A Prospective Observational Registry Study to Characterise Normal Conditions of Use, Dosing and Safety Following Administration of Vernakalant IV Sterile Concentrate

Post-Authorisation Safety Study (PASS)

Study Protocol Incorporating Amendments 1 and 2

Sponsor: Cardiome Pharma Corp.

Sponsor Protocol Identifier: 6621 049-00

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INVESTIGATOR SIGNATURE PAGE

STUDY TITLE:

A Prospective Observational Registry Study to Characterise Normal Conditions of Use, Dosing, and Safety Following Administration of Vernakalant IV

Sponsor Protocol Identifier: 6621-049-00

Dated: 3 August 2016

I have read and understand the protocol and agree that it contains the ethical, legal, and scientific information necessary to participate in this Study. I will personally oversee conduct of the Study as described herein and in the participating site agreement.

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences (SAEs) as defined in the SAFETY MEASUREMENTS section of this protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

I will provide copies of this protocol as needed to all physicians, nurses, and other healthcare professional personnel responsible to me who will participate in the Study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the conduct of the Study. I am aware that this protocol will need to be approved by an appropriate Ethics Committee prior to any patients being enrolled and that I am responsible for verifying whether

that requirement is met. I agree to adhere to the attached protocol, to the ethical principles that have their origin in the Declaration of Helsinki and to applicable national and regional laws. If requested to provide copies of medical information for the purpose of verification of submitted information, I will comply.

INVESTIGATOR SIGNATURE	Date
Investigator Name	Institution Name

1 ABBREVIATIONS

AE	Adverse experience
AF	Atrial Fibrillation
BP	Blood pressure
bpm	Beats per minute
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
EC	Ethics Committee
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
HCP	Health Care Provider
HLT	High Level Term
HOI	Health Outcome of Interest
ICH	International Committee on Harmonisation
IEC	Independent Ethics Committee
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NSAE	Non-serious adverse experience
NYHA	New York Heart Association
PASS	Post-Authorisation Safety Study
PSUR	Periodic Safety Update Report
PT	Preferred Term
SADR	Serious Adverse Reaction
SAE	Serious Adverse experience
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SRC	Safety Review Committee
SOC	System Organ Class
VT	Ventricular tachycardia

2 SYNOPSIS

Study Title: A Prospective Observational Registry Study to Characterise Normal Conditions of Use, Dosing and Safety Following Administration of Vernakalant IV			
Condition/Disease: Atrial fibrillation			
Number of Patients	2000	**Duration of Patient Participation**	24 hours
Number of Sites (approx.)	45	**Duration of Study**	3rd Quarter, 2011 – 1st Quarter 2018 (approx.)

Rationale: Vernakalant IV, an atrial-selective ion channel blocker, has a differing mechanism of action that mitigates some of the main safety concerns of other anti-arrhythmic treatments. Vernakalant IV (Brinavess™) has been recently approved by the European Commission for rapid cardioversion of recent onset atrial fibrillation (<=3 days duration for post-cardiac surgery and <=7 days duration for non-surgical patients). In view of the recognised limitations of spontaneous reporting, the Sponsor will conduct a post-authorisation safety study (PASS) of vernakalant IV in order to collect information about normal conditions of use and appropriate dosing, and to quantify possible medically significant risks associated with the use of vernakalant IV in real-world clinical practice.

Study Design: Observational, prospective PASS (no study intervention or procedures) of patients administered vernakalant IV within a network of clinical sites across EU member countries. Countries currently included are Austria, Denmark, Germany, Spain, and Sweden. Finland, and other EU and non-EU countries may be included but selection is conditional on a number of factors, including, but not limited to, the actual date of product launch in each country and rate of market uptake of vernakalant IV.

Objectives:

The primary objectives of the study are to:

1. Estimate the incidence of the following medically significant health outcomes of interest (HOIs) reported during treatment and during the first 24 hours after last infusion of vernakalant IV or until discharge/end of medical encounter, whichever occurs earlier.
   - **Significant hypotension** defined as: symptomatic hypotension with systolic BP <90 mmHg, requiring treatment with vasopressors
   - **Significant ventricular arrhythmia** defined as:
     - Sustained ventricular tachycardia (VT) with a ventricular heart rate > 120 beats per minute with duration > 30 seconds or VT that required intervention with either electrical shock or anti-arrhythmic drugs, or
     - Torsade de Pointes with a duration of >10 seconds, or
     - Ventricular fibrillation of any duration
   - **Significant atrial flutter** defined as: atrial flutter with 1:1 atrioventricular conduction of >10 seconds duration and a ventricular rate of >200 bpm
   - **Significant bradycardia** defined as: bradycardia requiring electrical pacing (temporary or permanent) or any other serious adverse event reports involving bradycardia

2. In order to investigate the potential risk of overdose and medication error, describe vernakalant IV administration/dosing by summarising patient body weight, total dose with each intravenous (IV) infusion, and length of time for each IV infusion.

3. To evaluate the effectiveness of the risk minimisation activities by*:*

- Describing the appropriateness of selection of patients for treatment with vernakalant IV, monitoring of patients during and after vernakalant IV administration, and use of anti-arrhythmics before and after vernakalant IV, as consistent with the label and risk minimization activities (Pre-Infusion Checklist and healthcare provider (HCP) educational card)
- Monitoring for the occurrence and incidence of serious adverse events (SAEs) and HOIs to review with the EU Regulatory Agency with respect to risk minimization activities

The secondary objective of the study are to:

1. Summarise the count and rate of all serious adverse experiences (SAEs) for HOIs that may not meet the definitions of medically significant HOIs as defined above, as well as all other SAEs reported during treatment and during the first 24 hours after the last infusion of vernakalant IV or until discharge/end of medical encounter, whichever occurs earlier.
2. Characterise patients administered vernakalant IV in terms of patient demographics, medical history, and presenting conditions. Specific conditions to be summarised include:
    - Heart failure, New York Heart Association (NYHA) class
    - Prolonged QT, severe bradycardia, sinus node dysfunction, second or third degree heart block, clinically meaningful valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis
    - History of hyperthyroidism
    - Severe aortic stenosis, Low systolic blood pressure (BP)
    - Recent acute coronary syndrome (including myocardial infarction [MI])
    - Presence of pacemaker/year of implantation
    - Hepatic impairment
3. Document the administration of concomitant treatment modalities to restore or maintain sinus rhythm during the hospitalisation/medical encounter (e.g., oral or IV anti-arrhythmics, electrical cardioversion, ablation, Maze procedure).
4. Describe the rate of successful cardioversion to sinus rhythm for at least one minute within 90 minutes of start of first vernakalant IV administration and time (in hours) from vernakalant infusion until discharge/end of medical encounter.

Treatment:

The study will not provide or recommend any treatment. All direction for medical treatment and medication usage is solely at the discretion of the physician in accordance with their usual practice.

Inclusion Criteria:

- Patients will be treated with vernakalant IV, independently of this study
- Subjects and/or legal guardians willing to provide informed consent and/or informed assent according to local regulations

Exclusion Criteria:

- Enrolment in an investigational drug or device clinical trial in the 30 days prior to study enrolment. Participation in another non-interventional drug or device study or registry is permitted.

Statistical Analysis:
Descriptive analyses including the frequency and measures of central tendency, range, and dispersion of the clinical characteristics of the population administered vernakalant IV, as well as details of administration and dosing will be conducted. Frequencies and cumulative incidence of HOIs and other SAEs following vernakalant IV administration will be reported for the 24-hour follow-up period, or until end of medical encounter, whichever occurs earlier. Ninety-five percent confidence intervals for the cumulative incidence measures for HOIs will be computed. Descriptive listings of patients with HOIs with relevant medical history, concomitant medications, and concurrent illnesses will also be generated.

Ethical Considerations:
Ethics Committee approval of study documents will be obtained, in accordance with the requirements in each country and at each site. The study will be conducted in compliance with local and/or national regulations, the European Union (EU) Directive on Data Protection, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

3 BACKGROUND INFORMATION AND RATIONALE

Atrial fibrillation (AF) contributes a considerable burden of disease, affecting 4.5 million people in the European Union (EU) [Ref. 5.4: 72, 431] and 2.3 million in North America. [Ref. 5.4: 431,432] With an overall prevalence of 6% in Europe, [Ref. 5.4: 72, 431]an even higher prevalence of AF can be found in the elderly, which will contribute to even greater disease burden as the population ages. Causes of AF include underlying disease (e.g., myocardial infarction, pulmonary embolism), cardiac or thoracic surgery, heart disease, or familial cause, with the primary associated risk factors being obesity (elevated body mass index). [Ref. 5.4: 345]Defined by the American College of Cardiology/American Heart Association/European Society of Cardiology practice guidelines as a "supraventricular tachyarrhythmia characterised by uncoordinated atrial activation with consequent deterioration of atrial mechanical function," AF can present as paroxysmal (self-terminating within 7 days, and usually less than 24 hours), persistent (lasts greater than 7 days), or permanent (refractory arrhythmia with failed cardioversion or treatment considered inappropriate). [Ref. 5.4: 345]Considered one of the most common arrhythmias, AF results in cardiac rhythm disturbance hospitalisations, stroke risk, [Ref. 5.4: 62]reduced quality of life, [Ref. 5.4: 434]increase in CHF exacerbations and is associated with a tremendous cost burden. [Ref. 5.4: 430, 433]Ten to -15% of congestive heart failure (CHF) patients present with AF, [Ref. 5.4: 445]and co-morbidities associated with AF pose increased morbidity and mortality for this patient population.

Treatment algorithms are based on a combination of patient factors (e.g., symptoms, haemodynamics compromise, co-morbidities) and arrhythmia characteristics (e.g., first episode of temporal pattern) which contribute to clinical decision-making between two basic strategies: heart rate control or rhythm control. [Ref. 5.4: 345, 431] Several clinical trials have been performed to address the relative merits of rate control versus rhythm control, [Ref. 5.4: 345] including the AFFIRM trial which demonstrated no statistically significant difference in outcomes between rate and rhythm control. [Ref. 5.4: 150] However, severely symptomatic patients and those in whom adequate rate control cannot be achieved may require rhythm control. [Ref. 5.4: 345] Rhythm control options to restore sinus rhythm include cardioversion with anti-arrhythmic drugs (e.g., dofetilide, ibutilide, propafenone, amiodarone) or electrical cardioversion. The primary safety concern with any cardioversion is the risk of thromboembolic complications. However, with currently marketed anti-arrhythmic treatment, additional safety concerns involve ventricular tachycardia (VT), especially Torsade de Pointes. Additional potential risks with various anti-arrhythmic therapies include QT prolongation, bradycardia, and hypotension. Electrical cardioversion, while considered effective, has its own safety concerns

unique to this technique, including skin burns, complications of sedation and malfunctions of a pacemaker or internal defibrillator. [Ref. 5.4: 104]
The potential adverse events of both electrical and pharmacological cardioversion and the limited efficacy of pharmacological cardioversion have warranted the development of novel therapeutic options. [Ref. 5.4: 371, 441]

Vernakalant, a medicine that acts preferentially in the atria, has a novel and unique mechanism of action. Controlled clinical trials [Ref. 5.4: 441] of vernakalant IV have been conducted to define the efficacy and safety profile of vernakalant IV. Two phase III randomised trials demonstrated that the conversion rate of recent onset (≤7 days) AF to sinus rhythm was significantly better for Vernakalant compared to placebo (51.1% versus 3.8%, respectively; p<0.0001) with an open-label trial demonstrating a conversion rate of 50.9%. [Ref. 5.4: 442] Another phase III randomised trial of post-cardiac surgery patients (CAD and/or VHD) demonstrated that Vernakalant was significantly better compared to placebo in the conversion of recent onset (≤3 days) AF to sinus rhythm (47% versus 14%, respectively; p<0.001). [Ref. 5.4: 210] In patients who converted to sinus rhythm, the median time to conversion was 11-13 minutes in those studies.

Clinically significant adverse reactions occurred infrequently. Clinically significant adverse reactions observed in the clinical program and described in detail in the Summary of Product Characteristics (SmPC) included: hypotension, ventricular arrhythmia, atrial flutter and bradycardia. Incidence rates for these adverse reactions are presented below, using pooled data from the placebo-controlled phase 2 and phase 3 clinical trials (773 patients received vernakalant, 335 received placebo). Because vernakalant IV is rapidly cleared from the circulation, adverse events from the start of infusion through the first 2 hours after infusion are considered, as these occur during the period of peak vernakalant exposure.

Adverse Reaction	**Vernakalant**	**Placebo**	**Δ (95%CI)**
Hypotension	7.6%	5.1%	2.5 (-0.6, 5.6)
CHF subpopulation	*16.1%*	*4.7%*	*11.4 (3.3, 19.4)*
Clinically meaningful hypotension*	1.2%	0%	---
CHF subpopulation	*2.9%*	*0%*	---
Ventricular arrhythmia	3.9%	3.2%	0.8 (-1.6, 3.2)
CHF subpopulation	*7.3%*	*1.6%*	*5.7 (0.4, 11.0)*
Clinically meaningful ventricular arrhythmia*	0.6%	0%	---
CHF subpopulation	*2.2%*	*0%*	---
Atrial flutter	10.0%	2.5%	7.5 (4.7, 10.3)
Clinically meaningful atrial flutter*	0.1%	0%	---
Bradycardia	5.4%	3.8%	1.6 (-1.1, 4.3)
Clinically meaningful bradycardia	1.3%	0%	---

* "Clinically meaningful" events included serious adverse events (SAEs) and events leading to discontinuation of therapy.

In these studies, hypotension typically occurred early, either during the infusion or early after the end of the infusion, and could usually be corrected by standard supportive measures. Ventricular arrhythmias typically presented as asymptomatic, monomorphic, non-sustained (average 3-4 beats) ventricular tachycardias. Bradycardia was observed predominantly at the time of conversion to sinus rhythm. In general, bradycardia responded well to discontinuation of vernakalant and/or administration of atropine.

Due to the higher incidence of hypotension and ventricular arrhythmia in patients with CHF, vernakalant should be used cautiously in haemodynamically stable patients with CHF functional classes NYHA I to II. There is limited experience with the use of vernakalant in patients with previously documented LVEF ≤ 35% and its use in these patients is not recommended. The use of vernakalant IV in CHF patients corresponding to NYHA III or NYHA IV is contraindicated.

These clinically significant adverse reactions are being monitored as identified and potential risks in the vernakalant Risk Management Plan (RMP). In addition, although there were no examples of vernakalant IV overdosing in the clinical trials, in consideration of the logistical complexity of weight-based dosing regimens such as that used for vernakalant, potential risk of overdose is also being monitored through the RMP.

Vernakalant IV was approved 1 September 2010 by the European Commission for rapid cardioversion of recent onset AF (<=3 days duration for post-cardiac surgery and <=7 days duration for non-surgical patients).

The clinically significant adverse reactions discussed above are being monitored and have been identified as potential risks in the vernakalant IV Risk Management Plan (RMP). In addition, specific contraindications such as heart failure (NYHA III and IV), severe aortic stenosis, myocardial infarction (MI) or acute coronary syndrome (ACS) in 30 days prior to administration, prolonged QT at baseline (uncorrected > 440 msec), severe bradycardia, sinus node dysfunction, second degree and third degree heart block in the absence of a pacemaker, and use of intravenous rhythm control antiarrhythmics (class I and class III) within 4 hours prior to vernakalant IV administration are also being monitored.

Key prescribing information from the SmPC are included as part of the package leaflet in the Brinavess™ packaging, and distributed with the product directly to the point-of care site. Additionally, the SmPC accompanies the HCP education card packs that are distributed to all anticipated prescribers and users of the product. In addition to this, SmPCs are handed out at the occasion of each customer contact, at national and international conferences, as well as in local educational events. The SmPC is accessible on Cardiome's Brinavess™ website through hyperlinks to the EMA website. The SmPC is

also attached to each written answer from the Medical Information Service to healthcare professionals' (HCPs) questions on the use of vernakalant IV.

The risk minimization measure to incorporate a Pre-Infusion Checklist with drug packaging was initiated in 2012. The checklist provides specific instructions on how to determine the eligibility and potential risks of a patient (including contraindications) to be administered vernakalant IV, and for monitoring of the patient for the duration of the infusion and for at least 15 minutes after the completion of the infusion for signs and symptoms of a sudden decrease in blood pressure or heart rate. Within the SmPC, an HCP is reminded to use the Pre-Infusion Checklist before administering vernakalant IV.

The risk minimization plan requires information gathering on whether the risk minimisation tools (Pre-Infusion Checklist and HCP Educational Card) are reaching the target audience and whether they are being used.

The Sponsor, in collaboration with the designated CRO, will conduct a post-authorisation safety study (PASS) of vernakalant IV in order to collect information about normal conditions of use and dosing of vernakalant IV, and to quantify possible medically significant risks of hypotension, ventricular arrhythmia, bradycardia, and atrial flutter in real-world clinical practice. Due to expected limitations of existing registries and electronic healthcare records systems in EU countries (e.g., AFNET, THIN, GPRD, Nordic Country Hospital Registries) for obtaining all data elements necessary to address the study's research objectives, the PASS will employ prospective data collection using a network of clinical sites across multiple countries in the EU.

4 OBJECTIVES

The research objectives of the study are to describe patients receiving vernakalant IV, to characterise the normal use and dosing of the product, and to better estimate the incidence of medically significant HOIs. Collection of information on dosing/administration and patient selection for vernakalant IV will help characterise prescribing in the context of the product label. The proportion of subjects in whom successful cardioversion to sinus rhythm following vernakalant IV administration is achieved will also be reported.

Specifically, the **primary objectives** of the PASS are to:

1. Estimate the incidence of the following medically significant health outcomes of interest (HOIs) reported during treatment and during the first 24 hours after last infusion of vernakalant IV or until discharge/end of medical encounter, whichever occurs earlier.

    - **Significant hypotension** defined as: symptomatic hypotension with BP <90 mmHg, requiring treatment with vasopressors

- **Significant ventricular arrhythmia** defined as:
  - Sustained ventricular tachycardia (VT) with a ventricular heart rate > 120 beats per minute with duration > 30 seconds or VT that required intervention with either electrical shock or anti-arrhythmic drugs, or
  - Torsade de Pointes with a duration of >10 seconds, or
  - Ventricular fibrillation of any duration
- **Significant atrial flutter** defined as: atrial flutter with 1:1 atrioventricular conduction of >10 seconds duration and a ventricular rate of >200 bpm

- **Significant bradycardia** defined as: bradycardia requiring electrical pacing (temporary or permanent) or any other serious adverse event reports involving bradycardia

2. In order to investigate the potential risk of overdose and medication error, describe vernakalant IV administration/dosing by summarising patient body weight, total dose with each intravenous (IV) infusion, and length of time for each IV infusion.
3. To evaluate the effectiveness of the risk minimisation activities by*:*
   - Describing the appropriateness of selection of patients for treatment with vernakalant IV, monitoring of patients during and after vernakalant IV administration, and use of anti-arrhythmics before and after vernakalant IV, as consistent with the label and risk minimization activities (Pre-Infusion Checklist and (HCP) healthcare provider educational card)

   - Monitoring for the occurrence and incidence of SAEs and HOIs to review with the EU Regulatory Agency with respect to risk minimization activities

The **secondary objectives** of the PASS are to:

1. Summarise the count and rate of all serious adverse experiences (SAEs) for HOIs that may not meet the definitions of medically significant HOIs as defined above, as well as all other SAEs reported during treatment and during the first 24 hours after the last infusion of vernakalant IV or until discharge/end of medical encounter, whichever occurs earlier.
2. Characterise patients administered vernakalant IV in terms of patient demographics, medical history, and presenting conditions. Specific conditions to be summarised include:

   - Heart failure, New York Heart Association (NYHA) class
   - Prolonged QT, severe bradycardia, sinus node dysfunction, second or third degree heart block, clinically meaningful valvular stenosis, hypertrophic obstructive

cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis
- History of hyperthyroidism
- Severe aortic stenosis, Low systolic BP
- Recent acute coronary syndrome (including MI)
- Pacemaker implantation
- Presence of pacemaker/year of implantation
- Hepatic impairment

3. Document the administration of concomitant treatment modalities to restore or maintain sinus rhythm during the index hospitalization/medical encounter (e.g., oral or IV anti-arrhythmics, electrical cardioversion, ablation, Maze procedure).
4. Describe the rate of successful cardioversion to sinus rhythm for at least one minute within 90 minutes of start of first vernakalant IV administration and time (in hours) from vernakalant infusion until discharge/end of medical encounter.

5 STUDY DESIGN

5.1 Description

This prospective, observational, PASS will be conducted in compliance with the Guideline on good pharmacovigilance practices (GVP), Module VIII [Ref. 5.4: 436] and Volume 9A of The Rules Governing Medicinal Products in the EU Guidelines on Pharmacovigilance of Medicinal Products for Human Use. [Ref. 5.4: 435].

The study will not provide or recommend any medication use or other treatment. All direction for medication usage and treatment is at the discretion of the physician in accordance with their usual practice; participation in this study will not change or influence a patient's treatment in any way. The study will include a network of clinical sites in inpatient and acute care settings appropriate for IV pharmacologic treatment of AF. Patients being given vernakalant IV will be enrolled and followed for 24 hours after the last vernakalant IV infusion or until end of medical encounter, whichever occurs first, for medically significant HOIs and SAEs. Data collection will be performed prospectively during and shortly following vernakalant IV administration, with abstraction of required data elements from patient medical charts as well as supplemental, prospective data collection of study-specific data elements.

Baseline	Follow-up time	Total period of follow up

Day 1 Start date of vernakalant IV administration	From start of first infusion through the 24-hour period following last infusion of vernakalant IV or until discharge/end of medical encounter (whichever occurs earlier)	24 hours

5.2 Duration of Study

The study is anticipated to be launched by Q3 2011. The study is expected to take approximately 6-7 years to complete, dependent on the timing of vernakalant IV commercial availability in each country, local EU member regulatory approval of the PASS, and the rate of market uptake of vernakalant IV. Site recruitment for the study will begin in third-quarter 2010 and will continue through study launch or as needed. Interim reports will be provided with each periodic safety update report (PSUR/PBRER) for Vernakalant Sterile concentrate (Brinavess™) and submitted to CHMP after the study is launched. Assuming an estimated 74 months of active enrolment into the study, the final PASS report would be targeted for submission to CHMP by Q1 2018.

5.3 Study Population

The study population will include patients) who are treated with vernakalant IV in acute care and inpatient hospital settings. The decision to treat with vernakalant IV will be made by the treating physician independently of this study. The epidemiology of atrial fibrillation suggests that prospective patients are more likely to be elderly, and somewhat more likely to be male than female. At each site, consecutive patients will be enrolled into the PASS, to the extent possible.

5.4 Number of Patients

The study will enrol a total of 2,000 patients across participating EU member and other European countries, subject to adequate uptake and use of vernakalant IV within the 6-7 year study period to provide timely data regarding product safety. Based on the results of a pilot-test of procedures completed by the Sponsor in preparation for this study, it is recognized that enrolment of patients in hospital and urgent care setting may be challenging based not only on the estimated product uptake during the planned data collection period but also on the variability in clinical practice use of electrical versus pharmacological cardioversion in many European countries. If during the study it becomes apparent that the target patient number may not be met within the specified enrolment period, the Sponsor will initiate discussions with the CHMP in a timely fashion to ensure sample size is sufficient to provide reasonable statistical precision for the associated 95% confidence intervals for each HOI, as discussed in Section 10.7. A sufficient number of sites to meet enrolment requirements will be recruited to participate in the PASS.

6 SELECTION OF PATIENTS

6.1 Inclusion Criteria

The inclusion criteria for enrolment are:

- Patients treated with vernakalant IV, independently of this study

- Subjects and/or legal guardians willing to provide informed consent and/or informed assent according to local regulations

6.2 Exclusion Criteria

The exclusion criteria for enrolment are:

- Enrolment in an investigational drug or device clinical trial in the 30 days prior to study enrolment. Participation in another non-interventional drug or device study or registry is permitted.

6.3 Study Enrolment

6.3.1 Site Enrolment and Country Selection

The PASS will target clinical sites in multiple EU member countries to set up infrastructure for prospective data collection on vernakalant IV. Countries currently included are Austria, Denmark, Germany, Spain, and Sweden. Finland, and other EU and non-EU countries may be included but selection is conditional on a number of factors, including, but not limited to, the actual date of product launch in each country and rate of market uptake of vernakalant IV. In addition, country selection was based on the following considerations: (1) the desire for the study to reflect geographic variation of patients across the EU member countries; (2) the ability to capture expected variation in use of different treatment modalities and clinical settings for cardioversion of recent onset AF across EU member countries; and (3) the Sponsor's expectation that in several of these countries, vernakalant IV will be commercially available for use within the first 1-2 months following the expected Commission Decision on the CHMP marketing authorization approval (MAA). The latter consideration was adopted in order to ensure that the study will collect the most timely data on real-world use of vernakalant IV.

Site enrolment progress will be monitored closely following the marketing launch of vernakalant IV across Europe. Any substantial delays in a country with clinical sites will trigger a reevaluation of this country's appropriateness for inclusion in the PASS. Under such circumstances, the Sponsor will inform the CHMP of this development and will consider inclusion of additional countries if needed.

Clinical sites in each country reflecting both academic and community hospitals in which acute cardioversion is routinely performed (IV pharmacologic or electrical) will be targeted for participation in the study. Centres with adequate prescription, hospital encounter, discharge and diagnostic data will be targeted in order to obtain good quality data about administration and expected safety profile of vernakalant IV in the context of normal clinical usage. All efforts will

be made to enrol sites that can recruit an adequate number of AF patients during the study enrolment period. Regional variation within countries may also be considered in site selection.

6.3.2 Patient Enrolment

Patients who meet all the inclusion criteria and none of the exclusion criteria may be included in the PASS. Patients will be selected for enrolment in the PASS after the decision has been made to administer vernakalant IV. PASS participation will not influence their course of treatment in any way.

Sites will be required to maintain a screening log of eligible patients, including their gender and age. The log will document all patients that may be included or excluded from the PASS, in order to assess the potential study population. To the extent possible, consecutive eligible patients will be included and reasons for non-participation will be documented.

6.4 Patient Withdrawal

Patients may withdraw consent at any time. If a patient is withdrawn prior to completing the PASS follow-up period, the reason for withdrawal is to be documented. All information already collected as part of the study will be retained for analysis unless the patient requests otherwise.

7 DATA COLLECTION

7.1 Collection of Required Data Elements

Scheduled assessments for the study are presented in the Registry Assessment Flow Chart provided in this section. All data elements will be collected from information routinely recorded in the medical record, or will be prospectively recorded by the investigator for the purposes of the study.

Data will be collected via an electronic case report form (eCRF). Data describing vernakalant IV administration and dosing at baseline, and observations during study follow-up (from start of first infusion through the 24-hour period following last infusion of vernakalant IV or discharge/end of medical encounter, whichever is earlier) will be collected; site personnel will enter (or transfer if collected on a paper case report form) the collected data in the appropriate eCRFs. Information on concomitant medications and administration of other therapies to restore/maintain sinus rhythm during the index hospitalization for stays exceeding 24 hours following last infusion of vernakalant IV will be collected, up to a maximum of 7 days following last infusion of vernakalant IV. For prospectively recorded data elements, expected to include NYHA class [Ref. 5.4: 443] and elements of medical history at presentation which may not be available in the medical record, the investigator will record the data in the eCRF and add any

source documentation (described further in Section 11.2) such as paper worksheets, or printed ECG tracings to the medical record. Baseline ECG tracings recorded as part of standard of care during the index hospitalization and prior to vernakalant administration and ECGs corresponding to arrhythmic HOIs and SAEs during the follow-up period may also be requested.
No follow-up visits or examinations, laboratory tests, or procedures are mandated as part of this study.

7.1.1 Description of Key Data Elements

The list of key data elements to be collected is described below.

The main data elements that will be collected as part of the registry protocol will include:

- **Patient demographics** (date of birth or age, gender, race, body weight [kg], BMI)

- **Hospital admission/medical encounter in which Vernakalant IV was administered**
  - Setting (intensive care unit [ICU], coronary care unit [CCU], surgical unit, medical ward, emergency department [ED])
  - Date/time of admission and discharge
  - Primary complaint (reason for admission)
  - Medical condition for which vernakalant IV is prescribed (indication for use)

- **Characterisation of AF episode for which Vernakalant IV was administered**
  - AF type (surgery vs. non-surgery)
  - Duration of current AF episode (hours), date of onset
  - AF symptoms at presentation

- **Presenting medical conditions**
  - NYHA heart failure class [Ref. 5.4: 443]
    - Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
    - Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
    - Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
    - Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal

syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

- Myocardial infarction (MI) or acute coronary syndrome (ACS) within 30 days
- Haemodynamic stability
- Systolic/diastolic blood pressure
- Heart rate
- Severe aortic stenosis
- Severe bradycardia (without pacemaker)
- Sinus node dysfunction
- Heart block (2^{nd} or 3^{rd} degree)
- Left atrial clot (if known) - for those receiving routine echocardiogram
- Left ventricular hypertrophy (size of the left atrium), thickness of septum, left ventricular ejection fraction (if ascertained as part of usual care)
- Baseline electrocardiogram (rhythm, ventricular rate, QRS duration, QT interval)
- Hepatic impairment as determined by results of liver function testing performed as part of usual care

- **Concomitant Medications:** All prescription and non-prescription medications taken within 24 hours prior to, and during, the index hospitalisation**,** including (but not limited to)
  - Rate control
  - Rhythm control
  - Blood pressure regulation
  - Anti-thrombotics
  - Anti-coagulants
  - Hypercholesterolemia / hyperlipidemia

  Information on concomitant medications administered during the index hospitalisation for stays exceeding 24 hours following last infusion of vernakalant IV will be collected, up to a maximum of 7 days following last vernakalant infusion.

- **Selected blood chemistries** (with lab reference ranges) collected as part of usual care, including, but not limited to:
  - Serum potassium
  - Magnesium
  - Troponin
  - Creatinine

- Liver function tests and other analytes (e.g., platelets) required for estimation of liver function using established algorithms

- **Medical history**
  - History of heart failure (year of diagnosis)
    - Prior hospitalisations for acute heart failure (most recent, number in last 6 months)
    - Previously documented left ventricular ejection fraction (most recent)
  - History of AF
    - Year of initial diagnosis
    - Classification (first onset, paroxysmal, persistent, permanent, post-operative, Wolff-Parkinson-White, other?)
  - Pacemaker (yes/no, year implanted)
  - Implantable cardioverter defibrillator (ICD) (yes/no, year implanted)
  - History of cardiovascular disease
    - Valvular heart disease
    - Clinically meaningful valvular stenosis
    - Hypertrophic obstructive myopathy
    - Restrictive cardiomyopathy
    - Constrictive pericarditis
    - MI, angina, stroke, ACS, vascular surgery (stent, coronary artery bypass graft, etc.)
    - Hypertension
  - **Other medical and lifestyle history**
    - Diabetes
    - Smoking
    - Hyperlipidemia/ hypercholesterolemia

- **Dosing/Administration of vernakalant IV**
  - Total number of infusions during treatment episode
  - Total dose with each infusion
  - Start/stop times for each infusion
  - Amount of time between each infusion
  - Time to successful conversion

- **Methods of site monitoring of patients during and following each vernakalant infusion per SmPC guidance**

- Duration and frequency of blood pressure measurements during each infusion, during 15 minute post-infusion and up to two hours post-infusion, and type of healthcare provider performing such monitoring
- Type and duration of cardiac rhythm monitoring during and up to two hours post-infusion, and type of healthcare provider performing such monitoring

- **Administration of other therapies for restoration/maintenance of sinus rhythm during the index hospitalisation or medical encounter**
  - IV and oral rhythm control pharmacologic agents (drug class, administration time relative to any infusion of Vernakalant IV)
  - Electrical cardioversion (type [external, transvenous, or transesophageal] and administration time relative to any infusion of vernakalant IV)
  - Maze ablation pacemaker or ICD implantation or any other surgical procedures to restore sinus rhythm

  Information on other therapies to restore/maintain sinus rhythm administered during the index hospitalization for stays exceeding 24 hours following last infusion of vernakalant IV will be collected, up to a maximum of 7 days following last infusion of vernakalant IV

- **Pre-specified medically significant HOIs**
  - Significant hypotension (symptomatic hypotension with systolic BP <90 mmHg, requiring treatment with vasopressors)
  - Sustained ventricular tachycardia (VT) with a ventricular heart rate > 120 beats per minute with duration > 30 seconds or VT that required intervention with either electrical shock or anti-arrhythmic drugs, or
  - Torsade de Pointes with a duration of >10 seconds
  - Ventricular fibrillation of any duration
  - Significant atrial flutter defined as: atrial flutter with 1:1 atrioventricular conduction of >10 seconds duration and ventricular rate >200 bpm
  - Significant bradycardia defined as: bradycardia requiring electrical pacing (temporary or permanent) or any other serious adverse event reports involving bradycardia

- **Risk minimization materials**

Collection of data regarding use of risk minimization materials began in August 2014.

- Use of Pre-Infusion Checklist by HCP
- Health Care Provider/Appropriate Use of Brinavess™ card
  - Receipt and date of receipt by site
  - Read by HCP

7.1.2 Schedule of Assessments

Follow-up from start of first infusion through earlier of 24 hours after last infusion or hospital discharge/end of medical encounter)

Assessment	Source	Baseline	Follow-up from start of first infusion through earlier of 24 hours after last infusion or until discharge/end of medical encounter
Informed consent/assent obtained (may be prior to or following administration of vernakalant IV, see further detail in Section 12.1)	Patient unless incapacitated, may seek proxy consent or waiver of consent based on EC approval	X	
Inclusion/exclusion criteria	Site staff	X	
Patient demographics (date of birth or age, gender, race, body weight, BMI)	Medical record or supplemental collection	X	
Hospital admission/medical encounter in which vernakalant IV was administered (setting, date/time of admission and discharge, primary complaint/reason for admission)	Medical record	X	
Characterisation of atrial fibrillation episode for which vernakalant IV was administered (surgery or non-surgery setting, onset of current episode)	Medical record	X	
Presenting medical conditions (NYHA class, myocardial infarction, acute coronary syndrome, haemodynamic stability, systolic/diastolic blood pressure, severe aortic stenosis, severe bradycardia, sinus node dysfunction, 2nd or 3rd degree heart block, baseline electrocardiogram, left ventricular ejection fraction, hepatic impairment)	Medical record or supplemental collection- NYHA class is anticipated to require supplemental collection	X	

Concomitant Medications: prescription and non-prescription medications taken within 24 hours prior to, and during, the index hospitalization* (to include, but not limited to, cardiovascular medications such as rate control, rhythm control, blood pressure regulation, anti-thrombosis, hypercholesterolemia)	Medical record	X	X*
Standard of care blood chemistry (e.g. serum potassium, magnesium, troponin, creatinine, liver function tests)	Medical record	X	
History of heart failure (year of diagnosis, recent hospitalisations, left ventricular ejection fraction within last year, current medications)	Medical record or supplemental collection	X	
History of atrial fibrillation (year of initial diagnosis, classification: first onset, paroxysmal, persistent, permanent, post-operative, Wolff-Parkinson-White or other)	Medical record or supplemental collection	X	
Pacemaker (yes/no, year implanted)	Medical record or supplemental collection	X	
Implantable cardioverter defibrillator (ICD) (yes/no, year implanted)	Medical record or supplemental collection	X	
History of cardiovascular disease (valvular heart disease, clinically meaningful valvular stenosis, hypertrophic obstructive myopathy, restrictive cardiopathy, constrictive pericarditis, myocardial infarction, angina, stroke, acute coronary syndrome, vascular surgery, hypertension)	Medical record or supplemental collection	X	
Other medical and lifestyle history (diabetes, smoking, hyperlipidemia)	Medical record	X	

Dosing/Administration of Vernakalant IV (total number of infusions, total dose with each infusion, start/stop time for each infusion, amount of time between each infusion, time to successful conversion, and methods of site monitoring of patients during and following vernakalant infusion per SmPC guidance)	Medical record	X	X
Administration of therapies for restoration/maintenance of sinus rhythm during the index hospitalisation* (IV and oral rhythm control pharmacologic agents, electrical cardioversion, Maze ablation, pacemaker or ICD implantation or any other surgical procedure to restore sinus rhythm, start/stop time for IV or electrical treatments)	Medical record	X	X*
Mandatory reporting of pre-specified medically significant HOIs (see section 8 for definitions and reporting requirements)	Investigator/Site staff	X	X
Mandatory reporting of SAEs (see section 8 for definitions and reporting requirements)	Investigator/Site staff	X	X

*Data on concomitant medications and therapies (oral, IV meds, electrical cardioversion, and/or surgical procedures) for restoration/maintenance of sinus rhythm during the index hospitalization for stays exceeding 24 hours following last infusion of vernakalant IV will be recorded up to 7 days following the last vernakalant IV infusion.

7.2 Collection of Data Retrospectively

To minimize further delay to completion of the study, data will be collected retrospectively from patients who have received Brinavess™ but were not enrolled in the study. To reflect today's real world setting, retrospective data will only be collected from patients who received Brinavess™ after the additional risk minimization measures were implemented in April 2013. This would mean that data from patients would be included both retrospectively and prospectively at all new and existing sites.

The inclusion of these retrospective data from patients already treated with Brinavess™ would allow the primary objective study to be met fully, whilst facilitating the timely completion of this trial.

At the completion of the study, stratified analyses will be used to present the results. Full statistical methods and analyses will be described in the Statistical Analysis Plan (SAP).

Patients are consecutively enrolled into SPECTRUM based on when they present at the participating site. In order to minimize any potential selection bias at the patient level, retrospective data collection will be conducted to include all patients already treated with Brinavess™ but not enrolled in SPECTRUM, at existing and newly qualified sites, with available key data. Specifically, data will be included from all patients who;

1. Have received Brinavess™ since April 2013 but were not enrolled in SPECTRUM.
2. Have available in their hospital records the key data variables as stipulated in section 7.2.1.
3. Provide their informed consent or the site obtains a waiver from their IEC.

Both retrospectively and prospectively included patients have to fulfill the same inclusion and exclusion criteria. As neither group of patients are selected randomly, this approach is not expected to yield selection bias. In addition, results will be reported overall and stratified by method of enrollment. As those who refuse to consent to participate, will not have provided their consent to use their data it would not be possible to compare baseline characteristics of those who refuse vs those who participate. To ensure the overall sample is not dominated by any one site or country by the inclusion of retrospective data, any site or country who reaches their limit based on the inclusion of retrospective data will be closed and the resources used to open other sites/countries. Enrolment will be capped at 10% per site (200 patients) and 40% per country (800 patients). This cap includes collection of patient data both prospectively and retrospectively.

The limitations for enrolling patients prospectively include lack of available staff to discuss the study with the patient and ask for their consent, (this typically happens over the weekend, after hours, when the Investigator is on vacation or off duty for other reasons) and patients unwilling to give their consent to use their data. For retrospectively enrolled patients the limitations are the same. Some sites may not have sufficient staff to contact patients treated previously and again, the patient may be unwilling to give their consent to use their data.

As stated above both retrospectively and prospectively included patients will have to fulfill the same inclusion and exclusion criteria, neither group of patients would be selected randomly, thus this approach is not expected to yield selection bias. In addition, results will be reported overall and stratified by method of enrollment.

SPECTRUM is an observational study that does not use randomization to select the sample. Treated patients are sequentially enrolled, based on provision of informed consent. Inclusion of patients retrospectively will also not use randomization as the goal is to enroll all patients, at the selected sites, who were treated with Brinavess and provided their informed consent. This will ensure that patients

selected retrospectively and prospectively are selected in the same manner. This will minimize the risk of any potential selection bias.

Missing data is always a concern; and including patients retrospectively could increase the amount of missing data. However the impact of missing data on the evaluation of the HOIs and other rare events is not anticipated to be a concern as this information is routinely collected in the patient's hospital record. Therefore these event rates at the completion of the study would not be biased downward. Further, any possible observer bias by selecting patients retrospectively will be minimised by only including patients with the key data variables as stipulated in section 7.2.1 and the assessment of whether an event is characterized as an HOI is adjudicated by an independent Safety Review Committee (SRC).

Informed consent

Patients who fulfil the criteria above will be contacted either at clinic during their next routine follow up cardiology appointment, or by phone and / or mail. The approved informed consent form will then be discussed in detail with the patient and if they agree to take part, the patient will personally sign and date the consent form.
If local regulations permit, sites may also ask their IEC for an informed consent waiver.

Identification of retrospective patients

As soon as local regulatory and Ethics Committee approval are obtained (where applicable) sites will be able to enrol retrospective patients concurrently with prospective patients.

Strategies for identifying retrospective patients will vary between sites as a result of varying staff availability and record keeping. Sites with searchable electronic patient records for example will find it easier to identify patients than sites without.

Several methods will be employed to identify retrospective patients who have been treated with Brinavess since April 2013.

1. Patients will be approached at their routine clinic visit. If a study team member notices during this visit that Brinavess treatment has been previously given, the study will be discussed with the patient at this time and asked if they are willing to give their consent to take part.

2. Following a search of the hospital records,

    a. Identified patients will receive a telephone call, the study discussed with them and at their next routine visit asked if they are willing to give their consent to take part. OR

    b. Identified patients will receive a telephone call, the study discussed with them, information mailed to the patient and then the patient will be asked to sign and mail back the completed consent form. OR

c. Identified patients will receive a letter with information regarding the study and if willing to take part, sign the consent form at their next routine visit. OR

d. Identified patients will receive a letter with information regarding the study and if willing to take part, sign and mail back the completed consent form.

Example letters that the site may wish to use can be found in Appendix II. These letters will be sent by the study coordinator or Investigator to the patient. To maintain patient confidentiality copies of the letters sent will not be seen by, or provided to, the Sponsor.

7.2.1 Required key data elements for retrospective data collection

The data elements listed in section 7.1.1 will be collected for all patients enrolled retrospectively, with the exception of the following which may not be available retrospectively in the patients' hospital records;

Patient demographics

- Height

Presenting medical conditions

- NYHA heart failure class

Where NYHA class is not routinely recorded in the patients' hospital records, as the NYHA classification system is based on patients' symptoms, where possible the investigator should classify this retrospectively as any severe symptoms will be documented. Patient eligibility is expected to follow hospital's standard procedures and SmPC guidelines.

Other medical and lifestyle history

- Smoking

Dosing/administration of vernakalant IV

- Stop time for each infusion
- Time to conversion

The total infusion time is expected to follow both SmPC and hospital guidelines.

Methods of site monitoring of patients during and following each vernakalant IV infusion per SmPC guidance

- Duration and frequency of blood pressure measurements during each infusion, during 15 minute post-infusion and up to two hours post-infusion, and type of healthcare provider performing such monitoring

- Type and duration of cardiac rhythm monitoring during and up to two hours post-infusion, and type of healthcare provider performing such monitoring

8 SAFETY MEASUREMENTS

As discussed in Section 5.0, the study is a prospective, observational PASS of patients administered vernakalant IV under normal conditions of use. There are no mandated interventions or procedures, nor will the PASS provide or recommend any specific medication use or other treatment. All direction for medication usage and treatment is at the discretion of the physician in accordance with their usual practice.

8.1 Definitions of AEs

An **AE** is defined as any untoward medical occurrence in a patient administered a pharmaceutical product at any dose that does not necessarily have a causal relationship with vernakalant IV treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the pharmaceutical product. This definition includes intercurrent illnesses or injuries and exacerbation of preexisting conditions.

If the onset of an event occurred before the patient entered the study (e.g., any preplanned hospitalisation or non-emergency routine visits for a pre-existing condition), the condition or pre-existing condition would not be considered an AE unless it worsened following medicinal product use or hospitalisation was prolonged due to a worsening of the pre-existing condition.

A preexisting condition is a clinical condition (including a condition being treated) which is diagnosed prior to use of a Cardiome product or protocol-specified intervention, and which is documented as part of the subject's medical history (e.g., pre-planned hospitalization or a routine visit for the pre-existing condition). **Any worsening** of a preexisting condition temporally associated with the use of a Cardiome product is by definition an adverse experience.

8.2 Definition of SAEs

An **SAE** is defined as an adverse experience which is fatal or life threatening, results in persistent or significant disability, requires inpatient hospitalisation, prolongation of existing inpatient hospitalisation, or is a congenital anomaly, cancer, the result of an overdose or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalisation may be considered a SAE when based upon appropriate medical judgment, they may jeopardise the patient or subject and may require medical or surgical interventions to prevent one of the other outcomes listed previously.

Note: AEs which do not meet the above criteria are defined as **non-serious adverse experiences (NSAE)**. For regulatory reporting requirements in the European Union, SAEs and NSAEs that are at least possibly drug related are defined as serious adverse reactions (SADR) and non-serious adverse reactions, respectively.

8.3 Definition of Experiences of Clinical Interest

Medically significant HOIs are classified as experiences of clinical interest. Definitions of HOIs have been provided previously in Section 7.1.1.

For reporting purposes, Experiences of Clinical Interest (ECIs) must be identified and reported within the same timeframes as SAEs.

8.4 Reporting by Investigators

Reporting of all SAEs and HOIs that occur during the study follow-up period (earlier of 24 hours post vernakalant IV administration or hospital discharge) are mandated as part of this protocol and should be reported to the study CRO by the study investigator within 24 hours of identification. All serious AEs and HOIs that occur during the study follow-up period will be recorded by the investigator in the serious AE eCRF and will result in an automated notification to the study's CRO.
All subjects/patients with SAEs must be followed up for outcome of the event. Any follow-up information on the SAE should be provided by the investigator to the CRO within the same reporting period (within 24 hours of identification).

An investigator who is a qualified physician, will evaluate AEs for relationship to vernakalant IV according to the following categorisation:

- Definitely related
- Probably related
- Possibly related
- Probably not related
- Definitely not related

If a non-Cardiome Product is considered by the investigator to be co-suspect, the investigator is responsible for reporting the SAE to the manufacturer of the non-Cardiome Product.

If an investigator reports a non-serious AE, it will be collected in the non-serious AE eCRF.

8.5 Confirmation of SAEs and HOIs

All SAEs and HOIs that are reported in the eCRF by the study physician will be confirmed for

source verification through review of patient records at the treating medical centre and/or direct follow-up with the treating physician. If fatal events occur, a death certificate with cause of death will be requested. Baseline ECG tracings and ECGs corresponding to arrhythmic HOIs and SAEs may be requested.

Medical Dictionary for Regulatory Activities (MedDRA) will be the dictionary for all medical coding of SAEs and HOIs reported.

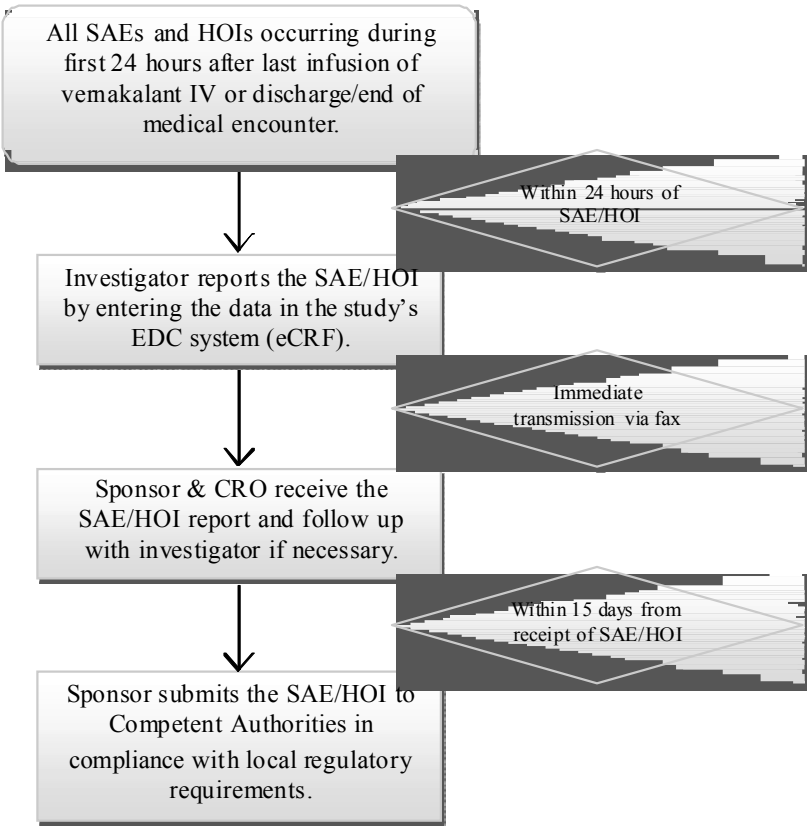
8.6 Safety Reporting to Competent Authorities

Once the investigator reports an SAE using the eCRF, the CRO will immediately transmit the SAE report to one of the individual(s) listed on the contact information page of the site study binder.

All SAEs and HOIs, regardless of attribution to vernakalant IV that occur during the study follow-up period (from start of first infusion through the 24-hour period following last infusion of vernakalant IV or discharge/end of medical encounter, whichever is earlier) will be reported to the relevant competent authority in compliance within local reporting requirements.

If an investigator becomes aware of an SAE that is at least possibly related to Vernakalant IV (BRINAVESS) that occurs after the study follow-up period has concluded, the investigator should report the event to the Sponsor in accordance with local requirements for spontaneous adverse event reporting.

In addition, non-interventional post-authorisation safety studies are covered by the provisions of the Directive 2001/83/EC, Regulation (EC) No. 726/2004 and the Guideline on good pharmacovigilance practices (GVP), Module VIII [Ref. 5.4: 436]. According to "Volume 9A of The Rules Governing Medicinal in the European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use" Section 7.4.2, [Ref. 5.4: 435] the Sponsor will be responsible to report all serious adverse reactions (SADR) arising from the study within the EU no later than 15 days following the receipt of the information to the Competent Authority of the Member State on whose territory the incident occurred. Further, in accordance with section 7.4.2, all SADRs will be included in PSURs. [Ref. 5.4: 435]



Reports of non-serious adverse reactions received by the CRO will be included in the end of study summary report to the CHMP.

The study investigator must comply with any applicable site-specific requirements related to the reporting of SAEs involving his/her patients to the Ethics Committee (EC that approved the study). When direct reporting by an investigator is not clearly defined by national or site-specific regulations, the study physician will be responsible for promptly notifying the concerned EC of any safety reports provided by the Sponsor and of filing copies of all related correspondence in the Site File.

8.7 SPONSOR Responsibility for Reporting Adverse Experiences

All AEs will be reported to the Competent Authorities, ECs, regulatory agencies, IECs, and investigators in accordance with all applicable global laws and regulations.

9 EFFECTIVENESS

9.1 Definition of Effectiveness Endpoint

Effectiveness of vernakalant IV will be assessed as a secondary endpoint, defined as the proportion of patients who are converted to sinus rhythm for at least one minute within 90 minutes of start of first vernakalant IV administration. [Ref. 5.4: 104]

10 STATISTICAL METHODS AND ANALYSES

10.1 Analysis Population

The population for analysis includes all enrolled patients who are documented as having received vernakalant IV.

10.2 Primary analyses

Analyses corresponding to the specific research objectives of the study are planned as follows.

Primary Objective 1*: Estimate the incidence of the following medically significant HOIs reported during treatment and during the first 24 hours after last infusion of vernakalant IV or until discharge/end of medical encounter, whichever occurs earlier.*

- ***Significant hypotension*** *defined as: symptomatic hypotension with systolic BP <90 mmHg, requiring treatment with vasopressors*
- ***Significant Ventricular arrhythmia*** *defined as:*
  - *Sustained ventricular tachycardia (VT) with a ventricular heart rate > 120 beats per minute with duration > 30 seconds or VT that required intervention with either electrical shock or anti-arrhythmic drugs, or*
  - *Torsade de Pointes with a duration of >10 seconds, or*
  - *Ventricular fibrillation of any duration*
- ***Significant atrial flutter*** *defined as: atrial flutter with 1:1 atrioventricular conduction of >10 seconds duration and a ventricular rate >200 bpm*
- ***Significant bradycardia*** *defined as: bradycardia requiring electrical pacing (temporary or permanent) or any other serious adverse event reports involving bradycardia*

Both adjusted (based on method of patient enrolment; prospective vs retrospective) and unadjusted cumulative incidence of HOIs (and their associated 95% confidence intervals) will be reported. In addition, results will also be reported separately by method of enrolment. For the significant bradycardia HOI, the adjusted (based on method of patient enrolment; prospective vs

retrospective) and unadjusted incidence and 95% confidence interval will be reported. In addition, results will also be reported separately by method of enrolment. Results will be calculated for the combined endpoint of (1) bradycardia requiring electrical pacing (temporary or permanent) or (2) any other serious adverse events reports involving bradycardia, and for each endpoint separately.

Numbers and rates of HOIs will also be presented according to time intervals since start of vernakalant IV administration, i.e., 0 to less than 2 hours, 2 to less than 4 hours, and 4 hours to a maximum of 24 hours. Characteristics of patients with HOIs, which may include prior medical history, presenting conditions, medication use, dosing/administration of vernakalant IV, and concomitant therapies, and assessment of relatedness as provided by the investigator will be summarised in a listing of individual HOI events in study reports. Case narratives will also be provided for each HOI.

The primary analysis for HOI incidence is the 0-2 hour post infusion timepoint. Given the lower expected sample size, vernakalant's mode of action and the non-interventional nature of the study design, the 2-4 and 4-24 hour post infusion timepoints are considered secondary and tertiary analyses, respectively.

It is anticipated that rates of HOIs may be somewhat higher in this real-world study setting compared to rates observed in the vernakalant clinical trial program due to the selective patient entry criteria of these randomized clinical trials. Likewise, comparisons to the published literature are not planned and would prove difficult due to differences in case definitions for each specific HOI and variability of reported follow-up periods from administration of a given study drug or intervention to time of the event. However, the frequency of HOIs will be carefully monitored by the Sponsor, the CRO, and the independent Safety Review Committee throughout the duration of the registry study.

Primary Objective 2*: In order to investigate the potential risk of overdose and medication error, describe vernakalant IV administration/dosing by summarising patient body weight, total dose with each IV infusion, and length of time for each IV infusion.*

Distributions of patient body weight, total dose administered with each IV infusion stratified by body weight, and length of time for each infusion will be summarised in tables overall and stratified by method of patient enrollment.

Continuous variables will be reported using appropriate measures of dispersion and central tendency (means, medians, ranges and standard deviations) while categorical variables will be summarised as number and percentage of the total study population. All results will be reported overall and stratified by method of patient enrollment.

Additionally characteristics of patients administered vernakalant IV according to the product label and any patients administered vernakalant IV outside of the dosing guidelines will be

described. Patient age, body weight, presenting conditions and medical history, and details of dosing and administration will be presented separately for each group. All results will be reported overall and stratified by method of patient enrollment.

10.3 Secondary Analyses

Safety

Secondary Objective 1: *Summarise the count and rate of all serious adverse experiences (SAEs) for HOIs that may not meet the definitions of medically significant HOIs as defined above, as well as all other SAEs reported during treatment and during the first 24 hours after the last infusion of vernakalant IV or until discharge/end of medical encounter, whichever occurs earlier.*

Tables with counts of SAEs will be provided and summarised by Medical Dictionary for Regulatory Activities (MedDRA), system organ class (SOC), high level term (HLT), and preferred term (PT), and also stratified by outcome (recovered, recovered with sequelae, not recovered), fatal or non-fatal, and relationship to the study drug (definitely related, probably related, possibly related, probably not related, definitely not related). These summaries will be reported overall and stratified by method of patient enrollment.

Characteristics of patients with SAEs, which may include prior medical history, presenting conditions, medication use, dosing/administration of vernakalant IV, and concomitant therapies, will be summarised in a listing of individual SAEs in study reports. Case narratives will also be provided for each SAE.

Non-serious AEs

Tables with counts of non-serious AEs will be provided and summarised by MedDRA SOC, HLT, and PT and stratified by relationship to the study drug once for the final study report. These summaries will be reported overall and stratified by method of patient enrollment.

Secondary Objective 2*: Characterise patients administered vernakalant IV in terms of patient demographics, medical history, and presenting conditions. Specific conditions to be summarised include:*

- *Heart failure, NYHA class*
- *Prolonged QT, severe bradycardia, sinus node dysfunction, second or third degree heart block, clinically meaningful valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis*
- *History of hyperthyroidism*
- *Severe aortic stenosis, low systolic BP*

- *Recent acute coronary syndrome (including MI)*
- *Pacemaker implantation*
- *Hepatic impairment*

Descriptive data summarising characteristics of enrolled patients will be reported for patient demographics including country, age, gender, race, medical history, and presenting conditions. Continuous variables will be reported using appropriate measures of dispersion and central tendency (means, medians, ranges and standard deviations) while categorical variables will be summarised as numbers and percentages of the total study population. These summaries will be reported overall and stratified by method of patient enrollment.

Secondary Objective 3*: Document the administration of concomitant treatment modalities to restore or maintain sinus rhythm during the index hospitalisation (e.g., oral or IV anti-arrhythmics, electrical cardioversion, ablation, Maze procedure)*

A table summarising the frequency of administration of each concomitant treatment modality during the index medical encounter, stratified by the timing of administration relative to vernakalant IV administration (prior, concurrent, subsequent), will be provided. This summarisation will include class I or III anti-arrhythmics as well as other concomitant medications received during the hospitalisation. These summaries will be reported overall and stratified by method of patient enrollment.

Effectiveness

Secondary Objective 4: *Rate of successful conversion to sinus rhythm for at least one minute within 90 minutes from the start of first vernakalant IV administration will be expressed as the proportion of patients with successful conversion, together with the associated 95% confidence interval. Time (in hours) from start of vernakalant infusion to patient discharge/end of medical encounter will be summarized using appropriate measures of dispersion and central tendency (means, medians, ranges and standard deviations*). These summaries will be reported overall and stratified by method of patient enrollment.

10.4 Subgroups

There are no pre-specified subgroups for analysis. Patient characteristics (and dosing information) will be presented for individual countries, however, rates of HOIs will not be reported by country as individual events are expected to be rare, and stratification of event rates will yield statistically unstable results.

Secondary analysis may be conducted for subgroups of patients with certain medical characteristics if the sample size is sufficient to allow for reasonably precise point estimates of

HOI incidence (in general, 500 patients or more). Regardless, a description of each patient with medically significant HOIs will be given in narrative form.

10.5 Statistical Analysis Plan

A detailed Statistical Analysis Plan (SAP) inclusive of further details and specification of analytic methods to be used and shell tables, figures, and listings for interim and final reports will be developed by the CRO and approved by the Sponsor prior to the start of any patient enrolment in the study.

10.6 Analysis Software and Coding

All AE verbatim terms will be recorded and coded using MedDRA terms and are presented by system organ class (SOC), high level term (HLT), and preferred term (PT).

All computations and generation of tables, listings and data for figures will be performed using SAS® version 9.2 (SAS Institute, Cary, NC, USA).

10.7 Sample Size

The study will enroll 2,000 patients across participating EU countries. The target sample size was selected in order to have adequate statistical precision as expressed by a 2-sided, 95% confidence limit around the expected incidence rate for each HOI for sample sizes of 500, 1,000 1,500; and 2,000 patients. The incidence of each HOI during the first 24 hours post-vernakalant IV administration as defined in Section 5.0 and 10.2 above among patients randomised to receive vernakalant IV in the pooled phase II/III clinical trial database (n=889, including the AVRO Study) ranged from 0% to 0.22% for each HOI.

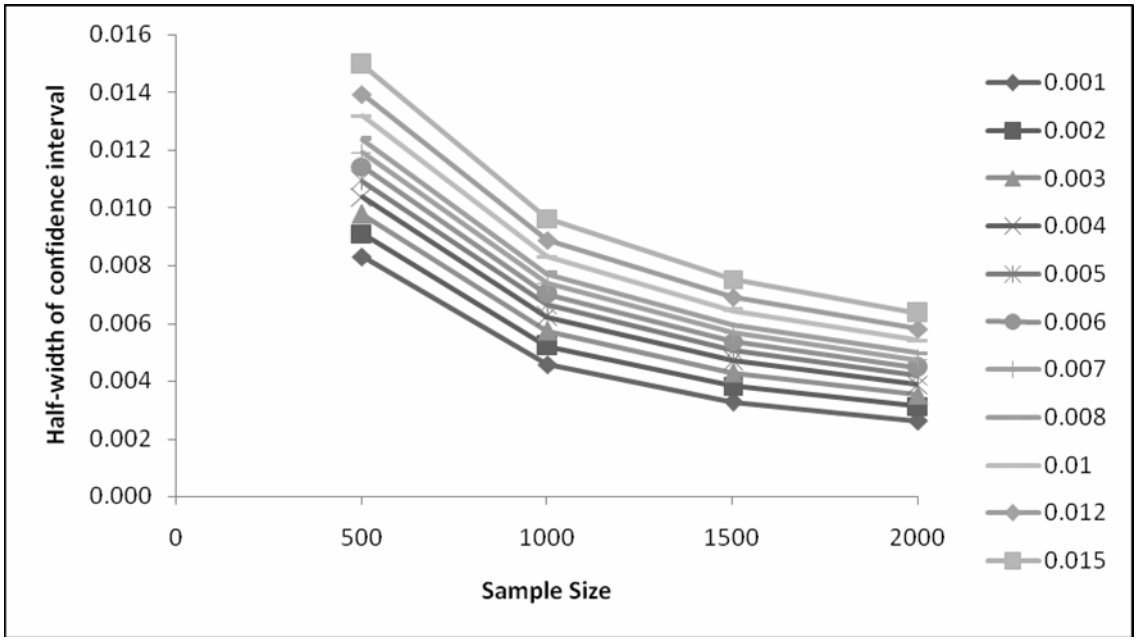
Table 1 shows the margins of error, defined as the distance from the expected proportion to the upper limit of the confidence interval as shown in the table, and confidence limits of the two-sided 95% confidence intervals with sample size of 500, 1,000, 1,500, and 2,000, respectively. For example, if the expected proportion of significant hypotension is 0.003 and the sample size is 1,500, the margin of error is 0.004, and the lower and upper bounds of the two-sided 95% confidence interval will be 0.001 and 0.007, respectively. The calculation of the confidence intervals was performed using the Clopper-Pearson exact method [Ref. 5.4: 406] and PASS software (2008, Kaysville, Utah).

Table 1. Margins of error and confidence limits of the two-sided 95% confidence intervals for one sample proportion with various sample sizes.

Since the confidence interval is not symmetric around the expected proportion of patients with events, the margin of error is the distance from the expected proportion to the upper limit of the confidence interval as shown in this table.

Sample Size	N=500		N=1,000		N=1,500		N=2,000	
Expected Prop.	Margin of Error	Lower and Upper Limit	Margin of Error	Lower and Upper Limit	Margin of Error	Lower and Upper Limit	Margin of Error	Lower and Upper Limit
0.001	0.008	0.000, 0.009	0.005	0.000, 0.006	0.003	0.000, 0.004	0.003	0.000, 0.004
0.002	0.009	0.000, 0.011	0.005	0.000, 0.007	0.004	0.000, 0.006	0.003	0.001, 0.005
0.003	0.010	0.000, 0.013	0.006	0.001, 0.009	0.004	0.001, 0.007	0.004	0.001, 0.007
0.004	0.010	0.000, 0.014	0.006	0.001, 0.010	0.005	0.001, 0.009	0.004	0.002, 0.008
0.005	0.011	0.001, 0.016	0.007	0.002, 0.012	0.005	0.002, 0.010	0.004	0.002, 0.009
0.006	0.011	0.001, 0.017	0.007	0.002, 0.013	0.005	0.003, 0.011	0.004	0.003, 0.010
0.007	0.012	0.002, 0.019	0.007	0.003, 0.014	0.006	0.003, 0.013	0.005	0.004, 0.012
0.008	0.012	0.002, 0.020	0.008	0.003, 0.016	0.006	0.004, 0.014	0.005	0.005, 0.013
0.010	0.013	0.003, 0.023	0.008	0.005, 0.018	0.006	0.006, 0.016	0.005	0.006, 0.015
0.012	0.014	0.004, 0.026	0.009	0.006, 0.021	0.007	0.007, 0.019	0.006	0.008, 0.018
0.015	0.015	0.006, 0.030	0.010	0.008, 0.025	0.008	0.009, 0.023	0.006	0.010, 0.021

Figure 1.Plot of sample size and margin of error at various levels of expected proportion of patients with events.



Footnote: Margin of error (half-width of confidence interval) is defined as the distance between the expected proportion (point estimate) and upper bound of the two-sided 95% confidence limit as the confidence interval is not symmetric.

10.8 Missing data

Reasonable attempts should be made by the treating physician and/or site personnel to limit the amount of missing data. No imputation will be made for missing data. The proportion of missing data is expected to be low for this study, especially with regard to the details of administration of vernakalant IV and concomitant therapies, collected blood chemistry values, and occurrence of HOIs during the brief, in-hospital follow-up period. Reasonable attempts will be made to limit the amount of missing medical history data to ensure that important information is captured

10.9 Interim and Final Analyses and Reporting

Interim analyses will include descriptive summaries of patient characteristics and vernakalant IV administration and dosing, as well as frequencies and cumulative incidence of HOIs and SAEs following administration. Two-sided 95% confidence intervals around rates of HOIs will be computed.

A final study report summarising patient characteristics and details of vernakalant IV administration and dosing, administration of concomitant treatment modalities, frequencies and cumulative incidence of HOIs and SAEs over the full study period, as well as effectiveness and frequencies of non-serious AEs will be prepared.

Full explanation of study methods, results, and discussion and interpretation will be included with interim and final study reports.

11 MANAGEMENT OF THE STUDY

The Sponsor has contracted with Outcome Sciences LLC (formerly operating as Outcome Sciences Inc.) together with its affiliate Quintiles Switzerland Sarl, a CRO specialising in registries and observational post market studies. The CRO will design and manage the study with input, review and approval by the Sponsor Each participating site will receive appropriate training, which describes all processes that the physician or representative must understand. The training will outline all processes required for enrolling patients, providing follow-up data on enrolled patients, maintaining study documents or files, reporting of medically significant HOIs and SAEs, and closing the study. All site staff who participate in enrolling patients and collecting or entering data for the study will be required to undergo appropriate training.

11.1 Data Entry

Data for the study will be collected using a secure web-based electronic data capture (EDC) system (Outcome System®). Data captured during or shortly following the administration of vernakalant IV are entered into the eCRF by the physician or delegated site staff in a timely manner.

11.2 Source Documents

The physician should maintain source documents for each patient enrolled in the study. Source documents include patient charts, doctors' notes, study-specific supplementation data collection forms, ECG tracings (including conversion to sinus rhythm ECGs within 90 minutes of vernakalant IV treatment), lab results slips, supportive documentation of all HOIs and SAEs, and worksheets designed to collect the data to be entered in the CRF and will be kept as part of the patients' medical records. Baseline ECG tracings recorded as part of standard of care during the index hospitalization and prior to vernakalant administration and ECGs corresponding to arrhythmic HOIs and SAEs during the follow-up period may also be requested.

Data recorded into the e-CRF should also be downloaded and stored on local computers at the site. Should this not be possible sites will print a date-stamped version of the completed CRF for each patient to be signed by the study physician and stored in files at the site.

11.3 File Retention and Archiving

The physician and trained staff at the study sites will maintain a record of each enrolled patient. Physicians will be instructed on source documentation that must be available to substantiate patient identification, eligibility and participation, proper informed consent procedures, dates of data collection, adequate reporting and follow-up of medically significant HOIs and SAEs, concomitant medication, and drug administration. Specific items required as source documents will be reviewed with the physician before the study.

Physicians must retain all study records required by the Sponsor and by the applicable regulations a secure and safe facility. The physician must notify the Sponsor or its representative before disposal of any study records, including the medical records of study participants, and must notify the sponsor of any change in the location, disposition, or custody of the study files. In the event that archiving of study records is not possible at the site, the physician will be instructed to notify the Sponsor or its representative.

11.4 Quality Assurance

The study database will be housed at the CRO in a physically and logically secure computer system maintained by the CRO in accordance with company written security policies. The system meets approved established standards for the security of health information and is validated. The system also meets the standards of the International Committee on Harmonisation (ICH) guideline E6R1 regarding electronic study data handling and is available for audit upon request. Each step of the data capture procedures and the handling of data, as well as the eventual study report may be subject to independent quality assurance audits. The CRO, the Sponsor, and the Competent Authorities may conduct site audits at any time during or after the study to ensure the validity and integrity of the data.

11.5 Data Management

A data management plan will be created and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

11.6 Monitoring

Monitoring will be performed by a CRO clinical research associate (CRA). During the site initiation visit, the CRA will provide training on the conduct of the study to the participating physician and all site staff involved in the study. All monitoring procedures and the frequency of monitoring visits will be described in a monitoring plan. The CRA will closeout each site after

the last patient's final follow-up assessment is completed and all e-CRF data has been entered and all outstanding monitoring issues have been resolved or addressed. In the case where a site is closed before completion of the study, the CRA will close out the site but will maintain contact with the physician regarding the study status and in case follow-up information is required.

11.7 External Safety Review Committee (SRC)

The Sponsor will assemble a team of external advisors for an SRC and will employ a charter for the SRC developed jointly by the Sponsor and the CRO. The SRC will consist of three members (single Chairperson and two members) based in Europe with expert knowledge in AF and therapeutic modalities for cardioversion. Two experts will have clinical experience in treatment of AF while the third member will be an applied epidemiologist or statistician with experience in the design and execution of observational safety study studies.

The Sponsor will contact each advisor to review the requirements and expectations of participation in the SRC. Regularly-scheduled meetings of the SRC (teleconference, webex, or face-to-face) will be convened prior to the start of study enrolment and at least annually thereafter, to review interim and final reports of safety data and monitor overall study progress. Specifically, the SRC will be responsible for (1) review of individual patient listings of serious adverse event (SAE) reports and aggregated data in the form of predefined tables and study result reports; (2) periodic assessment of subject accrual rate and study status; (3) evaluation on an *ad hoc* basis of any urgent safety issue identified by the Sponsor, CRO or the SRC; (4) document and communicate in writing all SRC activities to Sponsor, and (5) adjudication of Health Outcomes of Interest (HOIs)/Serious Adverse Events (SAEs).
Source documentation routinely collected for the study which may include ECG tracings corresponding to arrhythmic events if performed as part of standard of care will also be provided to the SRC for review of individual HOIs and SAEs.

11.8 Changes to Protocol

Changes to the protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the competent authorities and to the relevant ECs for approval or favourable opinion. In such cases, the amendment will be implemented only after approval or favourable opinion has been obtained. Minor (non-substantial) protocol amendments, including administrative changes, will be filed by the Sponsor and/or the CRO and at each participating site. They will be submitted to the relevant EC or to competent authorities where required by pertinent regulations.
As noted below in Section 12.1 regarding Informed Consent, any amendment that could have an impact on the patient's agreement to participate in the study (e.g., changing the nature of the data collected) requires re-consent of the patient prior to implementation, except if a waiver of consent has been approved by the relevant EC or competent authorities.

11.9 Publication Policy

The Sponsor will post a study design synopsis on www.clinicaltrials.gov within 60 days after the study protocol is approved by the CHMP, and will post final study results within 12 months after the last patient is enrolled in the study. In addition, publication may also include any or all of the following: posting of a synopsis online abstract and/or presentation at a scientific conference, or publication of a full manuscript.

In the event that the key design elements from the protocol, including methods, and main results of the study are made public through publication in peer-reviewed journals, it is anticipated that one central draft manuscript will be prepared with input from key investigators and leadership from the CRO and the Sponsor.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3. Significant contributions to study execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the study, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the study and writing, as discussed above. The first author is responsible to defend the integrity of the data, method(s) of data analysis, and the scientific content of the manuscript.

The Sponsor must have the opportunity to review and comment on all proposed abstracts, manuscripts, or presentations regarding this study 60 days prior to submission for publication/presentation. During this 60 day period, Sponsor may respond with any requested revisions. Any information identified by the Sponsor as confidential must be deleted prior to submission. If reasonably requested, Sponsor will take reasonable steps to expedite the review process to meet publication deadlines. Submission may be made upon notification by Sponsor that such review has been completed and after information identified by Sponsor as confidential is deleted. Sponsor also has the right to publish the results of this study. Publications and authorship will be guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journals Editors, updated April 2010.

12 ETHICAL AND REGULATORY CONSIDERATIONS

This is an observational study which sets forth to observe the safety outcomes of patients having been administered vernakalant IV. To ensure the quality and integrity of pharmacoepidemiologic research, the study will be conducted in compliance with all applicable national and local regulations and guidelines, accepted standards of Good Clinical Practice, the Guidelines for Good Pharmacoepidemiology Practices (GPP), [Ref. 5.4: 437] the ethical principles that have their origin in the Declaration of Helsinki [Ref. 5.4: 440],EudraLex Volume 9A, Part 1, Chapter I.7. [Ref. 5.4: 435] and the Guideline on good pharmacovigilance practices (GVP), Module VIII [Ref. 5.4: 436].

12.1 Patient Information and Informed Consent/Assent

It is expected that a prerequisite for a patient's participation in the study is informed consent from the patient or a legal representative; however the possibility of conducting this study with a waiver of consent will be explored in each country.

The physician will obtain written informed consent as needed from each patient or a legal representative if incapacitated prior to enrolment and data collection. The physician, or delegated personnel, is required to provide patient or legal representative with the informed consent in their local language. The informed consent document contains adequate information on risks of study participation, in this case, limited to communication of personal identifiers and health information. This informed consent document will be approved by the appropriate EC as will any revisions to the document. Each patient or legal representative will be provided a copy of the informed consent document and the original will be maintained at the site. Confirmation of signed informed consent documents obtained as required will be one of the primary activities performed by the CRA during onsite monitoring as defined in the monitoring plan.

12.2 Patient Identification and Privacy

By signing the protocol, the clinical site and/or physician commit to complying with all related applicable local laws and regulations as well as any applicable EU regulations, such as the *EU Data Protection Act*.

Each patient will be unambiguously identified by a code, which allows the identification of all the data reported for each patient. The code will be an 8-digit number resulting from the combination of the site number and the patient number. The first four digits represent the site and the last four digits represent the patient. Should a patient be withdrawn from the study, his or her unique identification number will not be reallocated.

12.3 Independent Ethics Committees

Patient enrolment will not start at any site before the Sponsor has obtained written confirmation of a favourable opinion/approval from the concerned EC. At certain sites it may be deemed unnecessary for an EC to review an observational study. If this is the case, confirmatory documentation will be maintained on file with both the Sponsor and the clinical site.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant EC in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant ECs during the course of the study in accordance with local regulations and requirements.

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A Prospective Observational Registry Study to Characterise Normal Conditions of Use, Dosing and Safety Following Administration of Vernakalant IV Sterile Concentrate

Post-Authorisation Safety Study (PASS) Study

Annex to Protocol for German Sites – 29 October 2015

Purpose of the Annex

To clarify selection of patients at German sites.

Inclusion Criteria

The inclusion criteria for enrolment are:

1. Patients treated independently from this study with vernakalant IV in accordance with the SmPC, for rapid conversion of recent onset atrial fibrillation to sinus rhythm in adults:
   - For non-surgery patients: atrial fibrillation ≤ 7 days duration
   - For post-cardiac surgery patients: atrial fibrillation ≤ 3 days duration

2. Subjects and/or legal guardians willing to provide informed consent and/or informed assent according to local regulations

Exclusion Criteria

The exclusion criteria for enrolment are:

1. Patients with the following contraindications:
   - Hypersensitivity to the active substance or to any of the excipients.
   - Patients with severe aortic stenosis, patients with systolic blood pressure < 100 mm Hg, and patients with heart failure class NYHA III and NYHA IV.
   - Patients with prolonged QT at baseline (uncorrected > 440 msec), or severe bradycardia, sinus node dysfunction or second degree and third degree heart block in the absence of a pacemaker.
   - Use of intravenous rhythm control antiarrhythmics (class I and class III) within 4 hours prior to, as well as in the first 4 hours after, BRINAVESS™ administration.
   - Acute coronary syndrome (including myocardial infarction) within the last 30 days.

2. Enrolment in an investigational drug or device clinical trial in the 30 days prior to study enrolment. Participation in another non-interventional drug or device study or registry is permitted.

A Prospective Observational Registry Study to Characterise Normal Conditions of Use, Dosing and Safety Following Administration of Vernakalant IV Sterile Concentrate

Post-Authorisation Safety Study (PASS) Study

Annex to Protocol for German Sites

INVESTIGATOR SIGNATURE PAGE

I have read and understand this Annex to the protocol dated 29 October 2015 and agree to conduct this clinical study in accordance with the provisions stated.

Investigator Signature	DATE

Investigator Name

A Prospective Observational Registry Study to Characterise Normal Conditions of Use, Dosing and Safety Following Administration of Vernakalant IV Sterile Concentrate

Post-Authorisation Safety Study (PASS) Study

Annex to Protocol for German Sites – 29 October 2015

SPONSOR SIGNATURE PAGE

Reviewed and Approved by:

Lucy Brindle	Date
Clinical Project Manager	

Dr Steen Juul-Moller	Date
Medical Director	

A Prospective Observational Registry Study to Characterise Normal Conditions of Use, Dosing and Safety Following Administration of Vernakalant IV Sterile Concentrate

Post-Authorisation Safety Study (PASS) Study

Appendix I

Calculation of Enrolment Rates Post Amendment 2 Approval

The table below shows an estimate of enrolment per country to enroll 810 patients and reach the 2000 patient recruitment target by Q4 2017.

Country	2015 average enrolment rate (pts/site/month)	Number active sites	Number pts to be enrolled		Enrolment rate post protocol amendment (pts/site/month)	Total number pts to be enrolled
			Prospectively	Retrospectively		
Austria	1.1	8	110	0	1.1	110
Denmark	1.1	1	15	0	1.1	15
Germany	0.4	8	55	0	0.4	55
Spain	0.6	7	60	20	0.8	80
Sweden	0.8	3	35	70	2.0	105
Finland (enrolment to start Jan 2017)	-	5	100	345	10	445
Total	0.64	33	375	435	3.4	810

Market Uptake of Brinavess

Vials sold per year since study started in 2011.

	No. vials sold 2011	No. vials sold 2012	No. vials sold 2013	No. vials sold 2014	No. vials sold 2015
Austria	705	844	537	919	1105
Denmark	120	117	118	130	70
Spain	60	326	139	360	529
Sweden	311	568	435	752	896
Germany	1773	1000	442	647	548
Finland	655	813	336	761	1320

A Prospective Observational Registry Study to Characterise Normal Conditions of Use, Dosing and Safety Following Administration of Vernakalant IV Sterile Concentrate

Post-Authorisation Safety Study (PASS) Study

Appendix II

Template letters that may be used to contact potential patients retrospectively

Site details

Patient address

DATE

Invitation to participate in an observational research study (called Spectrum)

Dear _____,

We would like to invite you to participate in an observational research study. You are being invited because your atrial fibrillation was treated with Brinavess (Vernakalant) at our clinic. As your next scheduled visit at our clinic is on DD MMM YYYY, we would like to approach you by means of this letter.

The purpose of the Spectrum study is to learn more about Brinavess (Vernakalant) and about how doctors use it to treat atrial fibrillation in the hospital. If you decide to take part, information from your medical chart will be collected. There will be no medications or other treatments as part of this study and there will be no extra visits or additional medical procedures.

For more information, I have enclosed two (2) copies of a patient information sheet and informed consent form for your review.

If you are interested in taking part, we will review and discuss the study and the consent form with you at your next clinic visit. We will also address any questions you may have about the study at this time.

You do not have to take part in the study. You can say no without giving any reason. This will not affect your future care or your relationship with your doctor.

If you have any questions or concerns about the study before your next clinic visit, please feel free to contact us at any time on <Phone no.>.

Sincerely,
<Name> <Title>

Site details

Patient address

DATE

Invitation to participate in an observational research study (called Spectrum)

Dear _____,

We would like to invite you to participate in an observational research study. You are being invited because your atrial fibrillation has been treated with Brinavess (Vernakalant) at our clinic. As your next scheduled visit is not due yet, we would like to approach you by means of this letter.

The purpose of the Spectrum study is to to learn more about Brinavess (Vernakalant) and about how doctors use it to treat atrial fibrillation in the hospital. If you decide to take part, information from your medical chart will be collected. There will be no medications or other treatments as part of this study and there will be no extra visits or additional medical procedures.

For more information, I have enclosed two (2) copies of the patient information sheet and informed consent form for your review.

I will call you shortly to review and discuss the study and the consent form with you. We will also address all your questions during the call.

You do not have to take part in the study. You can say no without giving any reason. This will not affect your future care or your relationship with your doctor.

If you would like to take part, we will discuss during our call how to complete the consent forms.

If you have any questions or concerns about the study, please feel free to contact us at any time on <phone>.

Sincerely,

<Name>
<Title>