Any hypotension event (all sources)	**1 (0.9)**	**1 (0.9)**	**0**	**(-13.2, 13.2)**
Hypotension from AE database[a]	1 (0.9)	1 (0.9)	0	(-13.2, 13.2)
Hypotension from vital signs[b]	0	1 (0.9)	-0.9	(-14.1, 12.4)
0-4 Hours Postdose				
Any hypotension event (all sources)	**1 (0.9)**	**2 (1.7)**	**-0.9**	**(-14.1, 12.4)**
Hypotension from AE database[a]	1 (0.9)	2 (1.7)	-0.9	(-14.1, 12.4)
Hypotension from vital signs[b]	0	2 (1.7)	-1.7	(-14.9, 11.5)

a Includes blood pressure decreased, blood pressure systolic decreased, and/or syncope.

b Hypotension from vital signs was defined as any post-baseline fall in SBP below 90 mmHg.

Source: Appendix Table 14.7.4.2, 14.7.4.3, and 14.7.4.4

One vernakalant subject and two amiodarone subjects had a hypotension event within 4 hours postdose.

There were no events of hypotension that led to discontinuation of study drug. There was one event that was reported as an SAE within 24 hours postdose, occurring in subject 305-1006-004 (vernakalant group), a 70-year-old black male with a history of hypertension. The subject received one infusion of vernakalant and converted to SR on Day 1. An SAE of syncope began approximately two hours after the start of the first infusion. The subject had intermittent episodes of syncope (20-30 seconds in duration), and was admitted to the cardiology department. The subject had experienced his first episode of syncope prior to receiving study drug. No further episodes of syncope were reported while the subject was hospitalized, and the subject was discharged after 3 days. The SAE of syncope was assessed by the investigator as being of moderate severity and unlikely related to study drug. A second SAE, pulmonary embolism (with dyspnea, weakness, and syncope), began on Day 7 and resolved 4 days later. The subject also had an AE of hypokalemia which started on the same day as the syncope, and AEs of decreased hemoglobin and anemia around the time of the pulmonary embolism.

A narrative with further details for this subject is provided in Appendix 16.4.2.

12.3.4.2 Bradycardia

Bradycardia events occurring within 0-2, 2-4, and 0-4 hours postdose, with the percent risk difference (vernakalant minus amiodarone), are presented for the safety set in Table 27.

Table 27. Incidence of Bradycardia Events from Multiple Data Sources (Safety Set)

Postdose Time Period Event	Number (%) of Subjects Vernakalant (N=116)	Number (%) of Subjects Amiodarone (N=116)	Percent Risk Difference (VERI-AMIO)	(95% CI)
0-2 Hours Postdose				
Any bradycardia event (all sources)	**2 (1.7)**	**3 (2.6)**	**-0.9**	**(-14.1, 12.4)**
Bradycardia from AE database[a]	1 (0.9)	2 (1.7)	-0.9	(-14.1, 12.4)
Bradycardia from Holter[b]	1 (0.9)	2 (1.7)	-0.9	(-14.1, 12.4)
Bradycardia from vital signs[b]	0	1 (0.9)	-0.9	(-14.1, 12.4)
2-4 Hours Postdose				
Any bradycardia event (all sources)	**1 (0.9)**	**2 (1.7)**	**-0.9**	**(-14.1, 12.4)**
Bradycardia from AE database[a]	1 (0.9)	0	0.9	(-12.4, 14.1)
Bradycardia from Holter[b]	0	2 (1.7)	-1.7	(-14.9, 11.5)
Bradycardia from vital signs[b]	0	0		
0-4 Hours Postdose				
Any bradycardia event (all sources)	**3 (2.6)**	**5 (4.3)**	**-1.7**	**(-14.9, 11.5)**
Bradycardia from AE database[a]	2 (1.7)	2 (1.7)	0	(-13.2, 13.2)
Bradycardia from Holter[b]	1 (0.9)	4 (3.4)	-2.6	(-15.8, 10.7)
Bradycardia from vital signs[b]	0	1 (0.9)	-0.9	(-14.1, 12.4)

AE: adverse event; AMIO: amiodarone injection; VERI: vernakalant injection.

[a] Includes bradycardia and/or heart rate decreased.

[b] Bradycardia from Holter and vital signs was defined as a heart rate <40 bpm.

Source: Appendix Table 14.7.1.2, 14.7.1.3, and 14.7.1.4

The incidence of bradycardia events within 4 hours postdose was low overall and similar between the two treatment groups.

There were no events of bradycardia that led to discontinuation of study drug. There was one event of bradycardia that was reported as an SAE within 24 hours postdose, occurring in subject 305-1505-005 (amiodarone group), an 80-year-old white female with a history of hypertension and AF. The subject received both infusions of amiodarone and was electrically cardioverted to sinus rhythm on Day 1. An SAE of sinus bradycardia (with an HR of 48-55 bpm) began on Day 2 (19 hours after the start of the first infusion of study drug), resulting in prolonged hospitalization. The subject had AEs of diarrhea, dizziness, and disorientation that started that same day, and an AE of AF recurrence on the following day. Due to the subject's age and condition, the investigator decided to implant a pacemaker. The sinus bradycardia resolved on Day 4 and was assessed by the investigator as being of moderate severity and not related to study drug.

A narrative with further details for this subject is provided in Appendix 16.4.2.

12.3.4.3 Ventricular Arrhythmia

Any ventricular arrhythmia events (Holter events or those identified by investigators as AEs) were over-read by an independent VEC blinded to the treatment group. Ventricular arrhythmia events occurring within 0-2, 2-4, and 0-4 hours postdose, with the percent risk difference (vernakalant minus amiodarone), are presented for the safety set in Table 28.

Table 28. Incidence of Ventricular Arrhythmia Events from Multiple Data Sources[a], based on Adjudication by the Ventricular Events Committee (Safety Set)

Postdose Time Period Event	Number (%) of Subjects Vernakalant (N=116)		Amiodarone (N=116)		Percent Risk Difference	(95% CI)
0-2 Hours Postdose						
Any ventricular arrhythmia event	**1**	**(0.9)**	**1**	**(0.9)**	**0**	**(-13.2, 13.2)**
Any torsades de pointes	0		0			
Any ventricular fibrillation	0		0			
Any ventricular tachycardia[b]	1	(0.9)	1	(0.9)	0	(-13.2, 13.2)
Unsustained monomorphic	1	(0.9)	1	(0.9)	0	(-13.2, 13.2)
Sustained monomorphic	0		0			
Unsustained polymorphic	0		0			
Sustained polymorphic	0		0			
2-4 Hours Postdose						
Any ventricular arrhythmia event	**1**	**(0.9)**	**0**		**0.9**	**(-12.4, 14.1)**
Any torsades de pointes	0		0			
Any ventricular fibrillation	0		0			
Any ventricular tachycardia[b]	1	(0.9)	0		0.9	(-12.4, 14.1)
Unsustained monomorphic	1	(0.9)	0		0.9	(-12.4, 14.1)
Sustained monomorphic	0		0			
Unsustained polymorphic	0		0			
Sustained polymorphic	0		0			
0-4 Hours Postdose						
Any ventricular arrhythmia event	**2**	**(1.7)**	**1**	**(0.9)**	**0.9**	**(-12.4, 14.1)**
Any torsades de pointes	0		0			
Any ventricular fibrillation	0		0			
Any ventricular tachycardia[b]	2	(1.7)	1	(0.9)	0.9	(-12.4, 14.1)
Unsustained monomorphic	2	(1.7)	1	(0.9)	0.9	(-12.4, 14.1)
Sustained monomorphic	0		0			
Unsustained polymorphic	0		0			
Sustained polymorphic	0		0			

[a] Data sources include AEs submitted by the investigator and events identified on the Holter monitor (as defined below in footnote 'b').

[b] Ventricular tachycardia was defined as ≥3 consecutive wide complex beats with a heart rate of >100 bpm.

Source: Appendix Table 14.7.2.2, 14.7.2.3, and 14.7.2.4

Two vernakalant subjects and one amiodarone subject had ventricular arrhythmia events within 4 hours postdose. All of these were unsustained monomorphic VT detected from the Holter device (4-9 beats, lasting 2-3 seconds), with the exception of one event from the AE database in the vernakalant group (Appendix 16.2.11.3).

There were two events of ventricular arrhythmia that were reported as an SAE within 24 hours postdose and which also led to discontinuation of study drug.

One of the ventricular arrhythmia events occurred in subject 305-1703-001 in the vernakalant group. The subject was a 56-year-old white male with a history of hypertension, ischemic heart disease, dyslipidemia, and NYHA Class II heart failure, who received one infusion of vernakalant. An SAE of ventricular tachycardia began 10 minutes after the start of the first

infusion, and resolved spontaneously approximately 3 minutes later. The Holter tracing at the time of the SAE of VT was assessed by the VEC as aberrant conduction; however, two short (4 and 9 beat) runs of unsustained monomorphic VT were identified on the Holter by the VEC approximately one hour later. The SAE of VT was assessed by the investigator as being of moderate severity and probably related to study drug, and study drug was permanently discontinued due to this SAE. Later that same evening the subject was electrically cardioverted to sinus rhythm; however, the following day the subject had an AE of AF recurrence. Electrical cardioversion was performed again and the subject was discharged in sinus rhythm.

The other ventricular arrhythmia event (not included in Table 28) occurred in subject 305-1614-005 in the amiodarone group. The subject was a 48-year-old white male with no significant medical history other than AF. An SAE of cardiac arrest began 37 minutes after the start of the first infusion of amiodarone. The first 60-minute infusion of amiodarone was permanently discontinued after 42 minutes when sudden bradycardia and dizziness were observed. Asystole with a loss of consciousness followed within one minute, after which cardiac massage was performed and atropine was administered. This was then followed by AF with tachycardia. Complete resolution of the symptoms occurred after approximately 15 minutes. The SAE of cardiac arrest was assessed by the investigator as being severe, life-threatening, and probably related to study drug. The VEC confirmed bradycardia and asystole on review of the subject's Holter tracing.

Narratives with further details on the events of ventricular tachycardia and cardiac arrest are provided in Appendix 16.4.2.

12.3.4.4 Atrial Flutter

Atrial flutter events occurring within 0-2, 2-4, and 0-4 hours postdose, with the percent risk difference (vernakalant minus amiodarone), are presented for the safety set in Table 29.

Table 29. Incidence of Atrial Flutter Events from Multiple Data Sources (Safety Set)

Postdose Time Period Event	Number (%) of Subjects Vernakalant (N=116)		Number (%) of Subjects Amiodarone (N=116)		Percent Risk Difference	(95% CI)
0-2 Hours Postdose						
Any atrial flutter event (all sources)	**10**	**(8.6)**	**1**	**(0.9)**	**7.8**	**(-5.5, 20.8)**
Atrial flutter from AE database	2	(1.7)	0		1.7	(-11.5, 14.9)
Atrial flutter from Holter	3	(2.6)	1	(0.9)	1.7	(-11.5, 14.9)
Atrial flutter from Holter extract	8	(6.9)	0		6.9	(-6.4, 20.0)
2-4 Hours Postdose						
Any atrial flutter event (all sources)	**5**	**(4.3)**	**0**		**4.3**	**(-9.0, 17.5)**
Atrial flutter from AE database	0		0			
Atrial flutter from Holter	1	(0.9)	0		0.9	(-12.4, 14.1)
Atrial flutter from Holter extract	5	(4.3)	0		4.3	(-9.0, 17.5)
0-4 Hours Postdose						
Any atrial flutter event (all sources)	**10**	**(8.6)**	**1**	**(0.9)**	**7.8**	**(-5.5, 20.8)**
Atrial flutter from AE database	2	(1.7)	0		1.7	(-11.5, 14.9)
Atrial flutter from Holter	3	(2.6)	1	(0.9)	1.7	(-11.5, 14.9)
Atrial flutter from Holter extract	9	(7.8)	0		7.8	(-5.5, 20.8)

Source: Appendix Table 14.7.3.2, 14.7.3.3, and 14.7.3.4

There was a higher incidence of AFL in the vernakalant group (8.6%) compared to the amiodarone group (0.9%) within 4 hours postdose. After 4 hours, there were two AEs of AFL in the amiodarone group and no additional AEs in the vernakalant group. Three of the ten vernakalant subjects who developed AFL converted to SR within 90 minutes postdose. None of the subjects who developed AFL had 1:1 atrioventricular conduction during the AFL episodes (Appendix 16.2.11.5).

There were no events of atrial flutter reported as an SAE within 24 hours postdose or that led to discontinuation of study drug.

12.4 ECG and Holter Variables and Electrical Cardioversion

12.4.1 ECG and Holter Variables

All ECG interval analyses are based on data collected from the 12-lead Holter and use the average of three 10-second strips.

Summary tables of continuous ECG parameters can be found in Appendix Table 14.6.1.1 to 14.6.3, and individual listings of 12-lead ECG and Holter data can be found in Appendix 16.2.10.2 and 16.2.11.2, respectively.

12.4.1.1 Heart Rate

A summary of the mean heart rate (based on ECG interval data) from 0 to 4 hours postdose, along with the mean change from baseline, is presented for the safety set in Table 30. A box plot of the raw HR data over time for subjects in AF and subjects in SR is presented in Figure 5.

Table 30. Summary of Mean Heart Rate (bpm) and Mean Change from Baseline (Safety Set)

	Treatment Group							
	Vernakalant				Amiodarone			
Time Point[a]	N	Mean Heart Rate (SD)	Change from Baseline[b]	Change from Baseline[c]	N	Mean Heart Rate (SD)	Change from Baseline[b]	Change from Baseline[c]
Baseline	98	108.4 (24.57)			106	103.1 (24.62)		
10 minutes	93	95.6 (22.50)	-14.3 (25.52)	-3.6 (1.33)	99	98.9 (23.94)	-4.4 (14.67)	-5.6 (1.24)
25 minutes	92	90.1 (22.93)	-19.5 (24.71)	-4.3 (1.36)	100	89.7 (20.48)	-13.3 (13.50)	-13.9 (1.24)
35 minutes	91	87.7 (21.42)	-21.9 (25.03)	-5.1 (1.38)	98	87.2 (18.75)	-16.6 (14.67)	-16.6 (1.25)
60 minutes	92	87.9 (23.65)	-21.4 (28.00)	-3.6 (1.39)	99	83.6 (18.21)	-19.4 (15.38)	-19.3 (1.24)
90 minutes	93	87.1 (24.84)	-22.3 (26.07)	-3.6 (1.41)	99	83.8 (18.64)	-19.7 (16.31)	-19.1 (1.24)
120 minutes	92	88.6 (24.76)	-21.2 (26.47)	-2.0 (1.44)	99	84.8 (19.93)	-19.2 (15.81)	-17.6 (1.24)
240 minutes	77	83.5 (23.17)	-27.4 (28.64)	-2.0 (1.76)	83	77.2 (22.57)	-26.1 (26.70)	-10.9 (1.40)

ECG intervals were extracted from Holter device data.

[a] All time points were on Day 1.

[b] Raw change from baseline; mean (SD).

[c] Modeled pure drug effect change from baseline, removing the effect of conversion on HR; LS mean (SE).

Source: Appendix Table 14.6.1.1 and 14.6.1.2

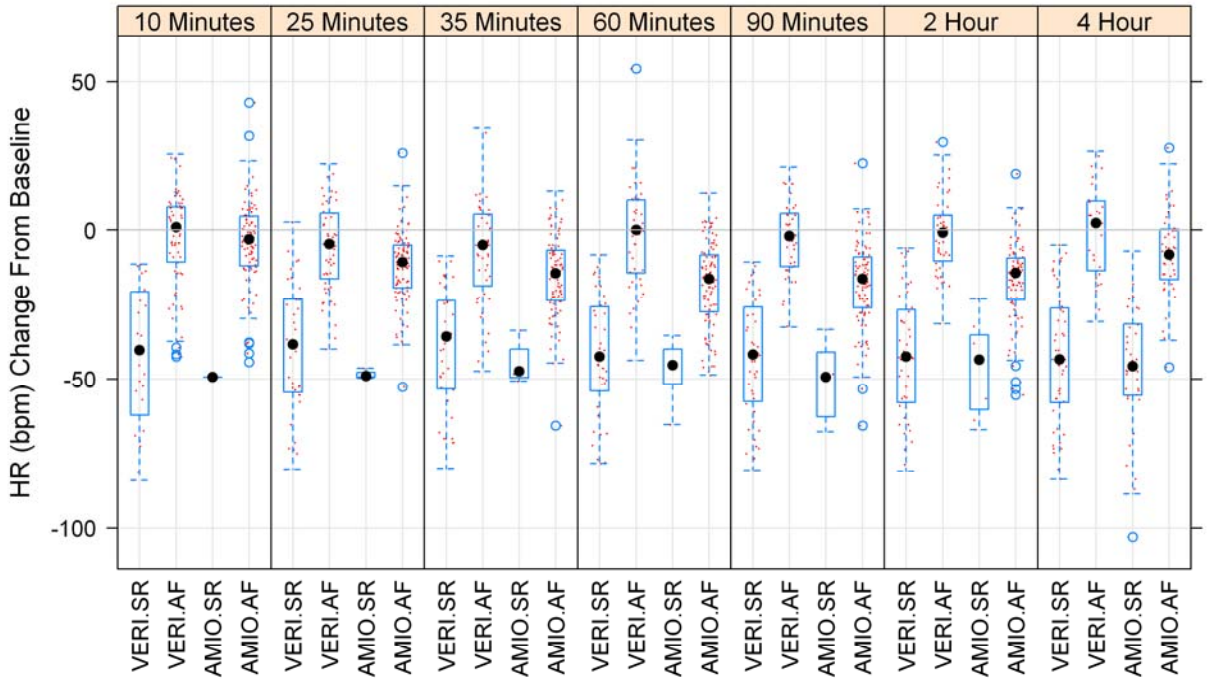


Figure 5. Mean Heart Rate Over Time for Subjects in AF and for Subjects in SR (Safety Set)

The mean heart rate at baseline was similar in the vernakalant group (108.4 bpm) and the amiodarone group (103.1 bpm). The mean heart rate decreased over time in both treatment groups; at 60 minutes postdose the heart rate was reduced by 21.4 and 19.4 bpm in the vernakalant and amiodarone groups, respectively. In the vernakalant group, a large part of the reduction in heart rate over time was due to conversion of AF to SR. Table 30 also shows the modeled change from baseline of the pure drug effect (i.e., removing the effects of conversion) for each treatment group. At 60 minutes postdose, in subjects remaining in AF the heart rate was reduced on average by 19.3 bpm in the amiodarone group, compared to 3.6 bpm in the vernakalant group. As expected, amiodarone showed a reduction in heart rate independent of conversion to SR (Figure 5).

There were no subjects in either treatment group who had a heart rate <40 bpm at any postdose time point based on ECG interval data (Appendix Table 14.6.2).

12.4.1.2 QRS Interval

A summary of the mean QRS interval from 0 to 4 hours postdose, along with the mean change from baseline, is presented for the safety set in Table 31.

Table 31. Summary of Mean QRS Interval (msec) and Mean Change from Baseline (Safety Set)

	Treatment Group					
	Vernakalant			Amiodarone		
Time Point[a]	N	Mean QRS (SD)	Change from Baseline[b]	N	Mean QRS (SD)	Change from Baseline[b]
Baseline	98	101.2 (10.98)		106	100.3 (11.05)	
10 minutes	93	107.4 (14.37)	5.9 (7.33)	99	101.0 (11.66)	0.9 (4.52)
25 minutes	92	107.5 (13.34)	6.0 (7.58)	100	101.7 (12.07)	1.5 (4.99)
35 minutes	91	108.7 (14.20)	7.4 (9.04)	98	102.9 (12.28)	2.7 (4.84)
60 minutes	92	107.1 (13.96)	5.7 (9.31)	99	102.5 (12.30)	2.3 (4.68)
90 minutes	93	105.9 (14.22)	4.5 (9.76)	99	102.6 (12.35)	2.4 (5.06)
120 minutes	92	105.5 (13.73)	4.1 (10.18)	99	102.3 (12.26)	2.2 (4.51)
240 minutes	77	105.4 (14.55)	4.0 (11.05)	83	103.0 (13.17)	1.9 (5.84)

ECG intervals were extracted from Holter device data.

[a] All time points were on Day 1.

[b] Raw change from baseline; mean (SD).

Source: Appendix Table 14.6.1.1

At baseline, the mean QRS duration was similar in vernakalant subjects (101.2 msec) and amiodarone subjects (100.3 msec). Vernakalant showed maximum mean increases of 7.4 msec, coinciding with the end of the second infusion, then decreasing over time. Amiodarone showed consistent increases of approximately 1-3 msec over time.

Shifts in QRS duration from $\leq$140 msec to >140 msec at any postdose time point occurred in 4 vernakalant subjects and 4 amiodarone subjects. The majority of these subjects tended to stay above 140 msec for the duration of the study. There were no subjects in either treatment group who had a shift in QRS duration to >180 msec at any time point (Appendix Table 14.6.2).

12.4.1.3 QTcB and QTcF Intervals

A summary of the mean QTcB and QTcF intervals from 0 to 4 hours postdose, along with the mean change from baseline, is presented for the safety set in Table 32.

Table 32. Summary of Mean QTcB and QTcF Intervals and Mean Change from Baseline (Safety Set)

	Treatment Group							
	Vernakalant				Amiodarone			
Time Point[a]	N	Mean (SD)	Change from Baseline[b]	Change from Baseline[c]	N	Mean (SD)	Change from Baseline[b]	Change from Baseline[c]
	QTcB Interval (msec)							
Baseline	98	434.1 (28.91)			106	427.5 (29.38)		
10 minutes	93	451.0 (34.42)	15.6 (30.61)	24.9 (2.30)	99	430.1 (29.45)	3.2 (22.49)	2.3 (2.15)
25 minutes	92	440.3 (35.45)	5.0 (29.55)	17.9 (2.36)	100	427.7 (25.83)	1.1 (20.60)	0.7 (2.14)
35 minutes	91	437.8 (37.43)	3.8 (30.67)	18.1 (2.40)	98	427.3 (27.43)	0.0 (21.20)	0.2 (2.16)
60 minutes	92	433.9 (39.01)	-0.4 (31.86)	13.8 (2.41)	99	428.6 (30.60)	1.3 (23.30)	1.7 (2.15)
90 minutes	93	431.3 (34.62)	-3.4 (28.20)	10.7 (2.44)	99	429.9 (28.76)	3.0 (21.72)	3.6 (2.15)
120 minutes	92	431.9 (32.31)	-3.0 (25.84)	10.6 (2.49)	99	431.2 (28.67)	3.4 (20.44)	5.4 (2.15)
240 minutes	77	430.9 (31.45)	-4.3 (24.59)	9.6 (3.02)	83	430.2 (31.50)	1.5 (25.56)	14.0 (2.42)
	QTcF Interval (msec)							
Baseline	98	395.1 (24.37)			106	392.4 (24.73)		
10 minutes	93	419.0 (26.40)	23.7 (18.51)	24.1 (1.79)	99	397.6 (24.47)	5.9 (14.62)	5.6 (1.67)
25 minutes	92	413.2 (26.67)	17.7 (18.62)	17.9 (1.83)	100	401.7 (22.60)	10.0 (14.85)	9.7 (1.66)
35 minutes	91	412.7 (28.85)	18.3 (19.23)	18.5 (1.86)	98	402.9 (23.80)	11.3 (14.23)	11.1 (1.67)
60 minutes	92	409.1 (29.67)	14.2 (19.34)	13.5 (1.87)	99	407.0 (25.99)	14.9 (16.42)	14.7 (1.67)
90 minutes	93	407.7 (27.69)	12.6 (18.76)	11.1 (1.89)	99	408.3 (24.31)	16.7 (14.75)	16.3 (1.67)
120 minutes	92	407.0 (26.05)	12.0 (17.05)	9.8 (1.92)	99	408.8 (24.95)	16.9 (15.00)	17.0 (1.67)
240 minutes	77	410.1 (26.78)	15.8 (18.60)	9.3 (2.33)	83	415.0 (27.77)	21.7 (19.73)	20.7 (1.87)

ECG intervals were extracted from Holter device data.

[a] All time points were on Day 1.

[b] Raw change from baseline; mean (SD).

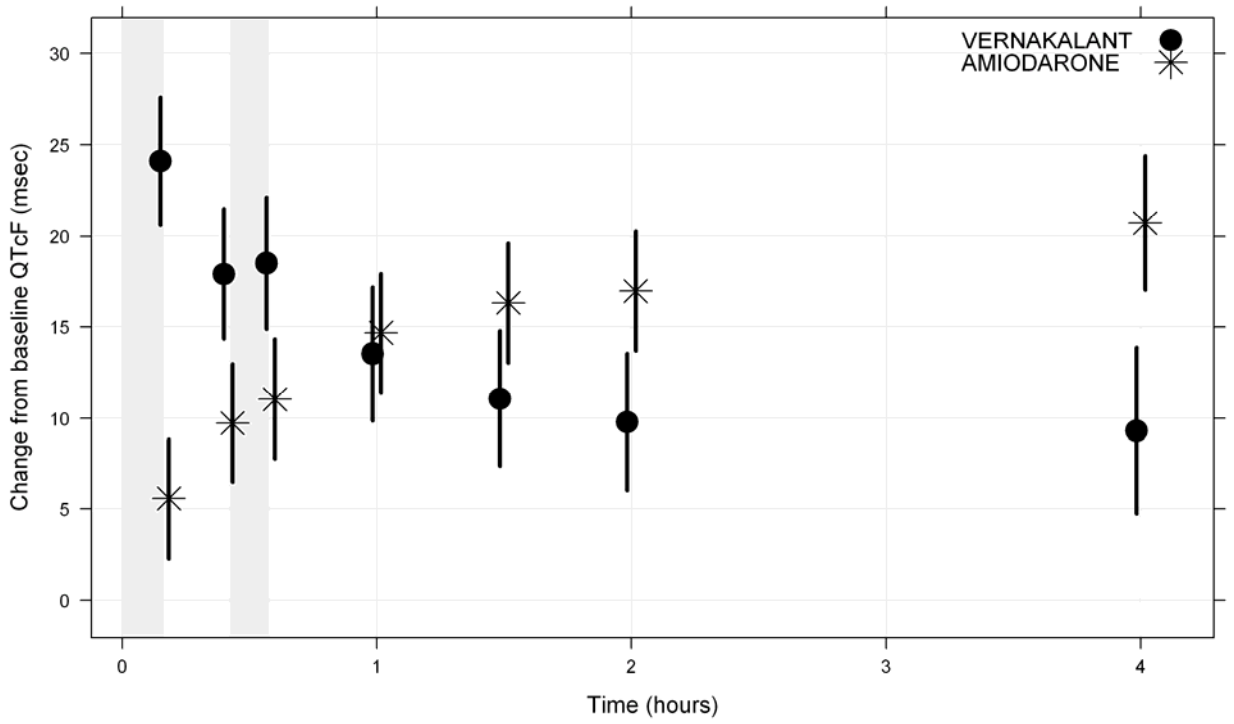
[c] Modeled pure drug effect change from baseline, removing the effect of conversion on HR; LS mean (SE).

Source: Appendix Table 14.6.1.1 and 14.6.1.2

At baseline, the mean QTcB and QTcF intervals were similar in the vernakalant group (434.1 and 395.1 msec, respectively) and the amiodarone group (427.5 and 392.4 msec, respectively). In the vernakalant group, QTcB and QTcF were elevated at 10 minutes postdose,

and then decreased over time. In the amiodarone group, QTcB remained essentially unchanged while QTcF steadily increased over time. The modeled change from baseline in QTcB and QTcF (reflecting the pure drug effects, independent of conversion) was very similar for both parameters. In the vernakalant group, change from baseline in QTc increased rapidly with a peak of 24-25 msec (at minute 10), after which QTc change from baseline fell to approximately 10 msec by 120 minutes postdose. In the amiodarone group, QTcB changes were modest until 240 minutes postdose, at which time they reached 14.0 msec; QTcF changes continued to increase during the course of the study, reaching a peak of 20.7 msec at 240 minutes postdose.

A plot of the modeled change from baseline for QTcF is shown for the safety set in Figure 6.



Based on a mixed effects model with treatment, time, and treatment by time interaction as fixed effects, baseline and time elapsed since conversion as covariates, and subject as a random effect. Estimates were based on subjects who remained in AF and represent the pure drug effect.

Figure 6. Estimated Mean Change from Baseline for QTcF (Safety Set)

A summary of the incidence of shifts in QTcB or QTcF intervals to >450, >480, or >500 msec is presented in Table 33 for the safety set.

Table 33. Summary of Shifts in QTcB or QTcF Intervals to >450, >480, or >500 msec (Safety Set)

	Number (%) of Subjects											
	>450 msec				>480 msec				>500 msec			
Time Point[a]	Vernakalant (N=74)		Amiodarone (N=81)		Vernakalant (N=89)		Amiodarone (N=102)		Vernakalant (N=97)		Amiodarone (N=105)	
	QTcB Interval											
10 minutes	31	(41.9)	8	(9.9)	12	(13.5)	6	(5.9)	5	(5.2)	1	(1.0)
25 minutes	18	(24.3)	4	(4.9)	9	(10.1	3	(2.9)	4	(4.1)	0	
35 minutes	20	(27.0)	8	(9.9)	8	(9.0)	3	(2.9)	7	(7.,2)	1	(1.0)
60 minutes	15	(20.3)	7	(8.6)	7	(7.9)	6	(5.9)	4	(4.1)	3	(2.9)
90 minutes	13	(17.6)	11	(13.6)	2	(2.2)	5	(4.9)	3	(3.1)	1	(1.0)
120 minutes	11	(14.9)	9	(11.1)	3	(3.4)	5	(4.9)	3	(3.1)	2	(1.9)
240 minutes	8	(10.8)	9	(11.1)	2	(2.2)	4	(3.9)	2	(2.1)	0	
	Vernakalant (N=97)		Amiodarone (N=105)		Vernakalant (N=98)		Amiodarone (N=106)		Vernakalant (N=98)		Amiodarone (N=106)	
	QTcF Interval											
10 minutes	11	(11.3)	3	(2.9)	1	(1.0)	0		0		0	
25 minutes	8	(8.2)	3	(2.9)	0		0		0		0	
35 minutes	8	(8.2)	4	(3.8)	0		0		0		0	
60 minutes	8	(8.2)	7	(6.7)	0		2	(1.9)	0		0	
90 minutes	5	(5.2)	5	(4.8)	0		0		0		0	
120 minutes	3	(3.1)	6	(5.7)	0		1	(0.9)	0		0	
240 minutes	6	(6.2)	9	(8.6)	0		2	(1.9)	0		0	

ECG intervals were extracted from Holter device data.

[a] All time points were on Day 1.

Source: Appendix Table 14.6.2

The incidence of shifts in QTcB to >450 and >480 msec was greater in the vernakalant group compared to the amiodarone group through 120 and 60 minutes postdose, respectively. Shifts in QTcB to >500 msec were consistently greater in the vernakalant group compared to the amiodarone group, although only a small number of subjects (≤7 vernakalant subjects and ≤3 amiodarone subjects at any time) had a QTcB interval >500 msec. The incidence of shifts in QTcF to >450 msec was greater in the vernakalant group than in the amiodarone group through 60 minutes postdose; shifts in QTcF to >480 msec were sporadic in both groups. No subjects in either treatment group had a shift in QTcF to >500 msec or a shift in QTcB or QTcF to >550 msec (Appendix Table 14.6.2).

The incidence of shifts for both QTcB and QTcF tended to systematically decrease after the end of the second infusion in the vernakalant group, and the incidence of shifts for QTcF tended to systematically increase through 4 hours postdose in the amiodarone group, largely reflecting the patterns seen in Table 32.

A summary of the incidence of changes in QTcB or QTcF intervals of ≥30 msec and ≥60 msec from baseline is presented in Table 34 for the safety set.

Table 34. Summary of Changes in QTcB or QTcF Intervals of ≥30 and ≥60 msec from Baseline (Safety Set)

Time Point[a]	Number (%) of Subjects			
	Change from Baseline ≥30 msec		Change from Baseline ≥60 msec	
	Vernakalant (N=116)	Amiodarone (N=116)	Vernakalant (N=116)	Amiodarone (N=116)
	QTcB Interval			
10 minutes	32 (27.6)	10 (8.6)	3 (2.6)	0
25 minutes	15 (12.9)	6 (5.2)	6 (5.2)	1 (0.9)
35 minutes	17 (14.7)	8 (6.9)	4 (3.4)	1 (0.9)
60 minutes	16 (13.8)	8 (6.9)	2 (1.7)	2 (1.7)
90 minutes	12 (10.3)	8 (6.9)	1 (0.9)	1 (0.9)
120 minutes	11 (9.5)	6 (5.2)	1 (0.9)	0
240 minutes	5 (4.3)	8 (6.9)	1 (0.9)	2 (1.7)
	QTcF Interval			
10 minutes	38 (32.8)	4 (3.4)	0	0
25 minutes	20 (17.2)	8 (6.9)	3 (2.6)	0
35 minutes	23 (19.8)	8 (6.9)	3 (2.6)	1 (0.9)
60 minutes	15 (12.9)	17 (14.7)	1 (0.9)	2 (1.7)
90 minutes	15 (12.9)	16 (13.8)	1 (0.9)	0
120 minutes	16 (13.8)	19 (16.4)	0	1 (0.9)
240 minutes	18 (15.5)	25 (21.6)	0	3 (2.6)

ECG intervals were extracted from Holter device data.

[a] All time points were on Day 1.

Source: Appendix Table 14.6.3

The incidence of shifts in QTcB and QTcF to ≥30 msec and ≥60 msec mirrors Table 32 and shifts to >450 and >480 msec illustrated above (Table 33). Vernakalant showed a relatively high incidence of shifts during infusion periods, before decreasing rapidly post-infusion. Amiodarone showed a slowly increasing number of shifts over time, with the incidence tending to be higher after 120 minutes postdose (QTcB) or after 35 minutes postdose (QTcF). Changes in QTcB or QTcF of ≥60 msec were observed in only a small number of subjects (≤6 at any time).

12.4.2 Electrical Cardioversion

12.4.2.1 Incidence and Success of Electrical Cardioversion

A summary of electrical cardioversion for the full analysis set set is provided in Table 35.

Table 35. Summary of Electrical Cardioversion (Full Analysis Set)

Parameter		Number (%) of Subjects	
		Vernakalant (N=116)	Amiodarone (N=116)
Was ECV attempted	Yes	41 (35.3)	68 (58.6)
	No	75 (64.7)	48 (41.4)
If yes, was subject successfully converted?[a]	Yes	38 (92.7)	65 (95.6)
	No	3 (7.3)	3 (4.4)
Was ECV attempted within 24 hours	Yes	35 (30.2)	66 (56.9)
	No	81 (69.8)	50 (43.1)
If yes, was subject successfully converted[a]	Yes	32 (91.4)	63 (95.5)
	No	3 (8.6)	3 (4.5)

ECV: electrical cardioversion.
[a] Percentages are based on the number of attempts.
Source: Appendix Table 14.8.1

Electrical cardioversion was permitted two hours after the start of infusion if the subject was still in AF. Within the first 24 hours, 30.2% of subjects in the vernakalant group and 56.9% of subjects in the amiodarone group underwent electrical cardioversion. The use of general anesthetics was higher in the amiodarone group compared to the vernakalant group (see Section 10.5.3), likely due to the higher rate of electrical cardioversion in the amiodarone group. Electrical cardioversion was successful in 91.4% of subjects in the vernakalant group and 95.5% of subjects in the amiodarone group. The median number of shocks and the median number of joules required for successful cardioversion was approximately the same in both treatment groups (one shock, 175-200 joules) (Appendix Table 14.8.1).

12.4.2.2 Pause Measured After Conversion to Sinus Rhythm

In order to further characterize what happens following conversion to SR, the time to recovery of electrical systole post-conversion (i.e., the interval between the last QRS in AF and the first QRS of sinus rhythm) was assessed in subjects who were successfully converted to SR (Table 36). The heart rate following conversion and the diagnosis of the first QRS complex post-conversion were also summarized.

Table 36. Heart Rate, Time to Recovery of Electrical Activity, and ECG Diagnosis of First QRS Complex Post-Conversion (Full Analysis Set)[a]

	Treatment Group	
	Vernakalant (N=42)	**Amiodarone (N=7)**
Heart Rate[b], bpm	**N=38**	**N=6**
Mean (SD)	70.2 (10.42)	63.2 (13.51)
Median (min, max)	69.5 (50, 91)	63.5 (40, 80)
HR ≥40 bpm, n (%)	38 (90.5)	6 (85.7)
Interval length between last QRS complex in AF and first QRS complex after conversion, seconds	**N=39**	**N=6**
Mean (SD)	1.69 (1.680)	1.38 (0.453)
Median (min, max)	1.35 (0.7, 10.4)	1.42 (0.7, 2.0)
ECG diagnosis of first QRS complex after conversion, n (%)	**N=42**	**N=7**
Supraventricular QRS conducted from sinus P wave	34 (81.0)	5 (71.4)
Supraventricular QRS conducted from non-sinus P wave	1 (2.4)	0
Junctional QRS complex	3 (7.1)	1 (14.3)
Ventricular QRS complex	1 (2.4)	0
Uninterpretable	3 (7.1)	1 (14.3)

AF: atrial fibrillation; ECG: electrocardiogram; HR: heart rate.

a As determined by the Clinical Events Committee's analysis of the Holter data for subjects who converted within two hours of study drug infusion.

b During the one-minute interval following the first QRS complex after AF converted to SR.

Source: Appendix Table 14.10.1, 14.10.2, and 14.10.3

Subjects who converted to SR within two hours of vernakalant infusion resumed SR after the last QRS in AF at a similar rate to subjects converting to SR on amiodarone. Heart rate following conversion was lower in subjects receiving amiodarone than subjects receiving vernakalant. Vernakalant did not suppress recovery of nodal function following termination of AF; a supraventricular QRS conducted from a sinus P wave was seen in a similar number of subjects converted with vernakalant (81.0%) compared to amiodarone-treated subjects (71.4%).

12.5 Clinical Laboratory Evaluations

12.5.1 Hematology

There were no clinically significant trends over time and no significant differences between treatment groups for any of the hematology lab parameters. Any clinically significant shifts from normal to either low or high were to have been reported as AEs.

Summary and shift tables of hematology laboratory data can be found in Appendix Table 14.4.1.1 and 14.4.1.2, respectively, and individual data listings for hematology parameters can be found in Appendix 16.2.8.1.

12.5.2 Serum Chemistry

There were no clinically significant trends over time and no significant differences between treatment groups for any of the serum chemistry lab parameters. Any clinically significant shifts from normal to either low or high were to have been reported as AEs.

Summary and shift tables of serum chemistry laboratory data can be found in Appendix Table 14.4.2.1 and 14.4.2.2, respectively, and individual data listings for serum chemistry parameters can be found in Appendix 16.2.8.2.

12.5.3 Urinalysis

There were no clinically significant trends over time and no significant differences between treatment groups for any of the urinalysis lab parameters. Any clinically significant shifts from normal to either low or high were to have been reported as AEs.

Summary and shift tables of urinalysis laboratory data can be found in Appendix Table 14.4.3.1 and 14.4.3.2, respectively, and individual data listings for urinalysis parameters can be found in Appendix 16.2.8.3 and 16.2.8.4.

12.6 Vital Signs

A summary of the change in mean systolic blood pressure over time for the safety set is shown in Figure 7.

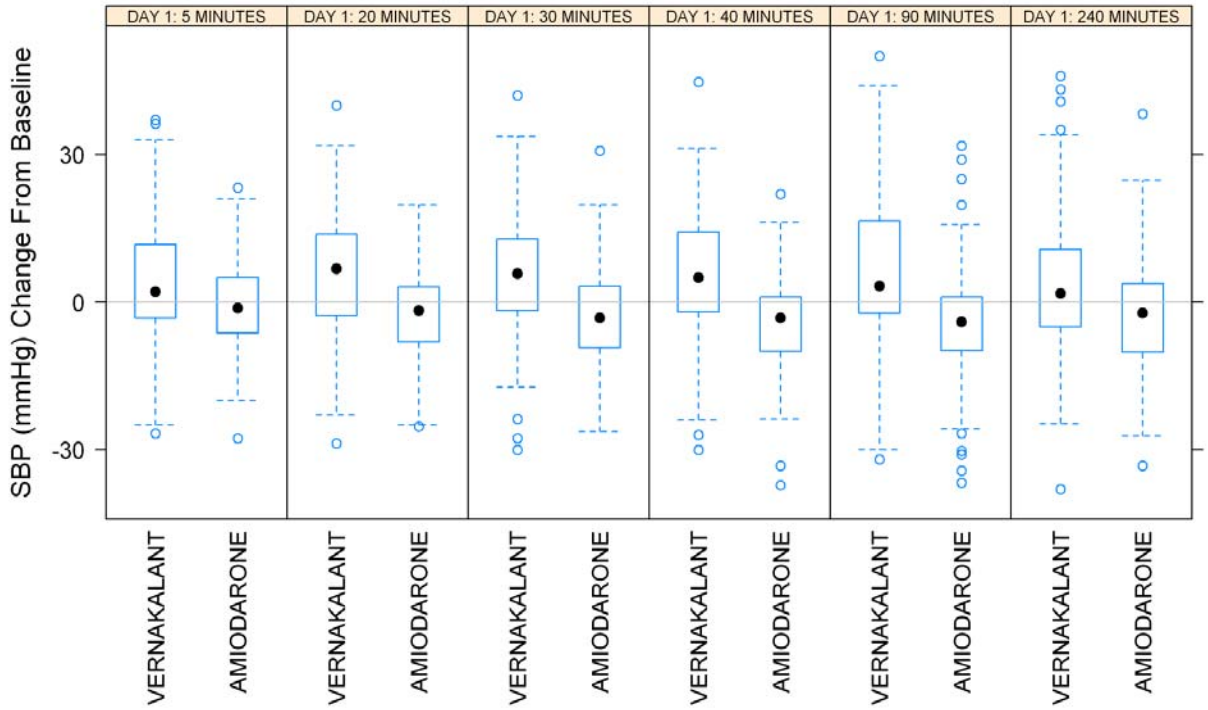


Figure 7. Change in Mean Systolic Blood Pressure Over Time (Safety Set)

The mean baseline values were similar between treatment groups for systolic blood pressure (128.4 and 125.5 mmHg for vernakalant and amiodarone subjects, respectively) and for diastolic blood pressure (79.5 and 78.2 mmHg for vernakalant and amiodarone subjects, respectively).

The greatest mean change from baseline for SBP was approximately 6 mmHg in the vernakalant group and approximately -5 mmHg in the amiodarone group (Appendix Table 14.5.1).

There were two subjects in the amiodarone group who had a shift in SBP to <90 mmHg, and no subjects in the vernakalant group with any such shifts. Subject 305-1606-006 shifted from a mean baseline SBP of 103 mmHg to 88 mmHg at 20 minutes postdose and to 84 mmHg at 40 minutes postdose, which was documented as an AE of blood pressure systolic decreased. Subject 305-1005-004 shifted from a mean baseline SBP of 100 mmHg to 84 mmHg at 240 minutes postdose, which was documented as an AE of blood pressure decreased. Both subjects returned to baseline values by discharge and Day 7, respectively.

Summary and shift tables of vital signs data can be found in Appendix Table 14.5.1 and 14.5.2, respectively, and individual data listings for vital signs can be found in Appendix 16.2.9.

12.7 Physical Examination

A physical examination was performed at screening and at the time of discharge. At the time of discharge, it was noted that there were 5 shifts from normal to abnormal in the vernakalant group and 2 shifts from normal to abnormal in the amiodarone group. Any shifts from normal to abnormal that were considered to be clinically significant were to have been reported as AEs.

A shift table of physical examination findings can be found in Appendix Table 14.9.1 and individual data listings for physical examination results can be found in Appendix 16.2.14.

12.8 Safety Conclusions

- The incidence of treatment-emergent AEs was higher in the vernakalant group than in the amiodarone group. Treatment-emergent AEs that occurred in 3 or more subjects within a treatment group within 24 hours postdose included dysgeusia, cough, dizziness, nausea, atrial fibrillation, sneezing, and hypertension, most of which occurred at a higher incidence in the vernakalant group compared to the amiodarone group. The exception was dizziness, which occurred in 3 subjects in each group. Additional treatment-emergent AEs that occurred in more than one subject in the amiodarone group within 24 hours postdose included insomnia and prolonged activated partial thromboplastin time
- The majority of related treatment-emergent AEs within 24 hours postdose occurred in the vernakalant group, with dysgeusia being the most common. Other related treatment-emergent AEs that occurred in two or more subjects in the vernakalant group were sneezing, cough, bradycardia, nausea, paresthesia, pharyngolaryngeal pain, and throat irritation, most of which were transient and occurred within two hours postdose. In the amiodarone group there were two related treatment-emergent AEs that occurred within 24 hours postdose: cardiac arrest (within 2 hours) and increased blood bilirubin (between 2 to 24 hours).
- The incidence of SAEs (11.2% vernakalant, 8.6% amiodarone) and related SAEs (2.6% vernakalant, 0.9% amiodarone) was low overall. Within 24 hours postdose, most of the SAEs that occurred in both treatment groups were cardiac disorders and none of the SAEs occurred in more than one subject. The SAEs occurring within 24 hours postdose

that were considered by the investigator to be related to study drug included angina pectoris, hypersensitivity, and ventricular tachycardia in the vernakalant group, and cardiac arrest in the amiodarone group. These related SAEs were the only events in the study that led to discontinuation of study drug.

- There was one death in the study, which occurred in the vernakalant group. The death occurred on Day 24 due to COPD and pulmonary embolism, and was not considered to be related to study drug.
- In regards to events of interest, hypotension, bradycardia, and ventricular arrhythmia were rare and occurred at a similar incidence rate between the two treatment groups. Within 24 hours postdose, there was one event of syncope reported as an SAE in the vernakalant group and one event of sinus bradycardia reported as an SAE in the amiodarone group. Additionally, there were two events of ventricular arrhythmia that were reported as an SAE within 24 hours postdose and which also led to discontinuation of study drug: ventricular tachycardia in the vernakalant group and cardiac arrest in the amiodarone group.
- There were no cases of torsades de pointes, ventricular fibrillation, or polymorphic or sustained VT in either treatment group.
- There was a higher incidence of atrial flutter in the vernakalant group (8.6%) compared to the amiodarone group (0.9%) within 4 hours postdose. Three of the ten vernakalant subjects who developed AFL converted to SR within 90 minutes postdose. There were no SAEs of atrial flutter and none of the subjects who developed AFL had 1:1 atrioventricular conduction during the AFL episodes.
- Based on the ECG interval data, there was a decrease in heart rate over time in both treatment groups; at 60 minutes postdose the heart rate was reduced by 21.4 and 19.4 bpm in the vernakalant and amiodarone groups, respectively. In the vernakalant group, the decrease in heart rate was primarily due to conversion to SR; in subjects remaining in AF there was a slight decrease in heart rate of approximately 4 bpm through 240 minutes postdose. Conversely, the decrease in heart rate in the amiodarone group appeared to be independent of conversion to SR.
- The greatest mean change from baseline for SBP was approximately 6 mmHg in the vernakalant group and approximately -5 mmHg in the amiodarone group. There were two subjects in the amiodarone group who had a decrease in SBP to <90 mmHg; no subjects in the vernakalant group had a decrease in SBP to <90 mmHg.
- Maximum mean increases (7.4 msec) in QRS were observed at 35 minutes postdose in the vernakalant group, and decreased over the remainder of the 4-hour period. Amiodarone showed consistent increases of approximately 1-3 msec over time.
- In the vernakalant group, maximum mean increases in QTcB (15.6 msec) and QTcF (23.7 msec) were observed at 10 minutes postdose, and decreased over the remainder of the 4-hour period. In the amiodarone group, QTcB remained relatively unchanged while QTcF progressively increased throughout the 4-hour observation period, with a maximum increase (21.7 msec) observed at 4 hours postdose.

- There were no clinically significant trends over time and no significant differences between treatment groups for any of the laboratory parameters.

13 DISCUSSION AND CONCLUSIONS

This was a phase 3, multicenter, randomized, double-blind, active-controlled, double-dummy study in subjects with symptomatic AF (of 3 to 48 hours duration) who were eligible for cardioversion. The primary objective was to demonstrate the superiority of vernakalant injection over amiodarone injection in the conversion of AF to SR within 90 minutes after the start of drug administration, and the secondary objective was to assess the safety of vernakalant compared to amiodarone.

This study recruited a broad population of subjects with recent onset AF, including older subjects (>75 years of age) and those with structural heart disease. The two treatment groups were generally well balanced in terms of demographic and baseline characteristics. A total of 254 subjects were enrolled in the study, with 128 subjects in the vernakalant group and 126 subjects in the amiodarone group. The majority of randomized subjects (116 in each treatment group) received at least one dose of study medication, with the exception of 12 subjects in the vernakalant group and 10 subjects in the amiodarone group. Nineteen of these 22 subjects (10 in the vernakalant group and 9 in the amiodarone group) spontaneously converted to SR prior to receiving study drug. Of the subjects who were treated, 6 vernakalant subjects and 1 amiodarone subject discontinued the study, mostly due to AEs. A total of 225 subjects completed the study through the Day 30 follow-up telephone call.

Vernakalant met all primary and secondary efficacy endpoints in this study. Treatment with vernakalant resulted in a statistically significantly greater proportion of subjects converting from AF to SR within the first 90 minutes compared to amiodarone (51.7% vernakalant vs 5.2% amiodarone, $P<0.0001$). Treatment with vernakalant also resulted in a faster conversion rate from AF to SR within 90 minutes, a greater proportion of subjects reporting no AF symptoms at 90 minutes, and a greater improvement in a subject's perception of their state of health at hour 2 (as measured by the EQ-5D quality of life assessment VAS), which was associated with the higher rate of conversion of AF to SR in the vernakalant group.

Vernakalant was safe and well tolerated when administered to subjects with recent onset AF. The SAEs occurring within 24 hours postdose that were considered by the investigator to be related to study drug included angina pectoris, hypersensitivity, and ventricular tachycardia in the vernakalant group, and cardiac arrest in the amiodarone group. These related SAEs were the only events in the study that led to discontinuation of study drug. There was one death in the study, which occurred in the vernakalant group on Day 24 due to COPD and pulmonary embolism, and was assessed as being not related to study drug.

Hypotension, bradycardia, and ventricular arrhythmia were rare and occurred at a similar incidence rate between the two treatment groups. There were no cases of TdP, ventricular fibrillation, or polymorphic or sustained VT in this study. There was a higher incidence of AFL in the vernakalant group compared to the amiodarone group within 4 hours postdose. Three of the ten vernakalant subjects who developed AFL converted to SR within 90 minutes

postdose. None of the subjects who developed atrial flutter had 1:1 atrioventricular conduction during the AFL episodes.

In the vernakalant group, increases in QRS, QTcB, and QTcF occurred during the infusion period and were transient. Amiodarone had little effect on QRS and QTcB, while QTcF progressively increased throughout the 4-hour observation period. Decreases in heart rate in the vernakalant group were associated with conversion to SR, whereas amiodarone showed substantial decreases in heart rate that appeared to be independent of conversion effects.

In summary, the data from this phase 3 study demonstrated that vernakalant injection had superior efficacy when compared directly to amiodarone injection for the rapid conversion of recent onset AF to SR within 90 minutes. Furthermore, both vernakalant injection and amiodarone injection were safe and well tolerated in this study, although generally there was a higher incidence of AEs in the vernakalant group.

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