EU-Risk Management Plan for BRINAVESS
(vernakalant hydrochloride)

RMP version to be assessed as part of this application:

RMP version number:	7.0
Data lock point for this RMP:	31 August 2018
Date of final sign off	03 July 2019

Rationale for submitting an updated RMP:

To align the EU RMP with recent integrated data analyses. The integration of data included pooled data from eight clinical studies of phase 2 and phase 3 (CRAFT, SCENE II, AVRO (vernakalant subjects only), ACT I, ACT II, ACT III, ACT IV, and ACT V). Also, this RMP includes updated data analysis based on the phase 3 Asia-Pacific study, on post-marketing data from the PASS SPECTRUM, and spontaneous cases.

RMP version 6.0 was submitted and partially assessed with the PSUR in 2016 but because not all the changes to the RMP were subsequent to the PSUR, those changes not related to the PSUR (i.e. integrated analysis data) were not assessed and Correvio was requested to submit a separate variation.

Summary of significant changes in this RMP:

The EU-RMP was aligned and revised in line with the requirements introduced in the Guideline on good pharmacovigilance practices Module V – Risk management systems (Rev.2) and accompanied Guidance on the format of the risk management plan in the EU – in integrated format (Rev. 2.0.1).

The following significant changes were introduced to the RMP:

- Post marketing data updated for each safety concern in Part II Module SVII
- PASS SPECTRUM deleted as an additional pharmacovigilance activity from Part III as the study has been completed and CSR finalised.

Other RMP versions under evaluation:

None

Procedure number: EMEA/H/C/PSUSA/03109/201608

Details of the currently approved RMP:

RMP version number: 5.0

Approved within procedure: EMEA/H/C/PSUSA/00003109/201508

Date of approval (opinion date): 17 March 2016

RMP version number: 6.0

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Partially approved on 09 March 2017 (only the changes in relation with the PSUR were assessed and approved)

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Table of contents

List of tables

List of abbreviations

AAD	Antiarrhythmic Drugs
ACS	Acute Coronary Syndrome
ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
AFL	Atrial Flutter
ARIC	Atherosclerosis Risk In Communities
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area Under Curve
AV	AtrioVentricular
BP	Blood Pressure
CCDS	Company Core Data Sheet
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CSR	Clinical Study Report
EAD	Early after Depolarisation
ECG	Electrocardiogram
ECV	Electrical Cardioversion
ED	Emergency Department
EEA	European Economic Area
EM	Extensive Metabolisers
EPAR	European Public Assessment Report
EU	European Union
GVP	Good Pharmacovigilance Practices
HCP	Health Care Professional
hERG	|Human *Ether-à-go-go*-Related Gene
HI	Hepatic Impairment
HMO	Health Maintenance Organisation
HOI	Health Outcome of Interest
HR	Heart Rate
ICSR	Individual Case Safety Report

INN	International Nonproprietary Name
IV	Intravenous
LEG	Legally binding Measure
LV	Left Ventricle
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MI	Myocardial Infarction
MTD	Maximum Tolerated Dose
NOAEL	|No Observable Adverse Effect Level
NYHA	New York Heart Association
PASS	Post Authorisation Safety Study
PBO	Placebo
PI	Product Information
PL	Package Leaflet
PM	Poor Metaboliser
PO	Oral
PT	Preferred Term (MedDRA coding)
PV	Pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SR	Sinus Rhythm
TdP	Torsades de Pointes
US	United States
VA	Ventricular Arrhythmia
VHD	Valvular Heart Disease
VT	Ventricular Tachycardia
WAES	Worldwide Adverse Experience System

PART I: Product(s) overview

Active substance(s) (INN or common name)	Vernakalant hydrochloride
Pharmacotherapeutic group(s) (ATC code)	Cardiac therapy, other antiarrhythmics class I and III (C01BG11)
Marketing authorisation Holder	Correvio
Medicinal product(s) to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	BRINAVESS®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class BRINAVESS contains the active substance vernakalant hydrochloride. Vernakalant hydrochloride is a synthetic enantiomerically pure chemical entity and is chemically described as (3~{R})-1-[(1~{R},2~{R})-2-[2-(3,4-dimethoxyphenyl)ethoxy]cyclohexyl]pyrrolidin-3-ol;hydrochloride. Vernakalant is an atria-specific multichannel blocker of certain potassium channels, atypical class III antiarrhythmic.
	Summary of mode of action Vernakalant acts preferentially in the atria to prolong atrial refractoriness and to rate-dependently slow impulse conduction. These anti-fibrillatory actions on refractoriness and conduction are thought to suppress re-entry and are potentiated in the atria during atrial fibrillation. The relative selectivity of vernakalant on atrial versus ventricular refractoriness is postulated to result from the block of currents that are expressed in the atria, but not in the ventricles, as well as the unique electrophysiologic condition of the fibrillating atria. However, blockade of cationic currents, including human *ether-à-go-go*-related gene (hERG) channels and cardiac voltage-dependent sodium channels, which are present in the ventricles has been documented.
	Important information about its composition None
Hyperlink to the Product Information	eCTD Module 1.3.1
Indication(s) in the EEA	Current: Rapid conversion of recent onset atrial fibrillation to sinus rhythm (SR) in adults

	-For non-surgery patients: atrial fibrillation ≤ 7 days duration -For post-cardiac surgery patients: atrial fibrillation ≤ 3 days duration
	Proposed: Not applicable
Dosage in the EEA	Current: BRINAVESS is dosed by patient body weight, with a maximum calculated dose based upon a body weight of 113 kg. The recommended initial infusion is 3 mg/kg to be infused over a 10-minute period. • For patients weighing ≥ 113 kg, the maximum initial dose of 339 mg (84.7 mL of a 4 mg/mL solution) should not be exceeded. If conversion to SR does not occur within 15 minutes after the end of the initial infusion, a second 10-minute infusion of 2 mg/kg may be administered. • For patients weighing ≥ 113 kg, the maximum second infusion of 226 mg (56.5 mL of 4 mg/mL solution) should not be exceeded. Cumulative doses of greater than 5 mg/kg should not be administered within 24 hours.
	Proposed: Not applicable
Pharmaceutical form(s) and strength(s)	Current: Concentrate for solution for infusion (sterile concentrate). Each ml of concentrate contains 20 mg of vernakalant hydrochloride which is equivalent to 18.1 mg of vernakalant free base. Clear and colourless to pale yellow solution with a pH of approximately 5.5.
	Proposed: Not applicable
Is the product subject to additional monitoring in the EU?	No

PART II: Safety Specification

PART II: Module SI- Epidemiology of indication(s) and target population(s)

Atrial fibrillation in non-surgery patients and post-cardiac surgery patients

Incidence and Prevalence

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia and in the last two decades, AF has become one of the most important public health issues and an important cause of health care expenditure in western countries (Munger, TM *et al* 2014). Within the developed countries, epidemiology studies of AF published between the end of the 20th century and the first years of the 21st century estimated AF prevalence between 0.5% and 1% of the general population (Go, AS *et al*. 2001, Murphy, NF *et al* 2007). However, in the last decade, the perceived prevalence of AF, by number of hospitalisations, emergency room visits, and burden of outpatient visits for AF, is markedly higher. The most recent studies have confirmed this perception and revealed the prevalence of AF in the general adult population of Europe is more than double that reported just one decade earlier, ranging from 1.9% in Italy, Iceland, and England to 2.3% in Germany and 2.9% in Sweden (Murphy, NF *et al* 2007, Ruskin JN and Singh JP 2004).

The Rotterdam Study, a population-based prospective cohort of residents in the Netherlands aged ≥ 55 (1990-1999) reported incidence rates of AF or Atrial flutter (AFL) of 9.9 per 1000 patient-years (11.5 among men, 8.9 among women). Age-specific rates increased from 1.1 per 1000 among subjects aged 55-59 years to 20.7 for subjects 80-84 years of age. Incidence was higher in males than in females across all age groups (Heeringa, J *et al*. 2006).

Among acute emergency medical admissions in the UK, 3–6% had AF, and about 40% were newly diagnosed (Lip, GYH *et al*. 2007). In Spain, the prevalence of AF in people >60 years of age was 9.3% for males and 7.9% for females (Cea-Calvo, L *et al*. 2007). In the Netherlands, the prevalence was estimated at 5.5% overall, rising from 0.7% in 55–59 years to 17.8% in those aged 85 years and above (Heeringa, J *et al*. 2006).

In the USA, approximately 2% of people younger than age 65 have AF, while about 9% of people aged 65 years or older have AF. It appears that the prevalence of AF has increased by 0.3% per year in Medicare beneficiaries older than 65 years, with an absolute growth of 4.5% (from 4.1% to 8.6%) in the period 1993–2007 (Friberg, L and Bergfeldt, L 2013).

The objective of the AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study was to estimate prevalence of atrial fibrillation and US national projections of the numbers of persons with atrial fibrillation through to the year 2050. It involved a cross-sectional study of adults aged 20 years or older who enrolled in a large health maintenance organisation (HMO) (n=17974) in California and who had atrial fibrillation diagnosed between 01 July 1996 and 31 December 1997. Prevalence of AF was 0.95% (men 1.1% vs. 0.8% women) among adults ≥20 years of age. Prevalence increased from 0.1% among adults younger than 55 years to 9.0% in persons aged 80 years or older. Among persons aged 50 years or older, prevalence of atrial

fibrillation was higher in whites than in blacks (2.2% vs 1.5%). Applying the age- and sex-specific prevalence calculations of atrial fibrillation in their study population to the 1995 United States census it was estimated at the time of the study that approximately 2.3 million US adults had atrial fibrillation. It was projected that this will increase to more than 5.6 million (lower bound, 5.0; upper bound, 6.3) by the year 2050, with more than 50% of affected individuals aged 80 years or older (Go, AS *et al*. 2001). During the period 1985-1999 hospitalisations for patients with a diagnosis of AF in the US tripled from approximately 0.8 million to more than 2 million (Wattigney, WA *et al* 2003).

Data extrapolated from the Framingham heart study, a long-term, ongoing cardiovascular cohort study on residents of the city of Framingham, Massachusetts, suggest an incidence of acute AF in men of 3 per 1000 patient-years at 55 years of age, rising to 38 per 1000 patient-years at 94 years of age. In women, the incidence was 2 per 1000 patient-years at 55 years of age and 32.5 per 1000 patient-years at 94 years of age. The prevalence of AF ranged from 0.5% for people aged 50–59 years to 9% in people aged 80 to 89 years (Lip, GYH and Watson T 2007).

Similar age-related increases in incidence were found in a recent study based on the Atherosclerosis Risk in Communities (ARIC) cohort (a multi-site, prospective, biracial cohort study from four U.S. communities) from 0 and 0.4 per 1000 patient-years in white and black women aged 45-49 years, to 33.1 and 29.3 per 1000 patient-years in white and black women 80+ years (Alonso, A *et al*. 2009). In men, the corresponding numbers were 1.4 and 0.7 per 1000 patient-years in white and black men aged 45-49 years, and 47.5 and 41.1 per 1000 patient-years in white and black men aged 80+ years (Alonso, A *et al*. 2009).

A Global Burden of Disease (GBD) 2010 study systematically reviewed population-based studies of AF published from 1980 to 2010 from the 21 GBD regions to estimate global/regional prevalence, incidence, and morbidity and mortality related to AF. The GBD 2010 Study was a collaborative effort led by a consortium that included Harvard University, the Institute for Health Metrics and Evaluation at the University of Washington, Johns Hopkins University, the University of Queensland, the University of Tokyo, Imperial College London, and the World Health Organisation. Of 377 potential studies identified, 184 met pre-specified eligibility criteria. The estimated number of individuals with AF globally in 2010 was 33.5 million (20.9 million men and 12.6 million women). Burden associated with AF, measured as disability-adjusted life-years, increased by 18.8% in men and 18.9% in women from 1990 to 2010. In 1990, the estimated age-adjusted prevalence rates of AF (per 100 000 population) were 569.5 in men and 359.9 in women; the estimated age-adjusted incidence rates were 60.7 per 100 000 person-years in men and 43.8 in women. In 2010, the prevalence rates increased to 596 in men and 373.1 in women; the incidence rates increased to 77.5 in men and 59.5 in women. Mortality associated with AF was higher in women and increased by 2-fold and 1.9-fold in men and women, respectively, from 1990 to 2010. Developed countries had higher prevalence rates compared with developing countries with this difference being more pronounced in men than in women. The lowest prevalence rates (2010) were estimated in the Asia-Pacific region for

both men and women (340.2 and 196.0, respectively) and the highest rates were estimated in North America (925.7 for men and 520.8 for women) (Chugh SS *et al* 2014)

The number of new cases each year of AF increases with age. In individuals over the age of 80, it affects about 8% (Fuster, V *et al* 2006). AF is also more common in males than in females, in European and North American populations (Schnabel RB *et al* 2015). The increase in AF prevalence can be attributed both to better detection of silent AF, alongside increasing age and conditions predisposing to AF (Kirchhof P *et al*. 2016; Schnabel RB *et al* 2015). In conclusion, as the population ages globally, AF is predicted to affect 12.1 to 15.9 million people in the USA by 2050 and 17.9 million in Europe by 2060 (Miyasaka, Y *et al*. 2006 and Krijthe, BP 2013). As AF is associated with significant morbidities and mortality, this increasing population burden of AF will have major public health implications.

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease

Among Euro Heart Survey participants with first or paroxysmal AF, mean age was 64-66 years, 43% were female (Nieuwlaat, R *et al*. 2005). Cross-sectional study of adults ≥20 years of age enrolled in large HMO organisation in California who were diagnosed with AF (n=17974) during 1996-1997, had a mean age of 71.2, 43% were female, and race/ethnicity distribution was White (85%), black (3.6%), hispanic/latino (2.5%), other (9.1%). Prevalence increased from 0.1% among adults younger than 55 years to 9.0% in persons aged 80 years or older (Go, AS *et al*. 2001).

In the ARIC cohort, the incidence increased for black women from 0.4 (age 45-49) years to 29.3 per 1000 patient-years (age 80+), and for white women from 0 to 33.1 per 1000 patient-years for the same age groups (Alonso, A *et al*. 2009). In men, AF incidence increased from 0.7 (black men) and 1.4 (white men) per 1000 patient-years for age 45-49 years, to as high as 41.1 (black men) and 47.5 (white men) per 1000 patient-years for age 80+ years (Alonso, A *et al*. 2009).

AF is a condition more common in older patients. Increasing age is associated with increased risk of developing AF in the developed countries. Other risk factors include heart disease, high blood pressure (BP), obesity, family history and chronic conditions for example, diabetes, thyroid problems, sleep apnoea, and metabolic syndrome.

AF is the most common sustained arrhythmia in adult clinical practice. It is most often recognised today because it causes symptoms that lead patients to seek help from their physicians or hospital emergency departments (Bhandari, AK *et al*. 1992). Atrial fibrillation accounts for approximately one-third of hospitalisations for cardiac rhythm disturbances (Fuster, V *et al*. 2006).

In addition to causing symptoms, AF carries with it an increased risk of morbidity and mortality. For example, the risk of having a stroke is increased 3-5 fold in persons who have AF and

approximately 15-30% of all strokes that occur are related to AF (Go, AS *et al*. 2001, Kannel, WB *et al*.1998, Kirchhof P *et al*. 2016).

Main treatment options

Atrial fibrillation can be treated either by rate control (i.e., allow the AF to continue but control the ventricular response rate by slowing the conduction through the atrioventricular node with calcium channel blockers, beta-blockers and/or digoxin) or by rhythm control (convert to SR with non-pharmacological and/or pharmacological therapies and attempt to maintain SR with maintenance medications), or a combination of rate and rhythm control therapy. Symptomatic patients generally seek treatment in order to reduce their symptoms. Although in several large clinical studies, no mortality difference was initially seen between generally asymptomatic patients in a rhythm control strategy versus a rate control strategy (Wyse, D *et al*. 2002), more recent data suggests that antiarrhythmic treatment of high-risk elderly AF patients was associated with reduced hospitalisations due to cardiovascular events or death as well as reduced cardiovascular mortality (Hohnloser, SH *et al*. 2009). In general, for acute onset AF with rapid ventricular response, rate control needs to be established before rhythm control is contemplated. Rhythm control can be achieved acutely by either electrical or pharmacological means as described in more detail below.

The comprehensive efficacy and safety of pharmacological versus electrical cardioversion (ECV) have not been compared directly in any prospective studies. While pharmacological approaches may be less efficacious, they are simpler and do not require either general anaesthesia or conscious sedation.

Both electrical and pharmacologic conversion success is influenced by the duration of AF: patients with AF of shorter duration (≤ 7 days) have a higher likelihood of electrical conversion as well as pharmacological conversion (Fuster, V *et al*. 2006). AF of longer duration (>7 days) has less frequent pharmacological conversion. Similarly, lower success rates of ECV have been observed in patients with longer duration AF (Dahlin, J *et al*. 2003, Van Gelder, IC *et al*. 1991). Interestingly, in a multicentre, multicohort study analysing 4356 electrical cardioversions, the relationship between AF episode duration and successful cardioversions showed a J-shaped curve; patients with AF episodes lasting 24 to 48 hours had the highest rate of successful cardioversions whereas the patient group with the shortest AF episodes (<24h) had slightly less successful cardioversions. In multivariate analysis, >48-hour duration of index episode of AF independently predicted unsuccessful CV (odds ratio [OR]: 1.79, 95% CI: 1.41–2.26, P < 0.01) (Hellman *et al*. 2018). In contrast, for pharmacological cardioversion, including with Brinavess, highest success rates are observed in patients with the shortest AF duration (Juul-Möller, S. *et al*. 2013; Carbajosa Dalmau, J *et al*. 2017)

ECV is commonly used for the conversion of AF to SR when a rapid ventricular response to AF does not respond promptly to pharmacological therapies and contributes to ongoing myocardial ischaemia, hypotension or heart failure. ECV is more effective than pharmacological conversion when biphasic shocks are used and has shown better efficacy in

the "acute phase". ECV is also the method recommended for haemodynamically unstable AF patients (January, CT *et al.* 2014). ECV can be highly effective with studies showing conversion rates of ~90% in clinical practice. ECV was defined as successful if sinus rhythm was obtained and maintained for at least 10 minutes after the last shock (Crijns, HJ *et al*. 2014; Stiell, IG *et al*. 2010). Adverse Events (AEs) associated with ECV include ventricular arrhythmia (ventricular tachycardia or fibrillation in association with delivery of non-synchronous shocks), hypotension, sinus pause, complete heart block, bradycardia, skin burns, pain, and pulmonary oedema (Gallagher, MM *et al*. 2008; Guedon-Moreau, L *et al*. 2007; Gronberg, T *et al*. 2013; Pisters, R *et al*. 2012). In a registry study of periprocedural complications of cardioversion, major complications in the electrocardioversion group included sick sinus syndrome, major bleeding, and non-sudden cardiac death (Pisters, R *et al*. 2012). ECV may prolong recovery of normal atrial contraction and increase the risk of stroke in the early post-cardioversion phase compared with pharmacological conversion (Fatkin, D *et al*. 1994; Harjai, KJ *et al*. 1997; Manning, WJ *et al*. 1989; Mattioli, AV *et al*. 1998). Pacemaker malfunction has also been reported (Waller, C *et al*. 2004).

While less effective than the electrical method in treating patients with atrial fibrillation of less than 48 hours duration, pharmacologic rhythm control has practical advantages. ECV requires additional staff for safe administration and can be frightening for some patients. An important benefit of pharmacological conversion is to provide an alternative to ECV and its associated risks, including risks associated with sedation and anaesthesia (Guedon-Moreau, L *et al*. 2007; Burton, JH *et al*. 2004 and 2006), ventricular tachycardia and fibrillation, bradyarrhythmias, skin burn or irritation from electrodes, muscle soreness, and reprogramming or altering implanted cardiac device function (January, CT *et al*. 2014; Knight, BP *et al*. 2015). Risks that may be associated with the sedation/anaesthesia for ECV include hypotension (Desai, PM *et al*. 2015), respiratory depression, hypoxaemia, respiratory arrest (sometimes requiring ventilator support), and aspiration pneumonia (Ambler, JS. *et al*. 2004; Botkin, SB *et al*. 2003; Canessa, R *et al*. 1991; Gallagher, MM *et al*. 2008; Gowda, RM *et al*. 2004; Guedon-Moreau, L. *et al*. 2007; Hullander, RM *et al*. 1993; Lewis, SR *et al*. 2015; Mitchell, ARJ *et al*. 2003; Niebauer, MJ *et al*. 2004). As per the latest ESC guidelines for AF, the decision for PCV or ECV for recent onset, hemodynamically stable AF should be by patient choice (Kirchhof, *et al*. 2016).
A prospective international multicentre observational study comparing pharmacological and electrical conversion found that pharmacological patients were converted sooner after admission and had a shorter stay in hospital (Crijns, HJ *et al*. 2014). Furthermore, ECV is not indicated for all patients with AF, such as patients with digoxin toxicity, severe hypokalaemia or other electrolyte imbalances (January, CT *et al*. 2014), and it is beneficial to have other treatment options for patients with impaired respiratory function, and patients who have recently undergone cardiac surgery. Pharmacological cardioversion may also reduce the risk of early recurrence of AF (Gillis, AM *et al*. 2011). Additionally, non-pharmacological treatment modalities exist (Gillis, AM. *et al* 2011).

Although, different treatment modalities for conversion of AF to SR already exist, treatment of AF is still unsatisfactory in certain patient populations. Additionally, logistical constraints complicate successful treatment of AF patients.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

If left untreated, persistent AF eventually becomes permanent. The mortality of patients with AF is approximately double that of patients in normal SR and is linked with the severity of the underlying heart disease (Fuster, V *et al*. 2006, Vidaillet, H *et al*. 2002). Among a 5% sample of Medicare recipients aged 65 to 89 years in the US (1991-1998), hospitalised for AF, the case-fatality rate was 1.7% (95% CI 1.6, 1.8) (Baine, WB *et al*. 2001). Long-term mortality among the AF population is available from the Framingham Heart Study. Among subjects 55 to 74 years of age who developed AF during the study, by 10- years of follow-up, 61.5% of men with AF had died compared to 30.0% without AF. Among women, 57.6% with AF had died compared to 20.9% without AF. Mortality at 30-days and between 30-days to 1-year following - detection of AF with Electrocardiogram (ECG) was 15.2% and 53.0% among men, and 14.5% and 48.0% among women, respectively (Benjamin, EJ *et al*. 1998).

Important co-morbidities

Hypertension was the most common co-morbid condition in the Euro Heart Survey, present in 62-63% of patients with AF ≤7 days. Other co-morbidities are as follows:

- Coronary artery disease was present in 32-34% of patients with AF ≤7 days.
- Heart Failure was present in 23-26% of patients with AF ≤7 days.
- Valvular heart disease was present in 19-21% of patients with AF ≤7 days.
- Cardiomyopathy was present in 7-8% of patients with AF ≤7 days.
- Sick sinus syndrome was present in 1-6% of patients with AF ≤7 days.
- Chronic obstructive pulmonary disease was present in 11-12% of patients with AF ≤7 days.
- Diabetes was present in 15-19% of patients with AF ≤7 days.
- Hyperlipidaemia was present in 32-40% of patients with AF ≤7 days.
- Prevalence of previous thromboembolic events in patients with AF ≤7 days:
- Previous thromboembolism (not specified): 9-11%

- Stroke: 4%
- Transient ischaemic attack: 3-6%
- Other thromboembolism: 2-3%

PART II: Module SII - Non-clinical part of the safety specification

The preclinical safety programme for vernakalant consisted of intravenous (IV) and oral studies evaluating single-dose toxicity, repeat-dose toxicity (tested in rats and dogs for up to 1 month in duration to support IV use, and up to 6 and 9 months for chronic oral use), reproductive and developmental toxicity (embryofoetal studies of vernakalant administered via the oral and IV routes, and male and female fertility and developmental and perinatal/postnatal reproduction toxicity studies in rat after IV use), an assessment of safety pharmacology, and genotoxicity testing. Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, single- and repeated-dose toxicity, and genotoxicity.

Table 1 Key safety findings from non-clinical studies and relevance to human usage:

Key safety findings	Relevance to human usage
Toxicity	
Single and repeat-dose toxicity The programme consisted of IV and oral studies evaluating single-dose toxicity and repeat-dose toxicity (tested in rats and dogs for up to 1 month in duration to support IV use, and up to 6 and 9 months for chronic oral use). The maximum tolerated dose (MTD) of intravenously administered vernakalant was 40 mg/kg, 50 mg/kg and 30 mg/kg, in rats, rabbits, and dogs, respectively. Prominent central nervous system (CNS) clinical signs including tremors, uncoordinated movement/gait, increased salivation, vomiting, decreased activity, convulsions, respiratory arrest, and decreased respiration in rats and dogs at maximal plasma concentrations (≥10,600 ng/ml) following IV administration of vernakalant. Adverse signs at the MTD may be related to the pharmacological activity (i.e. ion channel blockade) of vernakalant Repeat-dose IV vernakalant toxicology studies of 7 to 28 days in duration were conducted in rats at single doses up to 40 mg/kg/day administered as a 2-minute IV infusion. In the 28-day IV study, mortality was observed at 40 mg/kg/day. Clinical signs prior to death included tremors, uncoordinated gait, decreased respiration, and decreased activity. The effects of IV vernakalant at doses up to 20 mg/kg as a 10-minute infusion were examined in dogs in repeat dose studies of 7, 14 and 28 days duration. No mortality was observed. Findings at doses of 20 mg/kg IV when given for up to 14 days consisted of tremor, uncoordinated gait,	CNS-associated adverse effects were observed only at exposures considered sufficiently in excess of the maximum human exposure, (40 mg/kg IV in rats, 20 mg/kg IV in dogs) indicating little relevance to clinical use. The maximum plasma concentration (C_{max}) of vernakalant in dogs and rats was 2.5 and 6.0 times of that achieved in humans at the maximum recommended dose, respectively. It is also important to note that adverse effects seen in the nonclinical toxicology studies were C_{max} related, for which there are good safety margins relative to human exposure. The relatively low safety margins for Area under curve (AUC) exposure are likely of no clinical significance in view of the fact that vernakalant is intended for single acute administration (up to 5 mg/kg total dose), and the fact that in the 28-day toxicology studies, no target organ toxicity was found.

Key safety findings	Relevance to human usage
excessive salivation, and an episode of clonic convulsions. In both the 7- and 14-day studies, these clinical findings were limited to the initial hour post-dose. In the 28-day IV study, test article-related findings consisted of salivation, tremors and emesis at ≥10 mg/kg/day, with animals also exhibiting aggressive behaviour.	
Genotoxicity Vernakalant showed no evidence of mutagenicity in the bacterial reverse mutation assay (Ames test). In additional studies vernakalant was not genotoxic in the *in vitro* mouse lymphoma assay or the *in vivo* mouse micronucleus test (where vernakalant was administered via the IV route). Vernakalant caused chromosomal aberrations in Chinese hamster ovary cells, with and without metabolic activation (S9), but only under test conditions where cytotoxicity was greater than 60%.	No evidence of genotoxic effects
Reproductive/developmental toxicity Maternal/paternal toxicity of male and female rats consisted of mortality, discolouration (red to purple), and/or swelling at the injection site at doses of 20-40 mg/kg/day. The no observable adverse effect level (NOAEL) for general toxicity (parent generation) was 10 mg/kg/day. The reproductive NOAEL for reproductive toxicity of males and females was >40 mg/kg/day. In rats administered IV vernakalant on gestational days 6 to 17, the NOAEL for general toxicity of dams, reproductive function, and embryo-foetal development was 40 mg/kg/day, the highest dose tested. In rabbits administered vernakalant at doses of 3, 10, and 30 mg/kg/day on gestational days 7 to 18, mortality occurred at the 30 mg/kg/day dose level. Clinical findings at 30 mg/kg/day consisted of rapid breathing, ataxia, and dilated pupils, and occasionally tremors, convulsions, and splayed limbs. Based on these results, the NOAEL was determined to be 10 mg/kg/day for the general toxicity in dams and was 30 mg/kg/day for reproductive and embryonic developmental toxicity. Vernakalant was not teratogenic in this study. The effects of IV vernakalant at doses up to 40 mg/kg on pregnant rats were evaluated from implantation, through gestation, parturition, and	With respect to reproduction, no effects on pregnancy, embryo-foetal development, parturition or postnatal development were observed after IV administration of vernakalant at exposure levels (AUC) similar or below the human exposure levels (AUC) achieved after a single IV dose of vernakalant. Repeated oral administration of vernakalant was shown to induce teratogenic effects in animals. These effects were unlikely to occur in humans based on the recommended clinical dosage consisting of a single IV administration of vernakalant. However, as a precautionary measure, it is preferable to avoid the use of vernakalant during pregnancy.

Key safety findings	Relevance to human usage
lactation, with observation continued through sexual maturity of the F1 generation. Maternal toxicity included mortality in two females at 40 mg/kg/day, with clinical signs of hyperpnoea also observed. All other maternal parameters were unaffected at vernakalant. The maternal NOAEL was 20 mg/kg/day. The NOAEL for reproduction in the dams and viability and growth in the offspring was >40 mg/kg/day. In embryo-foetal development studies with oral administration of vernakalant two times a day resulting in exposure levels (AUC) generally higher than those achieved in humans after a single IV dose of vernakalant malformations (misshapen/absent/fused skull bones including cleft palates, bent radius, bent/misshapen scapula, constricted trachea, absent thyroid, undescendent testes) occurred in rats and increased embryo-foetal lethality, increased number of foetuses with fused and/or additional sternebrae were seen in rabbits at the highest doses tested.	
Safety pharmacology **Negative inotropy** In an exploratory anaesthetised dog study with IV vernakalant, there were decreases in ventricular contraction and cardiac output, and increases in total vascular resistance at a mean plasma concentration of 13.9 mcg/mL vernakalant. Heart rate and blood pressure were unaffected. However, cardiac output, cardiac contractility and blood pressure were decreased while heart rate and systemic vascular resistance increased at a mean vernakalant plasma concentration of 23.1 mcg/mL. This reduction in arterial blood pressure was mediated by the negative inotropic actions of vernakalant on cardiac function at these high plasma levels. The increase in heart rate or arterial vasoconstriction could not maintain arterial blood pressure at pretreatment these high, supra-therapeutic plasma levels at these high, supra-therapeutic doses of vernakalant. The no-effect levels of 3.16 mcg/mL vernakalant in dogs are equivalent to plasma concentrations achieved at the highest recommended human therapeutic dose of 3 + 2 mg intravenous vernakalant. The no-effect plasma level for hypotension in this study (13.9 mcg/mL) was 3 to 4-fold greater than the human therapeutic dose level	The data suggested that a potential underlying mechanism for the hypotension events seen in the vernakalant clinical trials may have been due to a negative inotropic effect. Subjects with underlying left ventricular dysfunction or CHF appear to be more sensitive to the putative negative inotropic effect of vernakalant.

Key safety findings	Relevance to human usage
Other toxicity-related information or data	
None	

PART II: Module SIII - Clinical trial exposure

The overall safety evaluation for vernakalant injection incorporates data from nine clinical studies, which included eight phase 2 and phase 3 safety and efficacy studies, and a phase 3 safety study (open-label study). Safety data were assessed in an integrated analysis that pooled data from eight of the nine studies that had similar patient populations and design elements (dose, duration of exposure, and safety data collection methods). Data from the Phase 3 MK 6621-010/Asia Pacific study were not presented in the integrated analysis, due to differences in the patient population and study design features, and these data are discussed separately.

Table 2 Exposure in all Completed Clinical Studies Conducted with Vernakalant IV

Study Number [Reference]	Study and Subject Type	Number of Subjects Treated		
		PBO	Vkt	Total
235-1-04-12-01	Phase 1 in HV	6	23	29
04-0-195 [a]	Mass balance in HV	0	8	8
VERI-103-PK (6517-CL-0011)	Dose proportionality in HV	13	12	25
MK-6621-006[a]	Biocomparison and bioavailability study in HV	0	20	20
1235-SMH1	Phase 2 in subjects undergoing EP evaluation	0	19	19
1235-1001 (CRAFT) [d]	Phase 2 in AF subjects	20	36	56
1235-0703 (ACT I)[d]	Phase 3 in AF subjects	115	221	336
1235-0504/04-7-010(ACT III)[d]	Phase 3 in AF or AFL subjects	131	134	265
1235-0104 (ACT II)[d]	Phase 3 in subjects with AF or AFL post-cardiac surgery	54	107	161
1235-0703B (SCENE 2)[d]	Phase 2/3 in AFL subjects	15	39	54
05-7-012 (ACT IV)[d]	Phase 3 in AF subjects	0	236	236
VERO-106-REN[a]	PK in subjects with RI	0	24	24
VERO-107-HEP[a]	PK in subjects with HI	0	24	24
VERI-305-AMIO [d]	Superiority vs amiodarone (n=116) in AF subjects	-	116	232[b]
6517-CL-0020 (ACT V)[c,d]	Phase 3 in AF subjects without CHF	68	129	197
6621-010 (Asia-Pacific)[c]	Phase 3 in AF patients	56	55	111
Total Number of Subjects Dosed in Completed Studies		**478**	**1203**	**1797[b]**

Atrial fibrillation; AFL: atrial flutter; CHF: Congestive Heart Failure; EP: electrophysiological; HI: hepatic impairment; HV: healthy volunteers; PBO: treated with placebo; PK: pharmacokinetic; RI: renal impairment; Vkt: treated with vernakalant.

[a] Subjects received vernakalant (oral) and vernakalant injection.

[b] Includes subjects that received amiodarone (n=116)

[C] Study terminated

[d] "All patients population" - an integrated safety analysis including safety data from clinical studies CRAFT, SCENE 2, ACT I, ACT II, ACT III, ACT IV, ACT V, and AVRO (vernakalant patients only)

Table 3 Age group and gender for All Patients Population

Exposure by age group and gender (by indication) IV Vernakalant						
	Persons					
	Male		**Female**		**All**	
Age group	**n**	**%**	**N**	**%**	**N**	**%**
<65 years	422	59%	116	32%	538	50%
>=65 years	292	41%	243	68%	535	50%
Total	714	100%	359	100%	1073	100%
<75 years	614	86%	239	67%	853	79%
>=75 years	100	14%	120	33%	220	21%
Total	714	100%	359	100%	1073	100%
All AF/AFL patients in CRAFT, ACT I, SCENE 2, ACT III, ACT II, ACT IV, ACT V, and AVRO (vernakalant patients only) studies who received any amount of study medication (refer to table 2).						

Table 4 Race and ethnic origin

Exposure By ethnic or racial origin (by indication) IV Vernakalant						
	Persons					
	Male		**Female**		**All**	
Ethnic/racial origin	**n**	**%**	**N**	**%**	**N**	**%**
White	653	91%	324	90%	977	91%
Non-White	61	9%	35	10%	96	9%
Total	714	100%	359	100%	1073	100%
All AF/AFL patients in CRAFT, ACT I, SCENE 2, ACT III, ACT II, ACT IV, ACT V, and AVRO (vernakalant patients only) studies who received any amount of study medication (refer to table 2).						

PART II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table 5 Exclusion criteria in pivotal clinical studies within the development programme

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Prolonged QRS complex (QRS interval >0.11 – 0.14 sec)	No published data are available regarding the background incidence of ECG QRS complex prolonged in patients with AF The PI warns against the use of BRINAVESS with significant prolongation of the QRS	No	Vernakalant demonstrates frequency- and voltage-dependent block of the peak sodium current in human embryonic kidney cells. Because of its rate-dependent action, vernakalant has limited ventricular effects on sodium current at normal rates, resulting in minor widening of the QRS interval at peak plasma levels during AF.
Patients with New York Heart Association (NYHA) class IV congestive heart failure (CHF), or heart failure requiring intravenous inotrope therapy	Listed within contraindications as patients with heart failure Class NYHA III and NYHA IV	Yes	Not applicable
Patients with known bradycardia or sick-sinus syndrome unless controlled by a pacemaker	Listed within contraindications as severe bradycardia, sinus node dysfunction or second degree and third-degree heart block in the absence of a pacemaker	Yes	Not applicable
Patients with significant valvular stenosis	Listed within contraindications for patients with	Yes	Not applicable

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	severe aortic stenosis		
Patients with prolonged QT (uncorrected >440msec)	Listed within contraindications for patients with prolonged QT at baseline (uncorrected >440 msec)	Yes	Not applicable
Patients had received IV Class I or Class III antiarrhythmic drugs or IV Amiodarone within 24 hours prior to dosing	Listed within contraindications in regard to use of IV rhythm control antiarrhythmics (class I and class III) within 4 hours prior to, as well as in the first 4 hours after, BRINAVESS administration.	Yes	Not applicable
Had a myocardial infarction (MI) or acute coronary syndrome (ACS) within 30 days prior to entry into the study	Listed within contraindications as ACS (including MI) within the last 30 days	Yes	Not applicable
Patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis	Listed within special warnings and precautions as 'not recommended'. Cautionary exclusion criterium, severe cases with CHF NYHA III and IV are contraindicated. Exclusion criteria added following the death of a patient with	Yes	Not applicable

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	severe aortic stenosis in the ACT III study, in order to avoid events of hypotension in the setting of restricted cardiac output.		
Hepatic impairment (HI)	Listed within special warnings and precautions as 'not recommended' Serious HI was excluded along with other serious or end stage diseases as a precautionary measure to avoid treatment of seriously ill patients	Yes	Not applicable
Use in pregnant or lactating women	The Summary of Product Characteristics (SmPC) for BRINAVESS advises against use in this population in the Fertility, pregnancy and lactation section. It is not appropriate to include pregnant or lactating females in a clinical trial of an unapproved medication	Yes	Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of ADRs such as rare ADRs, ADRs with a long latency, or those caused by prolonged or cumulative exposure. Prolonged exposure, i.e. long-term treatment is not to be expected due to the acute use short infusion of BRINAVESS.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 6 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Paediatric population (birth <18 years)	Not included in the clinical development programme
Elderly population	The mean age was 63.2 years (range 22 to 94 years, N=1073), for all vernakalant patients studied in the vernakalant development program. Among vernakalant-treated clinical trial subjects, 49.9% were ≥65 years of age (41% of total males and 68% of total females), and 20.5% were ≥ 75 years of age (14% of total males and 33% of total females). This is comparable with other atrial fibrillation populations such as the Euro Heart Survey in which the mean age was 65 years, n=3662. In an analysis of the Phase III population for the ranges, 65 years of age against ≥ 65 years of age, and < 75 years of age against ≥ 75 years of age the risk for ventricular arrhythmia (VA), hypotension, bradycardia or AFL with vernakalant was not affected by age category. No dose adjustments are necessary
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities: Patients with hepatic, renal or cardiac impairment	Overall, 15.3% of the vernakalant study population were documented as having abnormal hepatic function and 43.3% of the study population had mild or moderate/severe renal impairment. Patients with co-morbidities typical of the AF population such as hypertension, coronary artery disease, ischaemic heart disease and chronic heart failure (CHF) (excluding NYHA Class IV

Type of special population	Exposure
	heart failure, and including a limited number of patients with NYHA Class III heart failure) were included and represented a significant part of the population studied
Immunocompromised patients	Immune deficiencies were not exclusion criteria during clinical development
Population with relevant different ethnic origin	Race and ethnicity were not exclusion criteria, however most patients included in the clinical programme were Caucasian. The Asia Pacific Study evaluated the safety and efficacy of vernakalant injection in Asian patients (n=123). This study provides supportive evidence for a similar efficacy in Asian patients. Additionally, no meaningful differences compared to placebo were observed with regard to overall clinical and laboratory safety measures in the Asian study population
Subpopulations carrying relevant genetic polymorphism	CYP2D6 was identified as the primary isozyme responsible for vernakalant metabolism. Differences in vernakalant metabolism have been observed in CYP2D6 poor metabolisers (PMs) compared to extensive metabolisers (EMs) following a dose of vernakalant injection. Despite these differences, dose adjustment based on metaboliser status is not deemed necessary, due to the similarity in acute exposure (Cmax and AUC0-90min) in PMs and EMs resulting from the rapid distribution and elimination following the IV dose. Vernakalant concentration profiles are similar between EM and PM patients over the ~2 hour period from start of the first infusion to ~90 minutes post second infusion. Too few PMs (1.9%, 17/889 patients) were enrolled to allow a meaningful evaluation of safety by genotype (see Part II SIII; Cumulative Subject Exposure to vernakalant IV from Completed Clinical Trials by Baseline Characteristics). No potential impact of genetic polymorphisms is anticipated as vernakalant is intended as an acute use intravenous infusion

PART II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Vernakalant vials are for single use only and dosed by patient body weight. Post-marketing exposure was estimated using marketed product distribution data of the 500 mg vial of vernakalant, with the assumption that one vial of vernakalant concentrate corresponds to one course of treatment (one patient). As dosing of vernakalant IV is weight-based, and the approved treatment regimen allows for use of up to two infusions per course of treatment, it is possible that this algorithm may result in an over-estimate of post-marketing patient exposure.

SV.1.2 Exposure

The estimated cumulative exposure to BRINAVESS in the marketed setting from 01 September 2010 until 31 August 2018 is 50,276 treatment courses.

PART II: Module SVI - Additional EU requirements for safety specification

Potential for misuse for illegal purposes

As vernakalant is not a drug of abuse and produces no CNS effects sought by those who abuse drugs, it is unlikely that it will be misused for illegal purposes.

PART II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable since this is not an initial version of the Risk Management Plan (RMP).

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

None

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important identified risk 1: Hypotension

Potential mechanism(s):

The mechanism is not understood. To investigate potential mechanisms underlying hypotensive events associated with vernakalant injection, preclinical experiments were performed. Data from anaesthetised dogs suggest that a potential underlying mechanism for the hypotension events seen in the vernakalant clinical trials may have been due to a negative inotropic effect. However, the negative inotropic effect of vernakalant in anaesthetised dogs was seen at high plasma concentrations (there is a ≥3-fold margin above the C_{max} observed at therapeutic doses in clinical trials to the negative inotropic effect seen in dog studies). In the conscious IV dog cardiovascular safety pharmacology study, doses of up to 20 mg/kg were not associated with hypotensive findings, and exposures (C_{max}) attained in this study were 2.3-fold higher than those obtained at human therapeutic doses (3±2 mg/kg). AUC was approximately 1X of human anticipated AUC.

In an IV anaesthetised cardiovascular study in dogs, the no-effect level in dogs (2 mg/kg) was equivalent to 0.7X the plasma concentrations achieved at the highest recommended human therapeutic dose of 3 ± 2 mg IV vernakalant. At a dose of 8 mg/kg (3.2X), a decrease in cardiac output and dP/dt_{max} was observed along with an increase in left ventricular end diastolic pressure, dP/dt_{min}, tau, and total vascular resistance. Hypotensive findings (HR ↑ and MAP↓) were observed at a mean vernakalant plasma concentration of ~23100 ng/ml (5.3X), and could be an extension of/a secondary effect of the aforementioned negative ionotropic findings that began following dosing at 8 mg/kg. In conscious dogs at clinically relevant plasma levels (3-4 ug/ml at 15-30 min of IV infusion), a mild increase in BP, peripheral resistance and left ventricular end diastolic pressure, with no changes in HR, mean cardiac output, calculated ejection volume and rate of left ventricular (LV) pressure development (LV+dP/dt) was seen.

At higher doses in conscious dogs, decreases in LV+dP/dt and calculated ejection volume were observed. In a conscious dog, cardiac dysfunction model at clinically relevant plasma levels (3-4 ug/ml at 15-30 mins of IV infusion), similar haemodynamic effects, with increased HR, decreased mean cardiac output, calculated ejection volume with no change in LV+dP/dt were

observed. One dog in this model with the most severe cardiac dysfunction and a higher vernakalant plasma level (5.6 ug/ml at 9 mins of IV infusion) displayed abrupt hypotension and bradycardia and was not recovered. These data confirm and extend initial observations in the anesthetised dog study.

The effects of infusion rate on vernakalant's haemodynamic and ECG effects were assessed in the telemeterised conscious male Beagle dog prior to and after atrial remodelling (atrial tachy-pacing induced AF). Dogs were administered flecainide (positive control), in 2 dosing schemes (2.75 - 4 mg/kg), and vernakalant in 3 dosing schemes (4 - 8 mg/kg total dose). Haemodynamic parameters (systolic, diastolic, mean arterial pressure, peripheral venous pressure, left ventricular pressure, end diastolic pressure, + dP/dt, – dP/dt, maximum and mean cardiac output, stroke volume, temperature pulse respiration) and electrocardiographic parameters (including heart rate, P-wave duration, PR, QRS, QT/cV, paced QT interval and atrial effective refractory period) were recorded throughout the experiment. The results of this study showed a dose dependent and transient negative inotropic effect, as evidenced by moderate decreases from baseline in ventricular contractility (+dP/dt), with both vernakalant and flecainide infusions. At the infusion rates tested, the haemodynamic effects of vernakalant were similar or milder relative to dosing with the positive control, flecainide. In vernakalant treated healthy dogs, the effect on +dP/dt was compensated for (e.g., via increased peripheral resistance) leading to maintained systolic BP, as well as stable cardiac output. There was no evidence of drug induced vasodilation, or suppression of compensatory mechanisms with vernakalant infusion in the healthy dogs. The effects on contractility (dP/dt) were reversible upon termination of infusion, with recovery towards baseline evident during the subsequent hour of monitoring. The protocol originally included atrial tachy-pacing; however, due to a rapid ventricular response to atrial pacing with induction of heart failure and death of a dog, that portion of protocol was terminated.

In vitro studies conducted with 1-10 uM vernakalant in isolated human pre-contracted resistance arteries and in LV trabecular bundles stimulated to contract at a frequency of 1Hz demonstrated no significant effects on vascular tone or on contractile function, respectively. These *in vitro* mechanistic studies in human vascular and cardiac tissue do not support direct vasorelaxant or negative inotropic actions as underlying mechanisms for hypotension at the concentrations tested.

Evidence source(s) and strength of evidence:

Clinical trial data (BRINAVESS Company Core Data Sheet (CCDS); Marketing Application (MAA) Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO Clinical Study Report [CSR]; ACT V CSR); published information on other anti- arrhythmic products; post-marketing AE report data [company Pharmacovigilance (PV) database [Worldwide Adverse Experience System, WAES]), integrated safety analysis.

Characterisation of the risk:

Frequency

A recently performed integrated safety analysis included safety data from clinical studies SCENE 2, ACT I, ACT II, ACT III, ACT IV, ACT V, and AVRO (vernakalant patients only)

(All Patients population excluding CRAFT). Hypotension was characterised as an identified risk from analysis of a primary safety population consisting of all patients with atrial fibrillation or atrial flutter who received any amount of study medication (1365 total patients, including 982 vernakalant patients, 383 placebo patients). This population was used for all safety analyses and all tables were derived from this dataset. Hypotension events generally occurred within 15 minutes of the end of vernakalant injection and resolved without sequelae. Overall, treatment with vernakalant injection was not associated with a significantly increased number of hypotension events compared to placebo. In the analysis of hypotension from the AE database, a significantly increased incidence of hypotension in the first 2 hours post-dose became apparent. There were no differences in incidence of hypotension identified from vital signs (systolic BP <90 mmHg) between groups. Over the first 24 hours post-dose there was no significant increased incidence of hypotension with vernakalant treatment.

Frequency of Hypotension

Table 7 Frequency of Hypotension

Hours Post-dose	Vernakalant (%)	Placebo (%)	Risk difference	95% CI
0-2				
Any hypotension event	**5.7**	**5.5**	**0.2**	**-2.7, 3.1**
Hypotension from AE database	4.1	1.6	2.5	0.6, 4.4
Hypotension from vital signs	4.8	5.5	-0.7	-3.5, 2.1
2 and 24				
Any Hypotension Event	**3.5**	**6.0**	**-2.5**	**-5.4, 0.3**
Hypotension from AE database	1.5	2.1	-0.6	-2.4, 1.2
Hypotension from vital signs	2.6	5.0	-2.3	-4.9, 0.3

In patients with a history of CHF who received vernakalant, there was a significantly increased incidence of hypotension in the first 2 hours post-dose. This significantly increased incidence was not apparent in the 2-24 hour post-dose period and in the analysis of overall time period of the first 24 hours.

Frequency of Hypotension in patients with a history of CHF

Table 8 Frequency of hypotension with a history of CHF

Hours Post-dose	Vernakalant	Placebo	Risk difference	95% CI
Any	26/157 (16.6%)	7/64 (10.9%)	5.6	-5.1, 16.3
0-2	21/157 (13.4%)	3/64 (4.7%)	8.7	0.2, 17.2
2-24	9/157 (5.7%)	4/64 (6.3%)	-0.5	-8.6, 7.5

Note: All patients excluding CRAFT population includes the following studies: SCENE 2, AVRO (Vernakalant subjects only), ACT I, ACT II, ACT III, ACT IV, ACT V.

Multiple occurrences of the same event in one individual are counted only once. Within a data source, subjects may have experienced more than one type of event. The sum of terms by source may exceed 100%.

In patients without a history of CHF the incidence of hypotension was not significantly different during the first 2 hours after dose in patients treated with vernakalant compared to patients receiving placebo (35/825; 4.2% vs. 18/319; 5.6%, respectively; risk difference: -1.4, 95% CI, -4.5, 1.7).

Asia Pacific Study: Evaluated the safety and efficacy of vernakalant injection in Asian patients (n=123). The study was not part of the integrated analysis and is therefore described separately. There were no hypotension AEs within 0-24 hours post dose in the vernakalant group in the AP Study. Three PBO patients (5%, 3/56) had a hypotension AE within 2-24 hours post dose. There were zero (0) events of hypotension that led to discontinuation of study drug. One vernakalant patient (2%, 1/55) had a Serious Adverse Event (SAE) of neurogenic shock >24 hours post dose, considered unrelated to study drug.

PV database (including CT and Post-marketing data):

Cumulatively, a total of sixty-two (62) Individual Case Safety Reports (ICSRs) which included sixty-two (68) adverse events (AEs) of hypotension or suggestive of hypotension were received. Of the sixty-two (62) ICSRs, thirty-eight (38) were received from spontaneous sources: eighteen (18) were clinical study ICSRs, and five (5) were received from solicited sources (SPECTRUM, source: SPECTRUM CSR. Eight (8) AEs of hypotension in total were assessed as not related to BRINAVESS therapy.

Severity

In the SPECTRUM study, there were five (5) SAEs of Hypotension and all resolved (SPECTRUM CSR). Two SAEs of significant hypotension occurred simultaneously with the SAE of significant bradycardia (considered Health Outcomes of Interest (HOIs)). The two additional events of hypotension were not considered as HOIs. There is one additional case from the SPECTRUM study, which describes the occurrence of hypotension characterised as non-significant.

Reversibility

Clinically meaningful hypotension (i.e., reported as a SAE or requiring discontinuation of treatment) within the first 2 hours of study medication was reported in nine patients in the 'All Patients' population and the Asia Pacific study, 8 in the vernakalant group (8/1073; 0.7%) and 1 in the placebo group (1/459; 0.2%).

Among patients with a history of CHF, clinically meaningful hypotension during the first 2 hours post dose occurred in 1.8% (4/221) of vernakalant treated patients compared to 0.3% (4/1144) in patients without a history of CHF.

The median duration of the hypotension in the 'All Patients' population was 18.5 minutes and occurred at a median of 37 minutes from the start of the first infusion (i.e., 2 minutes after the end of the scheduled second infusion). Not all patients required treatment. In general, patients were placed in the Trendelenburg position and the hypotension responded to treatment with a saline infusion (see severity and nature of the risk). Overall, hypotension with vernakalant was generally transient and typically responded to discontinuation of the study drug and routine management.

A SAE of cardiogenic shock, occurring on day 1 after study drug administration, leading to death, occurred 29 days after study drug administration, in the study, ACT V ("A Phase IIIb Double-Blind, PBO Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of Vernakalant Hydrochloride Injection in Patients with Recent Onset Atrial Fibrillation" [protocol 6517-CL-0020]). The Investigator considered the event life-threatening and the causal relationship to be probably related to the study drug. The blind was broken showing that the patient was treated with vernakalant at the time of the event.

Long-term outcomes

None

Impact on quality of life

Hypotension with vernakalant, when administered in accordance with the CCDS, was generally transient and typically responded to discontinuation of study drug and routine medical management. However, hypotension with a fatal outcome has been reported in one patient with concomitant severe aortic stenosis and another patient in the ACT V study.

Risk factors and risk groups:

Clinical trial experience has identified populations at increased risk of hypotension:

- Haemodynamically unstable patients
- Patients with history of CHF

Preventability:

Patients should be haemodynamically stable at the outset of therapy.

In the AVRO study, patients with baseline systolic BP < 100 mmHg were excluded, and Investigators were advised that all patients were to be adequately hydrated and haemodynamically optimised prior to receiving treatment.

This may have played a role in decreasing the incidence of hypotension events in AVRO. Blood pressure should be closely monitored during and for at least 15 minutes after vernakalant infusion. Evidence of hypotension, or unexpected decreases in BP (even within the normal range) should prompt discontinuation of vernakalant infusion, and, if warranted, application of appropriate medical management.

Additional risk minimisation measures are in place and include the Health Care Professional (HCP) Education Card and Pre-Infusion checklist (refer to Part V.2).

Impact on the risk-benefit balance of the product:

Hypotension was identified in the clinical trials using AE. terms, and vital sign data. The following criteria were used to identify hypotension for calculation of frequency rates:

AE Terms (MedDRA): Cardiogenic shock, Circulatory collapse, Dizziness postural, diastolic hypotension, Hypotension, Hypovolaemic shock, Hypovolaemia, Orthostatic hypotension, Peripheral circulatory failure, Presyncope, Syncope, Shock, Blood pressure decreased, Blood pressure diastolic decreased, Blood pressure systolic decreased, Blood pressure orthostatic decreased.

- Vital Signs: Systolic BP < 90 mmHg

Clinically meaningful hypotension was defined as a hypotension event reported as a SAE or requiring discontinuation of vernakalant. When used in accordance with the CCDS, the public health impact of peri-infusional hypotension occurring in association with vernakalant therapy is anticipated to be small. The incidence rates of AEs of hypotension with vernakalant injection are similar to or lower than the background incidence based on existing treatments with other antiarrhythmic agents or ECV. In general, this risk can be anticipated and managed in the clinical setting. Routine pharmacovigilance activities including targeted follow-up questionnaire are in place (refer to Part III.1).

Public health impact:

When used in accordance with the CCDS, the public health impact of peri-infusional hypotension occurring in association with vernakalant therapy is anticipated to be small.

The incidence rates of AEs of hypotension with vernakalant injection are similar to or lower than the background incidence based on existing treatments with other antiarrhythmic agents or ECV

Important identified risk 2: Bradycardia

Potential mechanism(s):

Bradycardia may be associated with conversion to SR. In the analysis of the interval length between the last QRS complex in AF or AFL and the first QRS complex after termination of AF in the ACT I and ACT III trials, it was shown that the delay between cardioversion and first sinus beat was similar in patients who received vernakalant and PBO.

This indicates that vernakalant did not suppress recovery of sinus node function in patients undergoing cardioversion from AF and that bradycardia is associated with conversion of AF to SR irrespective of method of conversion.

Evidence source(s) and strength of evidence:

Clinical trial data [BRINAVESS SmPC; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; post-marketing AE report data [company PV database (WAES), integrated safety analysis.

Characterisation of the risk:

Frequency

A recently performed integrated safety analysis included safety data from clinical studies SCENE 2, ACT I, ACT II, ACT III, ACT IV, ACT V, and AVRO (vernakalant patients only) (All Patients population excluding CRAFT). Overall, treatment with vernakalant injection was not associated with a significantly increased number of bradycardia events. In the analysis of bradycardia from the AE database, a significantly increased incidence of bradycardia in the first 2 hours and first 24 hours post-dose became apparent. There were no differences in incidence of bradycardia identified from 12-lead ECG (data from start of first dose through day 10) and 24 hour Holter monitoring data between groups (refer to table 9). Bradycardia has been observed at the time of conversion to sinus rhythm. The majority of the bradycardia events occurring between 0 and 2 hours post dose were peri-infusional and resolved spontaneously. Bradycardia responded to discontinuation of vernakalant injection and rarely required intervention.

Incidence of bradycardia

Table 9 Incidence of bradycardia

Hours Post-dose	Vernakalant (%)	Placebo (%)	Risk difference	95% CI
0-2				
Any bradycardia event	4.8	2.9	1.9	-0.4, 4.2
Bradycardia from AE database	3.4	0.5	2.8	1.3, 4.4
Bradycardia from 12-lead ECG	1.5	0.8	0.7	-0.6, 2.1
Bradycardia from Holter	1.8	1.6	0.3	-1.4, 1.9
2 and 24				
Any bradycardia event	7.7	14.1	-6.4	-10.4, -2.3
Bradycardia from AE database	2.0	2.3	-0.3	-2.3, 1.6
Bradycardia from 12-lead ECG	2.0	4.7	-2.7	-5.1, -0.2
Bradycardia from Holter	4.5	9.7	-5.2	-8.6, -1.8

Note: All Patients Excluding CRAFT Population includes the following studies: SCENE II, AVRO (Vernakalant subjects only), ACT I, ACT II, ACT III, ACT IV and ACT V.

The incidence of bradycardia in the vernakalant group was significantly less than the incidence in placebo group after 2 hours – after 2 hours alternative methods of cardioversion were permitted.

Patients with a history of valvular heart disease (VHD) have been identified as a population with a higher incidence of bradycardia events in the first 2 hours post-dose. This significantly increased incidence was not apparent in the 2-24 hour post-dose period and in the analysis of overall time period of the first 24 hours. In patients without a history of VHD, the overall incidence of bradycardia during the first 2 hours was not significantly higher with vernakalant than with placebo. In the first 2 hours post-dose, bradycardia occurred in 11/125 vernakalant

patients (8.8%) with a history of VHD and 1/62 of placebo patients (1.6%) with a history of VHD, compared to an incidence of 4.2% (36/857) and 3.1% (10/321) in the vernakalant and placebo groups, respectively, for patients who did not have a history of VHD.

Asia Pacific Study

No placebo treated and one vernakalant treated patient had AEs of bradycardia and sinus arrest within 0-2 hours of infusion. One placebo (2%, 1/56) and one vernakalant (2%, 1/55) treated patient had AEs of bradycardia 2-24 hours. There were no SAEs or discontinuations for bradycardia within 0-24h in the study. One SAE of bradycardia occurred 2 days after vernakalant infusion and was considered unrelated.

PV database (including CT and Post-marketing data):

Cumulatively, a total of sixty-eight (68) ICSRs which included seventy nine (79) AEs of bradycardia or suggestive of bradycardia were received. Of the sixty eight (68) ICSRs, twenty-two (22) were received from spontaneous sources; thirty-one (31) were from clinical studies, and fifteen (15) were received from solicited sources (SPECTRUM). Seventeen (17) AEs of bradycardia in total were assessed as not related to BRINAVESS therapy.

Severity

Bradycardia was peri-infusional; associated with conversion from AF to SR; responded to discontinuation of vernakalant injection and rarely required intervention. Bradycardia generally responded to discontinuation of vernakalant and/or administration of atropine. Two (2) patients (one (1) vernakalant and one (1) placebo) had temporary pacing. Frequency in the 2-24 hours post dose period was higher in those on PBO compared to vernakalant (see below). Risk can be anticipated and managed in the clinical setting.

Reversibility

Bradycardia has been observed at the time of conversion to SR. The majority of the bradycardia events occurred between 0 and 2 hours post dose were peri-infusional and resolved spontaneously. Clinically meaningful bradycardia was infrequent and generally occurred at the time of conversion to SR. Bradycardia responded to discontinuation of vernakalant injection and did not usually require intervention.

Twelve patients in the All Patients population and the Asia Pacific study had a SAE of bradycardia or had study drug discontinued due to a bradycardia event within the first 2 hours of study medication; 12 in the vernakalant group (12/1073; 1.1%) and 0 in the placebo group.

In the SPECTRUM study, all fifteen (15) events of Bradycardia resolved without sequalae.

Long-term outcomes

Overall, bradycardia with vernakalant typically responded to discontinuation of study drug and did not usually require intervention.

Impact on quality of life

Bradycardia with vernakalant, when administered in accordance with the CCDS, usually resolves.

Risk factors and risk groups:

Conversion from AF to SR; patients with known bradycardia or sick sinus syndrome unless controlled by a pacemaker.

In patients with a history of VHD, bradycardia events occurred more frequently in the subgroup of patients treated with vernakalant, compared to those treated with placebo.

Preventability:

Bradycardia may be anticipated as a consequence of treatment of underlying condition and any prior use of rate control agents.

Vernakalant should be used with caution in patients with VHD.

Additional risk minimisation measures are in place and include the HCP Education Card and Pre-Infusion checklist (refer to Part V.2)

Impact on the risk-benefit balance of the product:

Bradycardia was characterised as an identified risk from analysis of a primary safety population consisting of all patients with atrial fibrillation or atrial flutter in Phase 2 and 3 studies (ACT I, ACT II, ACT III, ACT IV, SCENE 2, AVRO and ACT V) (vernakalant patients only) (All Patients population excluding CRAFT) who received any amount of study medication (1365 total patients, including 982 vernakalant patients, 383 placebo patients). This population was used for all safety analyses and all tables were derived from this dataset. Bradycardia was identified in the clinical trials using AE terms, ECG and Holter monitor data. The following criteria were used to identify bradycardia for calculation of frequency rates:

AE (MedDRA): SMQ of Bradyarrhythmia terms, nonspecific (PTs Bradyarrhythmia and Ventricular asystole) and MedDRA PTs: Bradycardia, Cardiac pacemaker insertion, Sinus arrhythmia, Cardiac arrest, Cardio-respiratory arrest, Heart rate decreased, Sinus bradycardia, Atrioventricular block complete, Sinus arrest, Sinus node dysfunction, and Nodal rhythm.

- 12-lead ECG Results: Third degree AV block, Sinoatrial block, Junctional rhythm, Second degree AV block (Mobitz Type I), Second degree AV block (Mobitz Type II), Heart rate < 40 beats per minute, Idioventricular rhythm
- Holter Monitor Results: Complete Heart Block, Heart rate < 40 beats per minute

Clinically meaningful bradycardia was defined as a bradycardia event reported as a SAE or requiring discontinuation of vernakalant. When used in accordance with the CCDS, the public health impact of peri-infusional bradycardia occurring in association with vernakalant therapy is anticipated to be small. Vernakalant injection does not appear to be associated with increased risk of bradycardia relative to existing pharmacological converting agents or ECV. Bradycardia generally responded to discontinuation of vernakalant and/or administration of atropine. In general, this risk can be anticipated and managed in the clinical setting. Routine PV activities including targeted follow-up questionnaire are in place (refer to III.1).

Public health impact:

When used in accordance with the SmPC, the public health impact of peri-infusional bradycardia occurring in association with vernakalant therapy is anticipated to be small. Vernakalant injection does not appear to be associated with increased risk of bradycardia relative to existing pharmacological converting agents or ECV.

Important identified risk 3: Atrial flutter

Potential mechanism(s):

Of the patients who developed AFL (with AF at baseline) ~30% converted to SR with continued vernakalant treatment. Thirty-eight (38) subjects that received vernakalant in the pooled primary studies developed AFL within 90 min. Of these 38 subjects, 31 had no pre-dose episodes of AFL. There were 31 patients with AF pre-treatment who developed AFL after receiving vernakalant injection. Of the 31 patients who developed AFL, 10 converted to SR within 90 minutes of treatment, 13 were converted to SR by ECV within 24 hours, four (4) converted to SR without additional anti-arrhythmics, and four (4) reverted to AF within 6 hours and remained in AF at hour 24. Of the 10 subjects that developed AFL and subsequently converted to SR within 90 min of treatment: eight (8) developed AFL after the first dose, two (2) of these converted to SR prior to second dose and six (6) converted to SR during or after the second dose; two (2) developed AFL after second dose and converted to SR prior to 90 minutes. Other sodium channel blockers (e.g., flecainide) have been shown to convert AF to AFL.

The importance of this issue pertains to patients for whom their AF converts to AFL with 1:1 conduction to the ventricle (i.e., a HR of 300 bpm [and subsequent hypotension]).

Evidence source(s) and strength of evidence:

Clinical trial data [BRINAVESS CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; post-marketing AE report data [company PV database (WAES)], integrated safety analysis.

Characterisation of the risk:

Frequency

PBO-Controlled Studies

Vernakalant treatment was associated with a significantly higher incidence of AFL in the first 2 hours post-dose, compared to PBO in clinical data submitted at the time of the Marketing Authorisation Application.

Incidence of AFL

Table 10 Incidence of AFL

Hours Post-dose	Vernakalant	Placebo	Risk difference	95% CI
0-2	74/737 (10.0%)	8/315 (2.5%)	7.5	CI 4.7 to 10.3
2 to 24	24/737 (3.3%)	8/315 (2.5%),	0.7	CI -1.4 to 2.9

Table 11 Incidence of AFL in subpopulation of subjects with background use of Class I antiarrhythmic agents.

Hours Post-dose	Vernakalant	Placebo	Risk difference	95% CI
0-2	9/51 (17.6%)	0/15 (0%)	17.6	CI 7.2 to 28.1

The frequency difference between vernakalant and PBO groups appeared to be greater in the subpopulation of subjects with background use of a Class I antiarrhythmic agent (between 0- and 2hours post-dose. However, the number of subjects using these antiarrhythmic agents (66 subjects) was small.

Pooled Phase 2 and Phase 3 trials

Clinically meaningful atrial flutter which was serious or resulted in discontinuation was reported in 0.3% (3/1018) of subjects within the first 2-hours after exposure to vernakalant and in 0% of PBO subjects.

No patient with AFL following treatment with vernakalant injection developed 1:1 atrioventricular (AV) conduction in the pre-approval clinical trials. Atrial flutter with 1:1 AV conduction has been seen in the post-marketing setting.

ACT V

Within 24 hours post dose, 0/68 PBO and 8/129 (6.2%) vernakalant patients had events of AFL. All of the AFL AEs occurred within 2-hours post-dose, and none led to the discontinuation of study drug. For two (2) subjects the AFL was considered to be serious.

AVRO study (amiodarone active-comparator study)

There was a numerically higher incidence of AFL in the vernakalant group compared to the amiodarone group within the first 4 hours after treatment (AE and Holter data):

Table 12 AFL incidence in the AVRO study

Hours Post-dose	Vernakalant	Amiodarone	Risk difference	95% CI
0 to 2	10/116 (8.6%)	1/116 (0.9%)	7.8	CI - 5.5, 20.8
2 to 4	5/116 (4.3%)	0/116 (0.0%)	4.3	CI - 9.0, 17.5

After 4 hours, there were two (2) AEs of AFL in the amiodarone group and no additional AEs in the vernakalant group. None (0) of the subjects who developed AFL had 1:1 AV conduction during the AFL episodes. There were no events of AFL reported as a SAE within 24 hours post-dose or that led to discontinuation of study drug.

Asia Pacific Study

There were no AEs or SAEs of atrial flutter reported in the AP study.

PV database (including CT and Post-marketing data):

Cumulatively, a total of fifty (50) ICSRs which included fifty (50) AEs of atrial flutter were received. Of the fifty (50) ICSRs, eighteen (18) were received from clinical study, thirty (30) were received from spontaneous sources, and two (2) ICSRs were received from solicited sources (SPECTRUM).

Severity

Treatment-emergent AFL was peri-infusional and tended to respond to further treatment with either vernakalant, or subsequent ECV without sequelae. Risk can be anticipated and managed in the clinical setting. There were no (0) cases of 1:1 AV conduction in the development programme (an event that has been observed following the administration of Vaughan-Williams type 1c antiarrhythmics, flecainide and propafenone, for the treatment of AF (Tambocor SPC 2007; Arythmol SPC 2008)). There were twelve (12) cases of AFL with 1:1 AV conduction with 10 cases reported from spontaneous sources (five literature and five HCP reports) including two cases from SPECTRUM.

In the SPECTRUM study, two (2) cases of atrial flutter with 1:1 conduction were reported (one atrial flutter and one ventricular tachycardia" event, which was considered "atrial flutter with 1:1 conduction" after SRC adjudication). Both resolved and were considered definitely related to vernakalant IV by the investigator.

Electrophysiologically, the transition from AF to AFL can potentially be considered part of the physiologic conversion to SR. This is further substantiated by electrophysiologic observation during invasive ablation procedures for AF as well as through the observation that during pharmacologic cardioversion, many of these patients with secondary AFL continue to

convert to SR. The adversity of secondary AFL has been predominantly attributed to the risk of 1:1 conduction as observed with Class Ic agents. Risk is low but present with vernakalant.

Reversibility

Atrial flutter resolved with or without treatment without sequelae in the completed clinical trials.

PBO-controlled studies

Patients who received vernakalant had an increased risk of experiencing AFL. Thirty-one (31) AF patients from the ACT I/III pooled population that did not have AFL at baseline developed new onset AFL within 90 minutes of the start of the initial dose of vernakalant, but the majority (87.1%) went on to convert to SR without sequelae. Specifically, 10 converted within 90 minutes of vernakalant treatment, four (4) converted after 90 minutes and 13 were electrically cardioverted within 24 hours. The remaining four (4) (12.9%) patients reverted to AF within 6 hours and remained in AF at hour 24. In the open label ACT IV study, there was one (1) SAE of AFL reported within the first 24 hours post dose.

ACT V

Two (2) patients (2/129 (1.6%) had AFL which was considered to be serious.

AVRO study (amiodarone active-comparator study)

Of the 10 vernakalant-treated patients that developed AFL within 2 hours of initiation of infusion, three (3) patients converted to SR within the 90 minutes efficacy period; two (2) additional patients spontaneously converted to SR between 90 minutes and 4 hours; two (2) patients were electrically cardioverted to SR between 90 minutes and 4hours; two (2) patients reverted from AFL to AF within 4 hours and were subsequently electrically cardioverted to SR; and one (1) patient had multiple brief episodes of AFL (including pre-dose) in a 'fib-flutter' pattern and converted without further intervention to SR within 24 hours.

The clinical trial experience, including AVRO, suggested that AFL that developed after initiation of treatment with vernakalant was generally a benign transitional rhythm, which either converted to SR, or reverted to AF.

In the SPECTRUM study, two (2) HOIs/SAEs of two cases of "Atrial flutter with 1:1 conduction" (one atrial flutter and one ventricular tachycardia" event was considered "atrial flutter with 1:1 conduction" after SRC adjudication) and both reported as resolved without sequalae.

Long-term outcomes

Treatment-emergent AFL tended to respond to further treatment with either vernakalant, or subsequent ECV without sequelae. Risk can be anticipated and managed in the clinical setting.

Impact on quality of life

AFL with vernakalant, usually resolved (see "Seriousness/outcomes"), however the impact on the individual patient may be life-threatening (necessitating resuscitation) if 1:1 AV conduction develop following AFL.

Risk factors and risk groups:

Class I antiarrhythmics, increase the risk of AFL

Preventability:

No identifiable risk mitigation factors at present. Additional risk minimisation measures are in place and include the HCP Education Card and Pre-Infusion checklist (refer to Part V.2).

Impact on the risk-benefit balance of the product:

AFL was characterised as an identified risk from analysis of a primary safety population consisting of all patients with atrial fibrillation or atrial flutter in Phase 2 and 3 studies (ACT I, ACT II, ACT III, ACT IV, SCENE 2, AVRO and ACT V) (vernakalant patients only) (All Patients population excluding CRAFT) who received any amount of study medication (1365 total patients, including 982 vernakalant patients, 383 placebo patients). This population was used for all safety analyses and all tables were derived from this dataset AFL was identified in the clinical trials using AE terms and ECG data. The following criteria were used to identify AFL for calculation of frequency rates:

- AE (MedDRA): Atrial flutter

- 12-lead ECG Results: Atrial flutter

The risk of AFL addresses new AFL identified from adverse event and ECG data during or after vernakalant infusion. Atrial flutter is not a recommended indication for vernakalant treatment. AFL is the most common arrhythmia associated with AF (Fuster *et al* 2006).

The background incidence of AF patients developing AFL is not clear, but may be inferred from patients that developed AFL following PBO treatment in the vernakalant clinical trials. When used in accordance with the CCDS, the public health impact of peri-infusional conversion of atrial fibrillation to atrial flutter occurring in association with vernakalant therapy is anticipated to be small. In the clinical trials, most patients who developed atrial flutter during vernakalant therapy went on to convert to SR without sequelae. Treatment-emergent AFL tended to respond to further treatment with either vernakalant, or subsequent ECV without sequelae. Risk can be anticipated and managed in the clinical setting. Routine pharmacovigilance activities including targeted follow-up questionnaire are in place (refer to III.1).

Public health impact:

When used in accordance with the CCDS, the public health impact of peri-infusional conversion of AF to AFL occurring in association with vernakalant therapy is anticipated to be small.

Important identified risk 4: ECG QRS complex prolonged

Potential mechanism(s):

Vernakalant demonstrates frequency- and voltage-dependent block of the peak sodium current (INa) in human embryonic kidney cells. Because of its rate- dependent action, vernakalant has

limited ventricular effects on sodium current at normal rates, resulting in minor widening of the QRS interval at peak plasma levels during AF.

Evidence source(s) and strength of evidence:

Clinical trial data [BRINAVESS CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); ACT IV CSR; AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; post-marketing AE report data [company PV database (WAES), integrated safety analysis.

Characterisation of the risk:

Frequency

PBO-controlled/ Open Label Studies

The preferred term (PT) of ECG QRS complex prolonged was reported in 2/773; 0.3% of the vernakalant treated patients and none in the PBO treated patients in clinical data submitted at the time of the Marketing Authorisation Application (MAA). Both patients discontinued study drug. ACT IV: The subject [redacted] a 74-year-old [redacted], was enrolled in the ACT IV open label study and received one (1) partial dose (57/60 mL) of vernakalant on 12–Jul-2006 from 10:52 to 11:02. [redacted] converted to SR at 11:00. An AE of QRS prolongation began during infusion 1 on 12-Jul-2006 at 11:02 and resolved the same day at 11:53. The Investigator assessed the severity of this AE to be mild and probably related to study drug. The Investigator had requested a waiver for this subject, due to a QRS interval >0.14 seconds at screening, as was approved by the medical monitor. The subject completed the study.

SCENE 2: The AFL patient [redacted], a [redacted]-year-old [redacted], was enrolled in the SCENE 2 trial and received one (1) dose of vernakalant on [redacted]–2004. [redacted] did not convert to SR. [redacted] was not electrically cardioverted. The second dose of vernakalant was not given due to an AE of QRS prolongation which began on [redacted]-2004 at 12:37 and resolved on [redacted]-2004 at 13:01. The Investigator assessed the severity of this event to be moderate and possibly related to study drug. The subject completed the protocol and the blind was not broken.

ACT V

There was one (1) case (1/129 (0.8%) of ECG QRS prolonged in the vernakalant group which was not serious but led to discontinuation and was considered related to study drug by the investigator. This AE occurred within 19 minutes after the start of the first infusion and resolved after 71 minutes.

AVRO

There were no (0) cases of ECG QRS complex prolonged.

Asia Pacific Study

There were no (0) cases of ECG QRS complex prolonged in the AP study.

PV database (including CT and Post-marketing data):

Cumulatively, a total of ten (10) ICSRs which included ten (10) AEs of electrocardiogram QRS complex prolonged were received. Of the ten (10) ICSRs, three (3) were clinical study ICSRs, six (6) were received from spontaneous sources and one (1) from solicited sources. One (1) case of non-sustained wide QRS complex tachycardia not considered HOI was received from SPECTRUM cumulatively.

Severity

In the initial clinical trial experience, there were three (3 serious events of ECG complex prolonged, all were non-sustained, asymptomatic and resolved without sequelae including one event considered as not related to vernakalant by the study investigator. In the clinical trial data submitted at the time of the MAA, at baseline the mean QRS duration was similar in PBO patients (96.9 msec) and vernakalant patients (97.1 msec). Peak PBO-subtracted increases from baseline of 7.7 msec (minute 10) and 6.9 msec (minute 35) were recorded. At minute 90 and hour 2, the PBO-subtracted increases from baseline were 3.2 msec and 2.4 msec, respectively. Maximum post-dose QRS duration values were 191 msec in PBO and 233 msec in vernakalant-treated patients. A total of 34 of 704 (5.1%) patients in the vernakalant group with a QRS duration ≤140 msec at baseline shifted to a QRS duration >140 msec at any post dose time point. These shifts occurred most frequently at the 10, 15 and 35 min time points. No PBO patients with QRS duration ≤140 msec at baseline had QRS duration >140 msec at any time point.

In AVRO, ACT V and the AP studies, as observed in the earlier development programme, vernakalant treatment results in a mild peri-infusional widening of the QRS. In AVRO, vernakalant showed maximum mean increases of 7.4 msec, coinciding with the end of the second infusion, then decreasing over time. Amiodarone showed consistent increases of approximately 1-3 msec over time. Shifts in QRS duration from ≤140 msec to >140 msec at any post dose time point occurred in four (4) vernakalant patients and four (4) amiodarone patients. The majority of subjects tended to stay above 140 msec for the duration of the study. There were no (0) subjects in either treatment group who had a shift in QRS duration to >180 msec at any time point.

Reversibility

There were zero (0) SAEs of ECG QRS complex prolonged in the clinical trial setting.

PV database (including CT and Post-marketing data):

Cumulatively, out of the 10 AEs (in 10 ICSRs) of "Electrocardiogram (ECG) QRS complex prolonged", eight (8) were serious and two (2) were non-serious. All but one (1) were assessed as related to vernakalant by the Marketing Authorisation Holder (MAH). All events resolved, except one (1) for which the outcome is unknown.

Long-term outcomes

ECG QRS complex prolonged with vernakalant is non-sustained, asymptomatic and usually resolves without sequelae

Impact on quality of life

ECG QRS complex prolonged with Vernakalant is rare and usually resolves.

Risk factors and risk groups:

Patients with known myocardial disease, background use of Class I antiarrhythmics, CHF, LV dysfunction or high ventricular rate.

Preventability:

Close monitoring of ECG parameters during the administration of vernakalant and discontinuation of vernakalant if a subject develops clinically meaningful ECG changes.

Additional risk minimisation measures are in place and include the HCP Education Card and Pre-Infusion checklist (refer to Part V.2)

Impact on the risk-benefit balance of the product:

AE (MedDRA): Electrocardiogram (ECG) QRS complex prolonged

ECG QRS complex prolonged was characterised as an identified risk from analysis of a primary safety population consisting of all patients with atrial fibrillation or atrial flutter in Phase 2 and 3 studies (ACT I, ACT II, ACT III, ACT IV, SCENE 2, AVRO and ACT V) (vernakalant patients only) (All Patients population excluding CRAFT) who received any amount of study medication (1365 total patients, including 982 vernakalant patients, 383 placebo patients). This population was used for all safety analyses and all tables were derived from this dataset. No published data are available regarding the background incidence of ECG QRS complex prolonged in patients with AF. When used in accordance with the CCDS, the public health impact of peri-infusional ECG complex prolonged is anticipated to be limited. In the clinical trial experience, events were rare. The events were non-sustained, asymptomatic and resolved without sequelae. Routine pharmacovigilance activities including targeted follow-up questionnaire are in place (refer to III.1).

Public health impact:

When used in accordance with the CCDS, the public health impact of peri- infusional ECG complex prolonged is anticipated to be limited. In the clinical trial experience, events were rare. The events were non-sustained, asymptomatic and resolved without sequelae.

Important identified risk 5: Ventricular arrhythmia in patients with history of valvular heart disease

Potential mechanism(s):

A potential causative mechanism for Torsades de Pointes (TdP) would be delay in Phase 3 of the action potential. The delay is mediated by block of the (hERG) potassium channel. This prolonged period of repolarisation and the heterogeneity of repolarisation times among myocardial fibres may allow a dysrhythmia to emerge. The initiating electrophysiologic mechanism may be triggered activity or re-entry. However, vernakalant is not expected to carry as high a risk for pro-arrhythmia as pure hERG blockers, due to blocking of late INa current, as demonstrated in non-clinical studies. Vernakalant blocks late INa within the

therapeutic range. Block of late INa by vernakalant limits the effects of IKr block on prolonging ventricular action potential duration and QT interval, and as such may underlie the ability of vernakalant to suppress Class III agent induced proarrhythmia in animal models. Class III IKr blocking agents are associated with the development of Early after Depolarisations (EADs), which underlie TdP proarrhythmia.

In cellular electrophysiologic studies in rabbit Purkinje fibre, vernakalant at test concentrations up to 30 mcM did not induce EADs. Vernakalant also suppressed and abolished EADs induced by the Class III antiarrhythmic IKr blocker dofetilide. In addition, vernakalant did not induce TdP in the methoxamine- infusion rabbit model, but rather suppressed and reversed the development of TdP in this model produced by the Class III IKr blocker clofilium. These preclinical findings, most likely due to block of late sodium current, suggest that vernakalant may have a lower risk of ventricular pro-arrhythmia clinically than medicines which more potently block potassium channels (e.g., Class III IKr blockers). Since vernakalant blocks potassium currents involved in ventricular repolarisation (e.g., IKr), it can be expected to lengthen action potential duration and hence the QT interval. The IC50 of vernakalant for IKr is 7 – 21 mcM in heterologous *in vitro* expression systems. Thus, at peak plasma levels clinically, vernakalant may impact IKr and affect the QT interval. However, despite QT prolongation in several preclinical species at high doses, vernakalant was not proarrhythmic in animal models susceptible to arrhythmias and may blunt the proarrhythmic effects of agents that block IKr. In anaesthetised rat and pig models of ischaemia-induced arrhythmia, administration of vernakalant prevented ventricular tachycardia (VT)/fibrillation and reduced animal mortality more potently and/or more effectively than lidocaine or flecainide. Transient prolongation of the QT interval corrected for HR was observed after vernakalant injection administration. In normal volunteers, mild QTc lengthening was observed at vernakalant doses of 4 and 5 mg/kg (infused over 10 minutes).

Across the Phase 3 population, vernakalant-treated patients had an increase in HR-corrected QT (using the Fridericia formula, QTcF) compared to PBO in the peri- infusion period. The QTcF increased after vernakalant administration by 22.1 msec and 18.8 msec (PBO subtracted peak values) after the first and second infusions, respectively. By 90 minutes, this difference was reduced to 8.1 msec.

Evidence source(s) and strength of evidence:

Clinical trial data [BRINAVESS CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; post-marketing AE report data [company PV database (WAES), integrated safety analysis].

In clinical trials, patients with a history of VHD showed a higher incidence of VA in the first two (2) hours post dose (6.4% for BRINAVESS compared to 0% in PBO). These arrhythmias typically presented as symptomatic, monomorphic, non-sustained (average 3-4 bpm) ventricular tachycardias. By contrast, Ventricular Arrhythmia's (VAs) were reported with similar frequencies in patients without a history of VHD who were treated with either BRINAVESS or PBO (2.7% for BRINAVESS vs. 3.1% for PBO).

Characterisation of the risk:

Frequency

A recently performed integrated safety analysis included safety data from clinical studies SCENE 2, ACT I, ACT II, ACT III, ACT IV, ACT V, and AVRO (vernakalant patients only) (All Patients population excluding CRAFT). Overall, treatment with vernakalant injection was not associated with a significantly increased number of VA events compared to placebo in the first 2 hours post-dose (3.2%, 31/982 vernakalant; 2.6%, 10/383 placebo). The incidence of events of VA in the 0–2 hour period in the All Patients population was similar for vernakalant and placebo (3.2%, 31/983 vernakalant; 2.6%, 10/383 placebo). The majority of the VA events seen in the vernakalant and placebo groups were asymptomatic monomorphic non-sustained (average 3-5 beats) ventricular tachycardia found on Holter monitor analysis. Patients with a history of VHD have been identified as a population with a higher incidence of VA events in the first 2 hours post-dose. This significantly increased incidence was not apparent in the 2-24 hour post-dose period and in the analysis of overall time period of the first 24 hours. Eight of 125 vernakalant patients (6.4%) with a history of HD experienced a VA event in the first 2 hours post-dose, compared to 0 of 62 placebo patients (0%) with a history of VHD. The incidence of VA events in the first 2 hours post-dose in patients who did not have a history of VHD was 2.7% (23/857) and 3.1% (10/321) in the vernakalant and placebo groups, respectively.

Asia Pacific Study

None of the 2 patients with VHD in the vernakalant group had an event of VA in the AP study.

PV database (including CT and Post-marketing data):

Cumulatively, a total of fifty-eight (58) ICSRs were retrieved from the database using the search criteria. Of the fifty-eight (58) ICSRs, nine (9) included VA in patients with underlyingVHD. Of these nine (9) ICSRs, six (6) were clinical study ICSRs, and three (3) ICSRs were from spontaneous sources.

Severity

The majority of VAs were asymptomatic non-sustained (2-3 bpm) VT found on Holter monitor analysis.

These events appear to be relatively common in this patient population as evidenced by PBO event rates (see Frequency).

There was one (1) case of TdP (in a patient with AFL) in the 24 hours following infusion of vernakalant injection in the clinical trial database. A nine (9) beat run of a VA was captured by Holter monitoring 2 hours and 20 minutes after initiation of the infusion of vernakalant injection and immediately following an infusion of ibutilide [redacted]. The event was not observed by the Investigator and was not recorded as an AE. The patient was asymptomatic. The rhythm was interpreted as TdP by the Chair of the data safety monitoring board. TdP was most likely related to the infusion of ibutilide. However, the association with vernakalant injection cannot be ruled out because of the temporal relationship to the infusion

of vernakalant. One (1) case of VF requiring intervention is described above (see Seriousness /outcomes, above).

Reversibility

PBO-controlled studies

Clinically meaningful VA was observed in patients with VHD.

Other VA events

Other clinically meaningful VA events were reported:

ACT III: Subject [redacted] – experienced an SAE of tachycardia (described as "wide complex tachycardia;" ECG read as non-sustained VT during the initial vernakalant infusion (dose was administered at double the recommended rate over 5 minutes, instead of over 10 minutes); vernakalant infusion was discontinued; event resolved (this patient had no history of CHF or VHD).

ACT III: Subject [redacted] – following the first dose of vernakalant, the patient required further fluid resuscitation. The subject experienced an SAE of ventricular fibrillation 12 minutes after the end of the second dose of vernakalant; and resuscitation was unsuccessful and the patient died. The subject had also an SAE of aortic stenosis. The investigator assessed the severity of both events to be severe and possibly related to study drug. The subject's clinical presentation of acute coronary syndrome should have excluded him from the study based on the protocol exclusion criteria. In addition, the subject's repeated episodes of hypotension should have led to cessation of dosing, based on the dose-stopping criteria for blood pressure <85 mmHg and intolerable side effects (patient's medical history included critical aortic stenosis, ejection fraction 36-49%, CHF, NYHA class II, hypotension and dyspnoea).

ACT V: Subject [redacted] – 73-year-old [redacted] subject with a medical history including hypotension and ejection fraction 48% had short runs of ventricular tachycardia the day before receiving vernakalant. The patient had an AE of hypotension 2h53 min after the first infusion of vernakalant infusion and 2 days after propofol treatment. The first infusion of vernakalant was stopped prematurely because of an SAE of bundle branch block right and ventricular tachycardia (ECG core lab and CEC – reported no ventricular tachycardia) started at 4 and 7 min respectively after the start of the infusion. The subject recovered spontaneously.

ACT V: Subject [redacted] – 77-year-old male subject with a medical history of hypertension and chronic alcohol abuse, along with recent dyspnea and palpitations. The subject had an SAE of cardiogenic shock, with symptoms of sweating and nausea along with decreased blood pressure and heart rate, beginning 10 minutes after the start of vernakalant infusion. The cardiogenic shock was assessed by the investigator as being life-threatening, severe, and possibly related to study drug. The patient lost consciousness and had several bradycardic events, as well as episodes of ventricular fibrillation which were terminated with defibrillation. He did not receive the second dose of vernakalant and was electrically cardioverted to SR approximately 4 hours later. The SAE of cardiogenic shock resolved 18 days later.

From Day 2 to 10, the patient also had an SAE of rhabdomyolysis, two SAEs of electromechanical dissociation, and AEs of gastritis and encephalopathy. Multiple additional

SAEs were reported and resulted in a fatal outcome, including coagulopathy, aspiration pneumonia, hepatic failure, acute renal failure, and sepsis (all beginning on Day 2); anaemia (starting on Day 4); gastrointestinal haemorrhage (starting on Day 12); ischaemic colitis (starting on Day 17); and hypovolemic shock (starting on Day 29). All of these AEs and SAEs were assessed by the investigator as not related to study drug.

CRAFT: Subject [redacted] – a [redacted]-year-old [redacted] with no relevant medical history. An SAE of ventricular fibrillation following a non-synchronised cardioversion for continuing atrial fibrillation at 1hr 54 min after the start of vernakalant infusion. After < 1 min the patient was defibrillated to SR. The subject fully recovered.

AVRO study (amiodarone active-comparator study)

There were no events of VF in the AVRO study. One (1) patient with CHF experienced a SAE of VT; this patient was treated with vernakalant:

AVRO: Subject [redacted] – a 56-year-old [redacted] with a history of HTN, ischaemic heart disease, dyslipidaemia, and New York Heart Association (NYHA) Class II heart failure, who received one (1) infusion of vernakalant. An SAE of VT began on Day 1, 10 minutes after the start of the first infusion, and resolved spontaneously 3 minutes later. The Holter monitor tracing at the time of the SAE of VT was assessed by the Endpoints Committee as aberrant conduction; however, two (2) short (4 and 9 bpm) runs of monomorphic VT were identified on the Holter monitor by the Endpoints Committee approximately one (1) hour later. The SAE of VT was assessed as being of moderate severity and probably related to study drug, and study drug was permanently discontinued due to this SAE. Later that same evening the subject underwent ECV to SR; however, the following day the subject had an AE of AF recurrence. ECV was performed again and the subject was discharged in SR.

Long-term outcomes

The majority of VA events were non-sustained, asymptomatic and resolved without sequelae.

Impact on quality of life

The majority of the VA events seen in the vernakalant and placebo groups were asymptomatic monomorphic non-sustained (average 3-5 beats) ventricular tachycardia found on Holter monitor analysis. VA usually resolves in patients with a history of VHD treated with Vernakalant, when administered in accordance with the CCDS. However, VA with fatal outcome has been reported.

Risk factors and risk groups:

In patients with a history of VHD, VA events occurred more frequently in the subgroup of patients treated with vernakalant, compared to those treated with PBO.

Preventability:

Treat other factors that may be pro-arrhythmogenic e.g. hypokalaemia. Vernakalant is contraindicated for use in patients with heart failure with functional class NYHA III or IV.

Vernakalant should be used cautiously in haemodynamically stable patients with CHF functional classes NYHA I to II.

Additional risk minimisation measures are in place and include the HCP Education Card and Pre-Infusion checklist (refer to Part V.2).

Impact on the risk-benefit balance of the product:

AE (MedDRA): SMQ of Ventricular tachyarrhythmias, SMQ - Torsade de pointes/QT prolongation, PTs Tachycardia and Tachyarrhythmia.

Ventricular arrhythmia in patients with history of VHD was characterised as an identified risk from analysis of a primary safety population consisting of all patients with atrial fibrillation or atrial flutter in Phase 2 and 3 studies (ACT I, ACT II, ACT III, ACT IV, SCENE 2, AVRO and ACT V) (vernakalant patients only) (All Patients population excluding CRAFT) who received any amount of study medication (1365 total patients, including 982 vernakalant patients, 383 placebo patients). This population was used for all safety analyses and all tables were derived from this dataset. AFL was identified in the clinical trials using AE term, ECG data and Holter monitor data. The following criteria were used to identify VA for calculation of frequency rates:

- AE Terms (MedDRA): Torsade de pointes, Ventricular fibrillation, Ventricular bigeminy, Syncope, Ventricular tachycardia, Ventricular extrasystoles, Tachycardia, Ventricular arrhythmia, Cardiac arrest
- 12-lead ECG Results: Idioventricular rhythm, Accelerated idioventricular rhythm, Ventricular tachycardia, Ventricular fibrillation, TdP, Ventricular flutter
- Holter Monitor Results: Ventricular tachycardia, Ventricular fibrillation, TdP, Ventricular flutter

Clinically meaningful VA was defined for the purpose of the safety review as a VA event reported as a SAE or requiring discontinuation of study drug. When used in accordance with the CCDS, the public health impact of peri-infusional A in patients with VHD is anticipated to be limited. In the clinical trial experience, clinically meaningful events were rare. The majority of VA events were non-sustained, asymptomatic and resolved without sequelae. Routine pharmacovigilance activities including targeted follow-up questionnaire are in place (refer to III.1).

Public health impact:

When used in accordance with the CCDS, the public health impact of peri- infusional VA in patients with VHD is anticipated to be limited.

In the clinical trial experience, clinically meaningful events were rare.

The majority of VA events were non-sustained, asymptomatic and resolved without sequelae.

Important identified risk 6: Ventricular arrhythmia in patients with history/evidence of congestive heart failure

Potential mechanism(s):

A potential causative mechanism for Torsade de Pointes would be delay in Phase 3 of the action potential. The delay is mediated by block of the hE

RG potassium channel. This prolonged period of repolarisation and the heterogeneity of repolarisation times among myocardial fibres may allow a dysrhythmia to emerge. The initiating electrophysiologic mechanism may be triggered activity or re-entry. However, vernakalant is not expected to carry as high a risk for proarrhythmia as pure hERG blockers, due to blocking of late INa current, as demonstrated in non-clinical studies. Vernakalant blocks late INa within the therapeutic range. Block of late INa by vernakalant limits the effects of IKr block on prolonging ventricular action potential duration and QT interval, and as such may underlie the ability of vernakalant to suppress Class III agent induced proarrhythmia in animal models. Class III IKr blocking agents are associated with the development of EADs, which underlie TdP proarrhythmia.

In cellular electrophysiologic studies in rabbit Purkinje fiber, vernakalant at test concentrations up to 30 mcM did not induce EADs Vernakalant also suppressed and abolished EADs induced by the Class III antiarrhythmic IKr blocker dofetilide. In addition, vernakalant did not induce torsades de pointes in the methoxamine- infusion rabbit model, but rather suppressed and reversed the development of TdP in this model produced by the Class III IKr blocker clofilium. These preclinical findings, most likely due to block of late sodium current, suggest that vernakalant may have a lower risk of ventricular proarrhythmia clinically than medicines which more potently block potassium channels (e.g., Class III IKr blockers). Since vernakalant blocks potassium currents involved in ventricular repolarisation (e.g., IKr), it can be expected to lengthen action potential duration and hence the QT interval. The IC50 of vernakalant for IKr is 7 – 21 mcM in heterologous in vitro expression systems. Thus, at peak plasma levels clinically, vernakalant may impact IKr and affect the QT interval. However, despite QT prolongation in several preclinical species at high doses, vernakalant was not proarrhythmic in animal models susceptible to arrhythmias, and may blunt the proarrhythmic effects of agents that block IKr. In anaesthetised rat and pig models of ischaemia-induced arrhythmia, administration of vernakalant prevented VT/fibrillation and reduced animal mortality more potently and/or more effectively than lidocaine or flecainide. Transient prolongation of the QT interval corrected for HR was observed after vernakalant injection administration. In normal volunteers, mild QTc lengthening was observed at vernakalant doses of 4 and 5 mg/kg (infused over 10 min).

Across the Phase 3 population, vernakalant-treated patients had an increase in HR- corrected QT (using the Fridericia formula, QTcF) compared to PBO in the peri- infusion period. The QTcF increased after vernakalant administration by 22.1 msec and 18.8 msec (PBO subtracted peak values) after the first and second infusions, respectively. By 90 minutes, this difference was reduced to 8.1 msec.

Evidence source(s) and strength of evidence:

Clinical trial data [BRINAVESS CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; post-marketing AE report data [company PV database (WAES), integrated safety analysis].

In clinical trials, patients with a history of CHF showed a higher incidence of VA in the first two (2) hours post dose (6.4% for BRINAVESS compared to 1.6% in PBO). These arrhythmias

typically presented as symptomatic, monomorphic, non-sustained (average 3-5 bpm) ventricular tachycardias. By contrast, VA were reported with similar frequencies in patients without a history of CHF who were treated with either BRINAVESS or PBO (2.5% for BRINAVESS vs. 2.8% for PBO).

Characterisation of the risk:

Frequency

A recently performed integrated safety analysis included safety data from clinical studies SCENE 2, ACT I, ACT II, ACT III, ACT IV, ACT V, and AVRO (vernakalant patients only) (All Patients population excluding CRAFT). Overall, treatment with vernakalant injection was not associated with a significantly increased number of VA events compared to placebo in the first 2 hours post-dose (3.2%, 31/982 vernakalant; 2.6%, 10/383 placebo). The incidence of events of VA in the 0–2 hour period in the All Patients population was similar for vernakalant and placebo (3.2%, 31/983 vernakalant; 2.6%, 10/383 placebo). The majority of the VA events seen in the vernakalant and placebo groups were asymptomatic monomorphic non-sustained (average 3-5 beats) ventricular tachycardia found on Holter monitor analysis. Patients with a history of CHF have been identified as a population with a higher incidence of VA events in the first 2 hours post-dose. This significantly increased incidence was not apparent in the 2-24 hour post-dose period and in the analysis of overall time period of the first 24 hours.

Ten of 157 vernakalant patients (6.4%) with a history of CHF experienced a VA event in the first 2 hours post-dose, compared to one of 64 placebo patients (1.6%) with a history of CHF. The incidence of VA events in the first 2 hours post-dose in patients who did not have a history of VHD was 2.5% (21/825) and 2.8% (9/319) in the vernakalant and placebo groups, respectively.

Asia Pacific Study

None of the 5 patients with CHF in the vernakalant group had an event of VA in the AP study. One of the 3 patients with CHF in the placebo group had a ventricular tachycardia AE within 2-24h after infusion. There were no VA SAEs in CHF patients in the study.

PV database (including CT and Post-marketing data):

Cumulatively, a total of fifty-eight (58) ICSRs were retrieved from the database using the search criteria. Of the fifty-eight (58) ICSRs with VA, the total number of patients with a history or absence of CHF is not known for all reports. The information is actively sought for all reports received. However, the observed reporting rate would be no greater than 0.2%.

Severity

The majority of VAs were asymptomatic non-sustained (2-3 bpm) VT found on Holter monitor analysis.

These events appear to be relatively common in this patient population as evidenced by PBO event rates (see Frequency). There was one (1) case of TdP (in a patient with AFL) in the 24 hrs following infusion of vernakalant injection in the clinical trial database. A nine (9 beat run of a VA was captured by Holter monitoring 2 hrs and 20 min after initiation of the infusion of

vernakalant injection and immediately following an infusion of ibutilide [redacted]. The event was not observed by the Investigator and was not recorded as an AE. The patient was asymptomatic. The rhythm was interpreted as TdP by the Chair of the data safety monitoring board (DSMB). TdP was most likely related to the infusion of ibutilide. However, the association with vernakalant injection cannot be ruled out because of the temporal relationship to the infusion of vernakalant. One (1) case of VF requiring intervention is described above (see Seriousness / outcomes, above).

Reversibility

PBO-controlled studies

Clinically meaningful VA was observed in patients with CHF.

Other VA events

Other clinically meaningful VA events were reported:

ACT III: Subject [redacted] – experienced an SAE of tachycardia (described as "wide complex tachycardia;" ECG read as non-sustained VT during the initial vernakalant infusion (dose was administered at double the recommended rate over 5 minutes, instead of over 10 minutes); vernakalant infusion was discontinued; event resolved (this patient had no history of CHF or VHD).

ACT III: Subject [redacted] – following the first dose of vernakalant, the patient required further fluid resuscitation. The subject experienced an SAE of ventricular fibrillation 12 minutes after the end of the second dose of vernakalant; and resuscitation was unsuccessful and the patient died. The subject had also an SAE of aortic stenosis. The investigator assessed the severity of both events to be severe and possibly related to study drug. The subject's clinical presentation of acute coronary syndrome should have excluded him from the study based on the protocol exclusion criteria. In addition, the subject's repeated episodes of hypotension should have led to cessation of dosing, based on the dose-stopping criteria for blood pressure <85 mmHg and intolerable side effects (patient's medical history included critical aortic stenosis, ejection fraction 36-49%, CHF, NYHA class II, hypotension and dyspnoea).

ACT V: Subject [redacted] – 73-year-old [redacted] subject with a medical history including hypotension and ejection fraction 48% had short runs of ventricular tachycardia the day before receiving vernakalant. The patient had an AE of hypotension 2h53 min after the first infusion of vernakalant infusion and 2 days after propofol treatment. The first infusion of vernakalant was stopped prematurely because of an SAE of bundle branch block right and ventricular tachycardia (ECG core lab and CEC – reported no ventricular tachycardia) started at 4 and 7 min respectively after the start of the infusion. The subject recovered spontaneously.

ACT V: Subject [redacted] – 77-year-old male subject with a medical history of hypertension and chronic alcohol abuse, along with recent dyspnea and palpitations. The subject had an SAE of cardiogenic shock, with symptoms of sweating and nausea along with decreased blood pressure and heart rate, beginning 10 minutes after the start of vernakalant infusion. The cardiogenic shock was assessed by the investigator as being life-threatening, severe, and possibly related to study drug. The patient lost consciousness and had several bradycardic

events, as well as episodes of ventricular fibrillation which were terminated with defibrillation. He did not receive the second dose of vernakalant and was electrically cardioverted to SR approximately 4 hours later. The SAE of cardiogenic shock resolved 18 days later.

From Day 2 to 10, the patient also had an SAE of rhabdomyolysis, two SAEs of electromechanical dissociation, and AEs of gastritis and encephalopathy. Multiple additional SAEs were reported and resulted in a fatal outcome, including coagulopathy, aspiration pneumonia, hepatic failure, acute renal failure, and sepsis (all beginning on Day 2); anaemia (starting on Day 4); gastrointestinal haemorrhage (starting on Day 12); ischaemic colitis (starting on Day 17); and hypovolemic shock (starting on Day 29). All of these AEs and SAEs were assessed by the investigator as not related to study drug.

CRAFT: Subject [redacted] – a [redacted]-year-old [redacted] with no relevant medical history. An SAE of ventricular fibrillation following a non-synchronised cardioversion for continuing atrial fibrillation at 1hr 54 min after the start of vernakalant infusion. After < 1 min the patient was defibrillated to SR. The subject fully recovered.

AVRO study (amiodarone active-comparator study)

There were no events of VF in the AVRO study. One (1) patient with CHF experienced a SAE of VT; this patient was treated with vernakalant:

AVRO: Subject [redacted] – a 56-year-old [redacted] with a history of HTN, ischaemic heart disease, dyslipidaemia, and New York Heart Association (NYHA) Class II heart failure, who received one (1) infusion of vernakalant. An SAE of VT began on Day 1, 10 minutes after the start of the first infusion, and resolved spontaneously 3 minutes later. The Holter monitor tracing at the time of the SAE of VT was assessed by the Endpoints Committee as aberrant conduction; however, two (2) short (4 and 9 bpm) runs of monomorphic VT were identified on the Holter monitor by the Endpoints Committee approximately one (1) hour later. The SAE of VT was assessed as being of moderate severity and probably related to study drug, and study drug was permanently discontinued due to this SAE. Later that same evening the subject underwent ECV to SR; however, the following day the subject had an AE of AF recurrence. ECV was performed again and the subject was discharged in SR.

Long-term outcomes

The majority of VA stained, asymptomatic and resolved without sequelae.

Impact on quality of life

The majority of the VA events seen in the vernakalant and placebo groups were asymptomatic monomorphic non-sustained (average 3-5 beats) ventricular tachycardia found on Holter monitor analysis. VA usually resolves in patients with a history of CHF treated with Vernakalant, when administered in accordance with the CCDS. However, VA with fatal outcome has been reported.

Risk factors and risk groups:

In patients with a history of CHF, VA events occurred more frequently in the subgroup

of patients treated with vernakalant, compared to those treated with PBO.

Preventability:

Treat other factors that may be pro-arrhythmogenic e.g. hypokalaemia. Vernakalant is contraindicated for use in patients with heart failure with functional class NYHA III or IV.

Vernakalant should be used cautiously in haemodynamically stable patients with CHF functional classes NYHA I to II.

Impact on the risk-benefit balance of the product:

AE (MedDRA): SMQ of Ventricular tachyarrhythmias, SMQ - Torsade de pointes/QT prolongation, PTs Tachycardia and Tachyarrhythmia.

Ventricular arrhythmia in patients with history of CHF was characterised as an identified risk from analysis of a primary safety population consisting of all patients with atrial fibrillation or atrial flutter in Phase 2 and 3 studies (ACT I, ACT II, ACT III, ACT IV, SCENE 2, AVRO and ACT V) (vernakalant patients only) (All Patients population excluding CRAFT) who received any amount of study medication (1365 total patients, including 982 vernakalant patients, 383 placebo patients). This population was used for all safety analyses and all tables were derived from this dataset. AFL was identified in the clinical trials using AE term, ECG data and Holter monitor data. The following criteria were used to identify VA for calculation of frequency rates:

- AE Terms (MedDRA): Torsade de pointes, Ventricular fibrillation, Ventricular bigeminy, Syncope, Ventricular tachycardia, Ventricular extrasystoles, Tachycardia, Ventricular arrhythmia, Cardiac arrest
- 12-lead ECG Results: Idioventricular rhythm, Accelerated idioventricular rhythm, Ventricular tachycardia, Ventricular fibrillation, TdP, Ventricular flutter
- Holter Monitor Results: Ventricular tachycardia, Ventricular fibrillation, TdP, Ventricular flutter

Clinically meaningful VA was defined for the purpose of the safety review as a VA event reported as a SAE or requiring discontinuation of study drug. When used in accordance with the CCDS, the public health impact of peri-infusional VA in patients with CHF is anticipated to be limited. In the clinical trial experience, clinically meaningful events were rare. The majority of VA events were non-sustained, asymptomatic and resolved without sequelae. Routine pharmacovigilance activities including targeted follow-up questionnaire are in place (refer to III.1).

Public health impact:

When used in accordance with the CCDS, the public health impact of peri- infusional VA in patients with CHF is anticipated to be limited.

In the clinical trial experience, clinically meaningful events were rare.

The majority of VA events were non-sustained, asymptomatic and resolved without sequelae.

Important potential risk 1: Overdose/medication error

Potential mechanism(s):

Medication errors and overdose would most likely occur due to error on the part of the HCP administering the drug.

Administrative errors may include miscalculated dose, improper dilution, increased rate of infusion or infusion for more than 10 minutes.

Evidence source(s) and strength of evidence:

Clinical trial data [BRINAVESS CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; post-marketing AE report data [company PV database (WAES), integrated safety analysis.

Characterisation of the risk:

Frequency

There have been three (3/1018) instances in which subjects received vernakalant injection more rapidly than the protocol defined infusion period of 10 minutes (bolusing). Two (2) of these subjects received the first dose of vernakalant injection over 10 minutes followed by the full second dose in either 6 minutes (ACT I, Subject [redacted]) or 5 minutes (ACT I, Patient [redacted]) without sequelae. The third patient (ACT III, Subject [redacted]) received the first infusion of study drug (3 mg/kg) over 5 minutes. The Investigator noted the occurrence of wide complex tachycardia (MedDRA PT: Tachycardia) and did not administer the second infusion. A four (4) beat run of polymorphic VT was read by the central cardiologist approximately 15 minutes following the initial observation of wide complex tachycardia by the Investigator. There were no findings of TdP for this subject and the tachycardia resolved without sequelae. This subject had seven (7) runs of non-sustained polymorphic VT pre-dose and did not convert to SR. Post dose, [redacted] experienced 17 runs of non-sustained (3-4 beat) VT between 22 min and 20 hours post-dose and 75 runs of non-sustained (3-21 beats) monomorphic VT between 66 min and 20 hours post-dose. It should be noted that the subject also experienced a GI haemorrhage with a 200-300 ml bloody stool with blood clots witnessed 10 minutes after the start of study drug infusion (considered unrelated to study drug).

PV database (including CT and Post-marketing data):

Cumulatively, a total of nineteen (19) ICSRs which included twenty-one (21) AEs of overdose/medication error were retrieved using the search with SMQ Medication errors. Of the nineteen (19) ICSRs, sixteen (16) were received from spontaneous sources, two (2) were clinical study ICSRs and one (1) was received from solicited sources (SPECTRUM). Cumulatively, no cases were found using the search with PT Intentional overdose.

Severity

In animals, toxicological findings at high doses appear to be an extension of the pharmacological activity of vernakalant (ion channel blockade) and include such findings as excessive salivation, vomiting, retching, tremors, impaired gait/coordination, decreased

activity, and convulsion. Healthy volunteers have received doses in excess of those recommended in the CCDS without ill effect.

In a Phase 1 study [1235-1-04-12-01] in healthy volunteers, subjects received vernakalant injection doses of 4 mg/kg and 5 mg/kg infused over 10 minutes (four [4] subjects at each dose level). Similar findings were seen in Study 6517-CL-0011, with 10 subjects dosed at 5 mg/kg. In Study SMH1 in subjects undergoing electrophysiological testing, 10 subjects received 2.0 mg/kg over 10 minutes followed by a maintenance infusion of 0.5 mg/kg/h for 35 minutes and nine (9) subjects received 4.0 mg/kg over 10 minutes followed by a maintenance infusion of 1.0 mg/kg/h for 35 minutes. Two (2) subjects in the higher dose group discontinued study drug prematurely due to AEs of AF induced during rapid atrial pacing (Subjects [redacted]) and vasovagal syncope and transient hypotension (Subjects [redacted]).

Reversibility

No cases of vernakalant injection overdose have been reported in clinical trials.

PV database (including CT and Post-marketing data):

Cumulatively, out of the 21 events (in 19 cases) of "Overdose/medication error", five were serious, and 16 non-serious. Fourteen (four serious and 10 non-serious) were assessed as related to vernakalant. Seven events resolved, one event resolved with sequelae, two events were resolving at time of reporting, and the outcome was unknown for eleven events. None had a fatal outcome.

Long-term outcomes

The majority of events resolve.

Impact on quality of life

Overdose/medication errors with Vernakalant when occurring are usually non- serious and resolve.

Risk factors and risk groups:

No risk groups or risk factors have been identified.

Preventability:

Vernakalant must be infused following dilution and over a period of 10 minutes. Detailed and specific instructions are provided in the SmPC on how to calculate the volume of infusion to be dosed by patient weight. In addition, the HCP Education Card includes relevant information on how to calculate the volume of vernakalant to be dosed. The MAH also conducted a post authorisation safety study (PASS), which collected information about vernakalant dosing. . The results revealed:

- Patients with body weight <113 kg: 2.0% of the first infusions (36/1,801) and 3.8% of second infusions (27/714; 3.8%) corresponded to a dosing higher than 105% of the weight-based dosing recommendation. Six percent of first infusions (107/1,801; 5.9%)

and 2.8% of second infusions were lower than 95% of the weight-based dosing recommendation.

- Patients with body weight ≥113 kg: 9.3% of the first infusions (9/97) and 15.9% of second infusions administered >105% of the weight-based recommended dose. The higher frequency of overdose in patients with body weight ≥113 kg might be explained by a fear of under dosing overweight patients, indeed, when adjusted to the actual body weight, only 1 patient would have received a dose > 110%. One patient experienced an SAE of overdose, manifested as nausea and vomiting, after administration of 151% of the weight-based recommended vernakalant IV dose. No other SAEs were reported among patients administered more than 105% of the weight-based recommended dose of vernakalant IV for either the first or second infusion.

Additional risk minimisation measures are in place and include the HCP Education Card and Pre-Infusion checklist (refer to Part V.2).

Impact on the risk-benefit balance of the product:

AE (MedDRA): Overdose, Accidental overdose, Intentional overdose, Drug administration error, Drug dose omission, Inappropriate schedule of drug administration, Incorrect dose administered, Incorrect drug administration duration, Incorrect drug administration rate, Underdose, Medication Error, Wrong technique in drug usage process.

Overdose/medication error was characterised as a potential risk from analysis of a primary safety population consisting of all patients with atrial fibrillation or atrial flutter in Phase 2 and 3 studies (ACT I, ACT II, ACT III, ACT IV, SCENE 2, AVRO and ACT V) (vernakalant patients only) (All Patients population excluding CRAFT) who received any amount of study medication (1365 total patients, including 982 vernakalant patients, 383 placebo patients). This population was used for all safety analyses and all tables were derived from this dataset. Limited clinical trial data is available. No cases of vernakalant injection overdose have been reported in clinical trials and one patient experienced an SAE of overdose in the SPECTRUM PASS study. Medication errors and overdose would most likely occur due to error on the part of the HCP administering the drug. When used in the controlled clinical setting, the public health impact in association with vernakalant overdose is anticipated to be small. Routine pharmacovigilance activities including targeted follow-up questionnaire are in place (refer to III.1).

Public health impact:

When used in the controlled clinical setting, the public health impact in association with vernakalant overdose is anticipated to be small.

SVII.3.2 Presentation of missing information

Missing information 1: Patients with heart failure NYHA Class III and IV

Evidence source: Patients with NYHA Class IV CHF were excluded during clinical trials. Patients with Class III CHF were enrolled but at a low rate.

Anticipated risk/consequence of the missing information:

Health care professional education materials-HCP Education Card and Pre-Infusion Checklist to identify the risk of hypotension and VA with vernakalant use in patients with heart failure, and provide appropriate advice to minimise this risk. Guidance for appropriate patient selection is provided, including the contraindication of vernakalant in patients with NYHA class III and IV heart failure, and precautions regarding patients with haemodynamically stable NYHA class I to II heart failure (use with caution).

Missing information 2: Patients with prolonged QT (uncorrected >440msec)

Evidence source:

Patients were excluded during clinical trials.

Anticipated risk/consequence of the missing information:

Health care professional education materials-HCP Education Card and Pre-Infusion Checklist to identify key patient selection criteria, including contraindications, and information about patient populations with limited information from clinical trials, including advice regarding patients with clinically meaningful valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis (use not recommended).

Missing information 3: Patients with severe bradycardia and second or third degree heart block

Evidence source:

Patients were excluded during clinical trials.

Anticipated risk/consequence of the missing information:

Health care professional education materials-HCP Education Card and Pre-Infusion Checklist to identify key patient selection criteria, including contraindications, and information about patient populations with limited information from clinical trials, including advice regarding patients with clinically meaningful valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis (use not recommended).

Missing information 4: Patients with clinically meaningful valvular stenosis

Evidence source:

Patients were excluded during clinical trials.

Anticipated risk/consequence of the missing information:

Health care professional education materials-HCP Education Card and Pre-Infusion Checklist to identify key patient selection criteria, including contraindications, and information about patient populations with limited information from clinical trials, including advice regarding patients with clinically meaningful valvular stenosis (use not recommended).

Missing information 5: Patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constructive pericarditis

Evidence source:

Patients were excluded during clinical trials.

Anticipated risk/consequence of the missing information:

Health care professional education materials-HCP Education Card and Pre-Infusion Checklist to identify key patient selection criteria, including contraindications, and information about patient populations with limited information from clinical trials, including advice regarding patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis (use not recommended).

Missing information 6: Use of Oral (PO) antiarrhythmic therapy (Class I and III)

Evidence source:

Patients using I.V antiarrhythmics Class I and III were excluded during clinical trials. Background use of PO Class I.

Anticipated risk/consequence of the missing information:

Health care professional education materials-HCP Education Card and Pre-Infusion Checklist to reinforce key patient management considerations, including advice that use of IV antiarrhythmic drugs (AADs) within the first 4 hours after vernakalant is contraindicated, and use of vernakalant between 4 and 24 hours following administration of intravenous class I and class III antiarrhythmic agents is not recommended.

Missing information 7: Off label use including: severe aortic stenosis, or systolic BP<100MMhG, Patients with recent MI or ACS, patients treated for arrhythmias other than AF, Use of IV AAD (Class I and Class III) within 4 hours prior to vernakalant administration and within the first 4hours after vernakalant administration.

Evidence source:

Patients were excluded during clinical trials.

Anticipated risk/consequence of the missing information:

Health care professional education materials-HCP Education Card and Pre-Infusion Checklist to identify key patient selection criteria, including indication for vernakalant use, contraindications, and information about patient populations at special risk.

PART II: Module SVIII - Summary of safety concerns

Table 13 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hypotension Bradycardia Atrial flutter ECG QRS complex prolonged Ventricular arrhythmia in patients with history of valvular heart disease Ventricular arrhythmia in patients with history/evidence of congestive heart failure
Important potential risks	Overdose/medication error
Missing information	Patients with heart failure NYHA Class III and IV Patients with prolonged QT (uncorrected >440msec) Patients with severe bradycardia and second or third degree block Patients with clinically meaningful valvular stenosis Patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constructive pericarditis Use of PO antiarrhythmic therapy (Class I and III) Hepatic impairment Off label use including: severe aortic stenosis, or systolic BP<100mmHg, patients with recent MI or ACS, patients treated for arrhythmias other than AF, use of IV AAD (Class I and Class III) within 4hours prior to vernakalant administration and within the first 4hours after vernakalant administration

PART III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- **Specific ADR follow-up questionnaires for hypotension, bradycardia, ventricular arrhythmia in patients with history of valvular heart disease; ventricular arrhythmia in patients with history/evidence of congestive heart failure, atrial flutter and ECG QRS complex prolonged** (appended in Annex 4):

The objective of the questionnaire is to assure continuous monitoring of AEs, and to collate more information on this patient population. The questionnaire is sent for all ICSRs in which one of the above mentioned safety concerns is reported as an adverse event or the events reported are suggestive of it. Following medical evaluation of the ICSR and confirmation that a specific ADR follow-up questionnaire is required, a total of three (3) follow-up attempts are sent every two weeks. If there is no response following the third attempt, the case will be closed as lost to follow-up (closed without completion). Information sought for each subgroup of safety concerns can be found in Annex 4.

Other forms of routine pharmacovigilance activities for hypotension:

Review of new case report data received for vernakalant on a weekly basis to identify new spontaneous cases of serious hypotension and generate a causality assessment for each such report. Identified case reports of hypotension will be sent to the Rapporteur as a legally binding measure (LEG) when received.

The objective is to assure capturing new cases of hypotension, assessing the seriousness, understanding potential different causes for hypotension, the time course of occurrence and the duration and sharing the information of each new case of serious hypotension with the rapporteur in an expedited fashion.

III.2 Additional pharmacovigilance activities

The pharmacovigilance plan does not include any additional pharmacovigilance activities.

III.3 Summary table of additional pharmacovigilance activities

Not applicable

PART IV: Plans for post-authorisation efficacy studies

There are no planned post-authorisation efficacy studies.

PART V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1 Routine risk minimisation measures

Table 14 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Hypotension	Routine risk communication: SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 4.2, 4.3, 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: The patient is required to be monitored for signs and symptoms of a sudden decrease in BP or heart rate for the duration of the infusion and for at least 15 minutes after the completion of the infusion Other routine risk minimisation measures beyond the PI: Legal status: Medicinal product subject to restricted medical prescription
Bradycardia	Routine risk communication: SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 4.2, 4.3, 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: The patient is required to be monitored for signs and symptoms of a sudden decrease in BP or HR for the duration of the infusion and for at least 15 minutes after the completion of the infusion Other routine risk minimisation measures beyond the PI: Legal status: Medicinal product subject to restricted medical prescription
Atrial flutter	Routine risk communication: SmPC sections 4.2, 4.4, and 4.8 PL sections 4.2, 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the PI: Legal status: Medicinal product subject to restricted medical prescription
ECG QRS complex prolonged	Routine risk communication: SmPC sections 4.4, and 4.8 PL sections 4.4

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the PI: Legal status: Medicinal product subject to restricted medical prescription
Ventricular arrhythmia in patients with history of valvular heart disease	Routine risk communication: SmPC sections 4.3, 4.4, and 4.8 PL sections 4.3, 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the PI: Legal status: Medicinal product subject to restricted medical prescription
Ventricular arrhythmia in patients with history/evidence of congestive heart failure	Routine risk communication: SmPC sections 4.3, 4.4, and 4.8 PL sections 4.3, 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the PI: Legal status: Medicinal product subject to restricted medical prescription
Overdose/medication error	Routine risk communication: SmPC sections 4.2, 4.9 PL sections 4.2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the PI: Legal status: Medicinal product subject to restricted medical prescription
Patients with heart failure NYHA Class III and IV	Routine risk communication: SmPC sections 4.3 PL sections 4.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the PI: Legal status: Medicinal product subject to restricted medical prescription

Safety concern	Routine risk minimisation activities
Patients with prolonged QT (uncorrected >440msec)	Routine risk communication: SmPC sections 4.3 PL sections 4.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the PI: Legal status: Medicinal product subject to restricted medical prescription
Patients with severe bradycardia and second or third degree block	Routine risk communication: SmPC sections 4.3, 4.4 PL sections 4.3, 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the PI: Legal status: Medicinal product subject to restricted medical prescription
Patients with clinically meaningful valvular stenosis	Routine risk communication: SmPC sections 4.4 PL sections 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the PI: Legal status: Medicinal product subject to restricted medical prescription
Patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constructive pericarditis	Routine risk communication: SmPC sections 4.4 PL sections 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the PI: Legal status: Medicinal product subject to restricted medical prescription
Use of PO antiarrhythmic therapy (Class I and III)	Routine risk communication: SmPC sections 4.4 PL sections 4.4

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the PI: Legal status: Medicinal product subject to restricted medical prescription
Hepatic impairment	Routine risk communication: SmPC sections 4.4 PL sections 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the PI: Legal status: Medicinal product subject to restricted medical prescription
Off label use including: severe aortic stenosis, or systolic BP<100mmHg, Patients with recent MI or ACS, patients treated for arrhythmias other than AF, Use of IV AAD (Class I and Class III) within 4hours prior to vernakalant administration and within the first 4hours after vernakalant administration	Routine risk communication: SmPC sections 4.31 PL sections 4.31 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the PI: Legal status: Medicinal product subject to restricted medical prescription

V.2 Additional risk minimisation measures

Additional risk minimisation 1:

HCP education materials: HCP Education Card and Pre-Infusion checklist.

Objectives:

The objectives of additional risk minimisation activities are to increase awareness by educating prescribers in the risks and means of minimising the risk.

HCP Education Card - HCP have received education materials, including an information card that reinforces key safety information from the SmPC, to help support appropriate prescribing behaviour. These materials identify the risk of hypotension with vernakalant use, and provide appropriate advice to minimise this risk. It has been distributed through national mailouts on a periodic basis and is available at the MAH's conference booths and during symposia.

Pre-Infusion Check-list - The MAH has developed an additional educational tool, the "Pre-Infusion Check-list" to provide further support for appropriate patient selection and monitoring. The new "Pre-Infusion Checklist" (1) highlights the contraindications for BRINAVESS use, in an accessible check-list format, and (2) provides instructions for patient monitoring and management of medically significant ADRs when administering BRINAVESS. This tool is included in the BRINAVESS package, and delivered directly to the point of care, thus increasing the exposure of HCPs to the education materials. The "Pre-Infusion Check-list" also reinforces the importance of careful review of the SmPC and the HCP Card prior to use of the product.

– List of addressed safety concern(s):

Hypotension

Bradycardia

Atrial flutter

ECG QRS complex prolonged

Ventricular arrhythmia in patients with history of valvular heart disease

Ventricular arrhythmia in patients with history/ evidence of congestive heart failure

Overdose/medication error

Patients with heart failure NYHA Class III and IV

Patients with prolonged QT (uncorrected >440msec)

Patients with severe bradycardia and second or third degree block

Patients with clinically meaningful valvular stenosis

Patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constructive pericarditis

Use of PO antiarrhythmic therapy (Class I and III)

Hepatic impairment

Off label use including: severe aortic stenosis, or systolic BP<100mmHg, patients with recent MI or ACS, patients treated for arrhythmias other than AF, use of IV AAD (Class I and Class III) within 4 hours prior to vernakalant administration and within the first 4 hours after vernakalant administration'

Rationale for the additional risk minimisation activity:

To minimise risk of vernakalant associated safety concerns in clinical practise.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Information from ongoing and planned pharmacovigilance activities (routine pharmacovigilance and the completed PASS registry study) will be evaluated to assess the frequency and severity of post-marketing ADRs relating to identified and potential risks. This

includes an assessment of the key elements described in the educational materials in the PASS study.

The study collected data on prescribing behaviour in actual commercial use of the product, including appropriate patient selection and pre- and post-dose medical management to minimise identified and potential risks. These data will permit real-world assessment of appropriateness of prescribing behaviour in the context of the SmPC.

Comprehension and understanding of the educational materials by HCP will also be assessed by means of a questionnaire, which will be completed during symposia.

The effectiveness of risk minimisation activities will be reported promptly in the Pharmacovigilance System Master File upon completion of evaluation and future updates of this RMP.

V.3 Summary of risk minimisation measures

Table 15 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypotension	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 4.2, 4.3, 4.4 Routine activities recommending specific clinical measures: The patient is required to be monitored for signs and symptoms of a sudden decrease in BP or heart rate for the duration of the infusion and for at least 15 minutes after the completion of the infusion Prescription status: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Pre- Infusion Check-list HCP Education Card	Routine PV activities beyond signal detection and ADRs reporting: - Specific ADR follow-up questionnaires - Review of new case report data received for vernakalant on a weekly basis to identify new spontaneous cases of serious hypotension Additional PV activities: None
Bradycardia	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 4.2, 4.3, 4.4 Routine activities recommending specific clinical measures:	Routine PV activities beyond signal detection and ADRs reporting: - Specific ADR follow-up questionnaires Additional PV activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	The patient is required to be monitored for signs and symptoms of a sudden decrease in BP or heart rate for the duration of the infusion and for at least 15 minutes after the completion of the infusion Prescription status: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Pre- Infusion Check-list - HCP Education Card	
Atrial flutter	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8 PL sections 4.2, 4.4 Routine activities recommending specific clinical measures: None Prescription status: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Pre- Infusion Check-list	Routine PV activities beyond signal detection and ADRs reporting: - Specific ADR follow-up questionnaires Additional PV activities: None
ECG QRS complex prolonged	Routine risk minimisation measures: SmPC sections 4.4, and 4.8 PL sections 4.4 Routine activities recommending specific clinical measures: None Prescription status: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Pre- Infusion Check-list	Routine PV activities beyond signal detection and ADRs reporting: - Specific ADR follow-up questionnaires Additional PV activities: None
Ventricular arrhythmia in patients with history of valvular heart disease	Routine risk minimisation measures: SmPC sections 4.3, 4.4, and 4.8 PL sections 4.3, 4.4	Routine PV activities beyond signal detection and ADRs reporting:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Routine activities recommending specific clinical measures: None Prescription status: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Pre- Infusion Check-list	- Specific ADR follow-up questionnaires Additional PV activities: None
Ventricular arrhythmia in patients with history/evidence of congestive heart failure	Routine risk minimisation measures: SmPC sections 4.3, 4.4, and 4.8 PL sections 4.3, 4.4 Routine activities recommending specific clinical measures: None Prescription status: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Pre- Infusion Check-list	Routine PV activities beyond signal detection and ADRs reporting: - Specific ADR follow-up questionnaires Additional PV activities: None
Overdose/medication error	Routine risk minimisation measures: SmPC sections 4.2, and 4.9 PL sections 4.2 Routine activities recommending specific clinical measures: None Prescription status: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Pre- Infusion Check-list	Routine PV activities beyond signal detection and ADRs reporting: None Additional PV activities: None
Patients with heart failure NYHA Class III and IV	Routine risk minimisation measures: SmPC sections 4.3 PL sections 4.3	Routine PV activities beyond signal detection and ADRs reporting: None Additional PV activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Routine activities recommending specific clinical measures: None Prescription status: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Pre- Infusion Check-list	None
Patients with prolonged QT (uncorrected >440msec)	Routine risk minimisation measures: SmPC sections 4.3 PL sections 4.3 Routine activities recommending specific clinical measures: None Prescription status: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Pre- Infusion Check-list	Routine PV activities beyond signal detection and ADRs reporting: None Additional PV activities: None
Patients with severe bradycardia and second or third degree heart block	Routine risk minimisation measures: SmPC sections 4.3, 4.4 PL sections 4.3, 4.4 Routine activities recommending specific clinical measures: None Prescription status: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Pre- Infusion Check-list	Routine PV activities beyond signal detection and ADRs reporting: None Additional PV activities: None
Patients with clinically meaningful valvular stenosis	Routine risk minimisation measures: SmPC sections 4.4 PL sections 4.4 Routine activities recommending specific clinical measures: None	Routine PV activities beyond signal detection and ADRs reporting: None Additional PV activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Prescription status: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Pre- Infusion Check-list	
Patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constructive pericarditis	Routine risk minimisation measures: SmPC sections 4.4 PL sections 4.4 Routine activities recommending specific clinical measures: None Prescription status: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Pre- Infusion Check-list	Routine PV activities beyond signal detection and ADRs reporting: None Additional PV activities: None
Use of PO antiarrhythmic therapy (Class I and III)	Routine risk minimisation measures: SmPC sections 4.4 PL sections 4.4 Routine activities recommending specific clinical measures: None Prescription status: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Pre- Infusion Check-list	Routine PV activities beyond signal detection and ADRs reporting: None Additional PV activities: None
Hepatic impairment	Routine risk minimisation measures: SmPC sections 4.4 PL sections 4.4 Routine activities recommending specific clinical measures: None Prescription status: Medicinal product subject to restricted medical prescription	Routine PV activities beyond signal detection and ADRs reporting: None Additional PV activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: Pre- Infusion Check-list	
Off label use including: severe aortic stenosis, or systolic BP<100mmHg, patients with recent MI or ACS, patients treated for arrhythmias other than AF, use of IV AAD (Class I and Class III) within 4hours prior to vernakalant administration and within the first 4hours after vernakalant administration	Routine risk minimisation measures: SmPC sections 4.1 PL sections 4.1 Routine activities recommending specific clinical measures: None Prescription status: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Pre- Infusion Check-list	Routine PV activities beyond signal detection and ADRs reporting: None Additional PV activities: None

PART VI: Summary of the risk management plan

Summary of risk management plan for BRINAVESS (vernakalant hydrochloride)

This is a summary of the RMP for BRINAVESS. The RMP details important risks of BRINAVESS, how these risks can be minimised, and how more information will be obtained about BRINAVESS's risks and uncertainties (missing information).

BRINAVESS's SmPC and its package leaflet (PL) give essential information to HCPs and patients on how BRINAVESS should be used.

This summary of the RMP for BRINAVESS should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of BRINAVESS's RMP.

I. The medicine and what it is used for

BRINAVESS is authorised for rapid conversion of recent onset atrial fibrillation to SR in adults for non-surgery patients with atrial fibrillation ≤ 7 days duration and for post-cardiac surgery patients with atrial fibrillation ≤ 3 days duration. It contains vernakalant hydrochloride as the active substance and it is given by concentrate for solution for infusion, 20 mg/ml.

Further information about the evaluation of BRINAVESS's benefits can be found in BRINAVESS's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of BRINAVESS, together with measures to minimise such risks and the proposed studies for learning more about BRINAVESS's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of BRINAVESS, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about ADRs is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. BRINAVESS is not widely prescribed and used only in an hospital setting by well qualified HCPs with continuous monitoring. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of BRINAVESS is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of BRINAVESS are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of BRINAVESS. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 16 List of important risks and missing information

Important identified risks	Hypotension Bradycardia Atrial flutter ECG QRS complex prolonged Ventricular arrhythmia in patients with history of valvular heart disease Ventricular arrhythmia in patients with history/evidence of congestive heart failure
Important potential risks	Overdose/medication error
Missing information	Patients with heart failure NYHA Class III and IV Patients with prolonged QT (uncorrected >440msec) Patients with severe bradycardia and second or third degree block Patients with clinically meaningful valvular stenosis Patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constructive pericarditis Use of PO antiarrhythmic therapy (Class I and III)

	Hepatic impairment Off label use including: severe aortic stenosis, or systolic BP<100mmHg patients with recent MI or ACS, patients treated for arrhythmias other than AF, use of IV AAD (Class I and Class III) within 4hours prior to vernakalant administration and within the first 4hours after vernakalant administration

II.B Summary of important risks

Table 17 Summary of important identified risk of hypotension

Identified risk: Hypotension	
Evidence for linking the risk to the medicine	Clinical trial data (BRINAVESS™ CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO Clinical Study Report [CSR]; ACT V CSR); published information on other anti- arrhythmic products; postmarketing AE report data [company PV database [Worldwide Adverse Experience System, WAES]), integrated safety analysis.
Risk factors and risk groups	Clinical trial experience has identified populations at increased risk of hypotension: • Haemodynamically unstable patients • Patients with history of CHF
Risk minimisation measures	Routine risk communication: SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 4.2, 4.3 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 18 Summary of important identified risk of bradycardia

Identified risk: Bradycardia	
Evidence for linking the risk to the medicine	Clinical trial data [BRINAVESS™ SmPC; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; postmarketing AE report data [company PV database (WAES), integrated safety analysis.
Risk factors and risk groups	Conversion from AF to SR; patients with known bradycardia or sick sinus syndrome unless controlled by a pacemaker. In patients with a history of VHD, bradycardia events occurred more frequently in the subgroup of patients treated with vernakalant, compared to those treated with PBO.
Risk minimisation measures	Routine risk communication: SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 4.2, 4.3, 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 19 Summary of important identified risk of atrial flutter

Identified risk: Atrial flutter	
Evidence for linking the risk to the medicine	Clinical trial data [BRINAVESS™ CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; postmarketing AE report data [company PV database (WAES)], integrated safety analysis.
Risk factors and risk groups	Class I antiarrhythmics, increase the risk of AFL
Risk minimisation measures	Routine risk communication: SmPC sections 4.2, 4.4, and 4.8 PL sections 4.2, 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures

Identified risk: Atrial flutter	
	HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 20 Summary of important identified risk of ECG QRS complex prolonged

Identified risk: ECG QRS complex prolonged	
Evidence for linking the risk to the medicine	Clinical trial data [BRINAVESS™ CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); ACT IV CSR; AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; postmarketing AE report data [company PV database (WAES), integrated safety analysis.
Risk factors and risk groups	Patients with known myocardial disease, background use of Class I antiarrhythmics, CHF, LV dysfunction or high ventricular rate.
Risk minimisation measures	Routine risk communication: SmPC sections 4.4, and 4.8 PL sections 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 21 Summary of important identified risk of ventricular arrhythmia in patients with history of valvular heart disease

Identified risk: Ventricular arrhythmia in patients with history of valvular heart disease	
Evidence for linking the risk to the medicine	Clinical trial data [BRINAVESS™CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; postmarketing AE report data [company PV database (WAES), integrated safety analysis.
Risk factors and risk groups	In patients with a history of VHD, VA events

Identified risk: Ventricular arrhythmia in patients with history of valvular heart disease	
	occurred more frequently in the subgroup of patients treated with vernakalant, compared to those treated with PBO.
Risk minimisation measures	Routine risk communication: SmPC sections 4.3, 4.4, and 4.8 PL sections 4.3, 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 22 Summary of important identified risk of ventricular arrhythmia in patients with history/evidence of congestive heart failure

Identified risk: Ventricular arrhythmia in patients with history/evidence of congestive heart failure	
Evidence for linking the risk to the medicine	Clinical trial data [BRINAVESS™CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; postmarketing AE report data [company PV database (WAES), integrated safety analysis.
Risk factors and risk groups	In patients with a history of CHF events occurred more frequently in the subgroup of patients treated with vernakalant, compared to those treated with PBO.
Risk minimisation measures	Routine risk communication: SmPC sections 4.3, 4.4, and 4.8 PL sections 4.3, 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 23 Summary of important potential risk of overdose/medication error

Important Potential risk: Overdose/medication error	
Evidence for linking the risk to the medicine	Clinical trial data [BRINAVESS™ CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; postmarketing AE report data [company PV database (WAES), integrated safety analysis.
Risk factors and risk groups	No risk groups or risk factors have been identified.
Risk minimisation measures	Routine risk communication: SmPC sections 4.2 and 4.9 PL sections 4.2 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 24 Summary of missing information of patients with heart failure NYHA Class III and IV

Missing information: Patients with heart failure NYHA Class III and IV	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3 PL sections 4.3 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 25 Summary of missing information of patients with prolonged QT (uncorrected >440 msec)

Missing information: Patients with prolonged QT (uncorrected >440msec)	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3 PL sections 4.3 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 26 Summary of missing information of patients with severe bradycardia and second or third degree heart block

Missing information: Patients with severe bradycardia and second or third degree block	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3, 4.4 PL sections 4.3, 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 27 Summary of missing information of patients with clinically meaningful valvular stenosis

Missing information: Patients with clinically meaningful valvular stenosis	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4 PL sections 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Missing information: Patients with clinically meaningful valvular stenosis	

Table 28 Summary of missing information of patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy or constructive pericarditis

Missing information: Patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constructive pericarditis	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4 PL sections 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 29 Summary of missing information of use of PO antiarrhythmic therapy (Class I and III)

Missing information: Use of PO antiarrhythmic therapy (Class I and III)	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4 PL sections 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 30 Summary of missing information of hepatic impairment

Missing information: Hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4 PL sections 4.4 No other routine risk minimisation measures beyond the PI

Missing information: Hepatic impairment	
	Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 31 Summary of missing information of off label use

Missing information: Off label use including: severe aortic stenosis, or systolic BP<100mmHg, Patients with recent MI or ACS, patients treated for arrhythmias other than AF, Use of IV AAD (Class I and Class III) within 4hours prior to vernakalant administration and within the first 4hours after vernakalant administration	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3 PL sections 4.3 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of BRINAVESS.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for BRINAVESS

PART VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Table of Contents

Atrial Flutter

Please fax to: add number **Or Email to: add email address**	**CASE number:**

PATIENT AND EVENT INFORMATION

PATIENT INITIALS	DATE OF BIRTH DD/MM/YYYY	AGE	GENDER M/F	WEIGHT kg	HEIGHT cm	EVENT ONSET DD/MM/YYYY
___/___/___	___/___/___	_____YEARS				___/___/___

REASON FOR THERAPY WITH BRINAVESS (tick box)

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
- ☐ Other (provide details below)

Please describe details of the observed adverse event of atrial flutter (time to onset after exposure to BRINAVESS, accompanying clinical symptoms, ECG values, specify if it was atrial flutter with 1:1 AV conduction, did atrial flutter resolve after withdrawal of BRINAVESS? If yes, how long did this take? Were therapeutic actions required?)

Please describe any other factors (concomitant drugs, co-existing medical conditions, etc) that could have contributed to the observed episode of atrial flutter.

Please describe if the subject had episodes of atrial flutter before the application of BRINAVESS (if yes, please provide details).

Bradycardia

Please fax to: add number **Or Email to: add email address**	**CASE number:**

PATIENT AND EVENT INFORMATION

PATIENT INITIALS	DATE OF BIRTH DD/MM/YYYY	AGE	GENDER M/F	WEIGHT kg	HEIGHT cm	EVENT ONSET DD/MM/YYYY
___/___/___	___/___/___	_____YEARS				___/___/___

REASON FOR THERAPY WITH BRINAVESS (tick box)

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**
- ☐ **Other (provide details below)**

Please describe details of the observed bradycardia (time to onset of bradycardia after exposure to BRINAVESS, lowest observed frequency, accompanying clinical symptoms; was bradycardia self-limiting or were therapeutic actions required).

Please describe any other factors (concomitant drugs, co-existing medical conditions, etc) that could have contributed to the episode of bradycardia observed.

Please describe if the subject had episodes of symptomatic bradycardia before the application of BRINAVESS (if yes, please provide details).

Hypotension

Please fax to: add number Or Email to: add email address	CASE number:

PATIENT AND EVENT INFORMATION

PATIENT INITIALS	DATE OF BIRTH DD/MM/YYYY	AGE	GENDER M/F	WEIGHT kg	HEIGHT cm	EVENT ONSET DD/MM/YYYY
___/___/___	___/___/___	_____YEARS				___/___/___

REASON FOR THERAPY WITH BRINAVESS (tick box)

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
- ☐ Other (provide details below)

Please describe details of the observed hypotension (time to onset of hypotension after exposure to BRINAVESS, extent of hypotension in mmHg, accompanying clinical symptoms; was hypotension self-limiting or were therapeutic actions required; was there any indication fora cardiac cause of hypotension).

Please describe any other factors (concomitant drugs, co-existing medical conditions, etc) that could have contributed to the episode of hypotension observed.

Please describe if the subject had episodes of symptomatic hypotension before the application of BRINAVESS.

Overdose/Medication error

Please fax to: add number **Or Email to: add email address**	**CASE number:**

PATIENT AND EVENT INFORMATION

PATIENT INITIALS	DATE OF BIRTH DD/MM/YYYY	AGE	GENDER M/F	WEIGHT kg	HEIGHT cm	EVENT ONSET DD/MM/YYYY
___/___/___	___/___/___	_____YEARS				___/___/___

REASON FOR THERAPY WITH BRINAVESS (tick box)

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**
- ☐ **Other (provide details below)**

Please describe details of the observed medication error or overdose (e.g. were medication error or overdose intentional or unintentional; accompanied by clinical adverse symptoms, if yes, describe the clinical symptoms)

Please describe any factors that caused or facilitated the observed medication error or overdose (e.g. deficiencies of the product or product packaging or label; or drug ineffective; patient conditions)

ECG QRS complex prolonged

Please fax to: add number **Or Email to: add email address**	**CASE number:**

PATIENT AND EVENT INFORMATION

PATIENT INITIALS	DATE OF BIRTH DD/MM/YYYY	AGE	GENDER M/F	WEIGHT kg	HEIGHT cm	EVENT ONSET DD/MM/YYYY
___/___/___	___/___/___	_____YEARS				___/___/___

REASON FOR THERAPY WITH BRINAVESS (tick box)

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**
- ☐ **Other (provide details below)**

Please describe details of the observed adverse event of "ECG QRS complex prolonged" (time to onset after exposure to BRINAVESS, accompanying clinical symptoms; did prolonged QRS complex normalise, after withdrawal of BRINAVESS? If yes, how long did this take?

Please describe any other factors (concomitant drugs, co-existing medical conditions, etc) that could have contributed to the observed episode of ECG QRS complex prolonged.

Please describe if the subject had episodes of QRS complex prolongation before the application of BRINAVESS (if yes, please provide details).

Ventricular Arrhythmia (in patients with valvular heart disease)

Please fax to: add number **Or Email to: add email address**	**CASE number:**

PATIENT AND EVENT INFORMATION

PATIENT INITIALS	DATE OF BIRTH DD/MM/YYYY	AGE	GENDER M/F	WEIGHT kg	HEIGHT cm	EVENT ONSET DD/MM/YYYY
___/___/___	___/___/___	_____YEARS				___/___/___

REASON FOR THERAPY WITH BRINAVESS (tick box)

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
- ☐ Other (provide details below)

How were the diagnoses of ventricular arrhythmia and valvular heart disease ascertained? Please provide details on clinical symptoms; technical measurement; type, severity and duration of the condition.

Please provide details on the time interval between the application of BRINAVESS and the diagnosis of cardiac arrhythmia (time-to-onset).

Please describe factors other than BRINAVESS-exposure that could have contributed to the causation of arrhythmia, if applicable (e.g. concomitant drugs, co-existing medical conditions).

Please describe if the subject had episodes of symptomatic arrhythmia before the application of BRINAVESS (if yes, please provide details).

Ventricular Arrhythmia (in patients without valvular heart disease)

Please fax to: add number **Or Email to: add email address**	**CASE number:**

PATIENT AND EVENT INFORMATION

PATIENT INITIALS	DATE OF BIRTH DD/MM/YYYY	AGE	GENDER M/F	WEIGHT kg	HEIGHT cm	EVENT ONSET DD/MM/YYYY
___/___/___	___/___/___	_____YEARS				___/___/___

REASON FOR THERAPY WITH BRINAVESS (tick box)

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
- ☐ Other (provide details below)

How was the diagnosis of ventricular arrhythmia ascertained? Please provide details on clinical symptoms; technical measurement; type, severity and duration of the condition.

Please provide details on the time interval between the application of BRINAVESS and the diagnosis of cardiac arrhythmia (time-to-onset).

Please describe factors other than BRINAVESS-exposure that could have contributed to the causation of arrhythmia, if applicable (e.g. concomitant drugs, co-existing medical conditions).

Please describe if the subject had episodes of symptomatic arrhythmia before the application of BRINAVESS (if yes, please provide details).

Ventricular Arrhythmia (in patients with congestive heart failure)

Please fax to: add number **Or Email to: add email address**	**CASE number:**

PATIENT AND EVENT INFORMATION

PATIENT INITIALS	DATE OF BIRTH DD/MM/YYYY	AGE	GENDER M/F	WEIGHT kg	HEIGHT cm	EVENT ONSET DD/MM/YYYY
___/___/___	___/___/___	_____YEARS				___/___/___

REASON FOR THERAPY WITH BRINAVESS (tick box)

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
- ☐ Other (provide details below)

How were the diagnoses of ventricular arrhythmia and congestive heart failure ascertained? Please provide details on clinical symptoms; technical measurement; type, severity and duration of the condition.

Please provide details on the time interval between the application of BRINAVESS and the diagnosis of cardiac arrhythmia (time-to-onset).

Please describe factors other than BRINAVESS-exposure that could have contributed to the causation of arrhythmia, if applicable (e.g. concomitant drugs, co-existing medical conditions).

Please describe if the subject had episodes of symptomatic arrhythmia before the application of BRINAVESS (if yes, please provide details).

Ventricular Arrhythmia (in patients without congestive heart failure)

Please fax to: add number **Or Email to: add email address**	**CASE number:**

PATIENT AND EVENT INFORMATION

PATIENT INITIALS	DATE OF BIRTH DD/MM/YYYY	AGE	GENDER M/F	WEIGHT kg	HEIGHT cm	EVENT ONSET DD/MM/YYYY
___/___/___	___/___/___	_____YEARS				___/___/___

REASON FOR THERAPY WITH BRINAVESS (tick box)

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
- ☐ Other (provide details below)

How was the diagnosis of ventricular arrhythmia ascertained? Please provide details on clinical symptoms; technical measurement; type, severity and duration of the condition.

Please provide details on the time interval between the application of BRINAVESS and the diagnosis of cardiac arrhythmia (time-to-onset).

Please describe factors other than BRINAVESS-exposure that could have contributed to the causation of arrhythmia, if applicable (e.g. concomitant drugs, co-existing medical conditions).

Please describe if the subject had episodes of symptomatic arrhythmia before the application of BRINAVESS (if yes, please provide details).

Annex 6 - Details of proposed additional risk minimisation measures

Approved key messages of the additional risk minimisation measures

The MAH shall ensure that all healthcare professionals (HCP) involved in the administration of BRINAVESS are provided with a HCP information pack containing the following:

- Educational material for HCPs
- The SmPC, package leaflet (PL) and labelling.

The MAH must agree about the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution.

Key elements to be included in the educational material:

1. BRINAVESS should be administered by IV infusion in a monitored clinical setting appropriate for cardioversion. Only a well-qualified HCP should administer BRINAVESS and should frequently monitor 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 BP or heart rate.

2. Appropriate measures to manage and minimise the risks, including the need for close monitoring during and after administration of BRINAVESS.

3. Patient selection criteria, including contraindications, special warnings and precautions for use and information about patient populations with limited information from clinical trials.

- Alert HCP on BRINAVESS contraindications:
  - Hypersensitivity to the active substance or to any of the excipients.
  - 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 IV 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 MI) within the last 30 days
  - Patients with severe aortic stenosis, patients with systolic BP < 100 mm Hg, and patients with heart failure class NYHA III and NYHA IV.
- Alert HCP about BRINAVESS special warnings and precautions in patients with, clinically meaningful valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis, previously documented LVEF ≤35%, advanced hepatic impairment.
- Alert HCP about the need of precautions when using BRINAVESS in haemodynamically stable patients with congestive heart failure NYHA I and NYHA II and the need to monitor patients with valvular heart disease closely.
- Alert HCP for ADRs, which may occur after BRINAVESS administration, including hypotension, bradycardia, atrial flutter, or ventricular arrhythmia.
- Alert HCP for use of antiarrhythmic drugs (AADs) prior to or after BRINAVESS.

- BRINAVESS cannot be recommended in patients previously administered IV AADs (class I and III) 4-24 hours prior to vernakalant, due to lack of data.
- BRINAVESS should be used with caution in patients on oral AADs (class I and III), due to limited experience. Risk of atrial flutter may be increased in patients receiving class I AADs.,
- Resumption or initiation of oral-maintenance antiarrhythmic therapy can be considered 2 hours after BRINAVESS administration.
- Intravenous rhythm control AADs should not be used in the first 4 hours after BRINAVESS administration.

4. Instructions on dose calculation, preparation of the solution for infusion, and method of administration.

5. BRINAVESS may be available in different vial sizes (available vial sizes to be inserted locally). The number of vials of BRINAVESS concentrate required to prepare the appropriate quantity of solution for the treatment of an individual patient will depend on the patient's weight, and the vial size.